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# Nonbonded, Attractive Cation−$\pi$ Interactions in Azide-Mediated Asymmetric Ring Expansion Reactions

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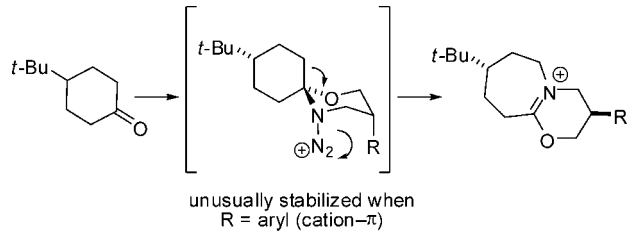


The influence of attractive, nonbonded interactions on the reactions of 1,2- and 1,3-hydroxyalkyl azides with ketones has been investigated through experimental and computational means. A series of 1,3-hydroxyalkyl azides bearing electronically tuned aromatic groups at the 2 position were prepared and reacted along with several derivatives designed to conformationally restrict the rotational orientation of the aromatic substituent. These studies showed that a cation−$\pi$ interaction between an aryl moiety and an $N_2^+$ leaving group plays a role in determining the stereoselectivity of these reactions. A series of ab initio calculations supported this hypothesis. A computational and experimental analysis suggested a primarily steric model for the analogous reactions of substituted 2-azido-1-ethanol analogues.

## Introduction

The covalent connection of two reactive moieties to facilitate an intramolecular reaction is a useful strategy in chemical synthesis.[1] In this context, a connecting tether is primarily used to increase the reaction rate by enforcing proximity between the functional groups. In addition, a tether can affect stereochemistry by the incorporation of substituents that influence the molecule's conformation en route to product. The outcomes of such reactions are usually predicted by analyzing steric interactions present in intermediates or transition structures leading to the observed products. Such analyses may be carried out computationally, but qualitative rationalizations based on common principles of conformational analysis are common.[1,2]

A tether may become part of the ultimate product or it may be temporarily deployed and then detached following the reaction of interest.[3] A third method being explored in our

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(1) The literature of intramolecularity in organic synthesis is vast. Some relevant reviews include: (a) Oppolzer, W. *Synthesis* **1978**, 793–802. (b) Ciganek, E. *Org. React.* **1984**, *32*, 4–374. (c) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416. (d) Schinzer, D. *Synthesis* **1988**, 263–273. (e) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139–145. (f) Namboothiri, I. N. N.; Hassner, A. *Top. Curr. Chem.* **2001**, *216*, 1–49. (g) Maryanoff, B. E.; Zhang; Han-Cheng; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628. (h) Zubkov, F. I.; Nikitina, E. V.; Varlamov, A. V. *Russ. Chem. Rev.* **2005**, *74*, 639–669.
(2) Sugimura, T. *Eur. J. Org. Chem.* **2004**, 1185–1192.



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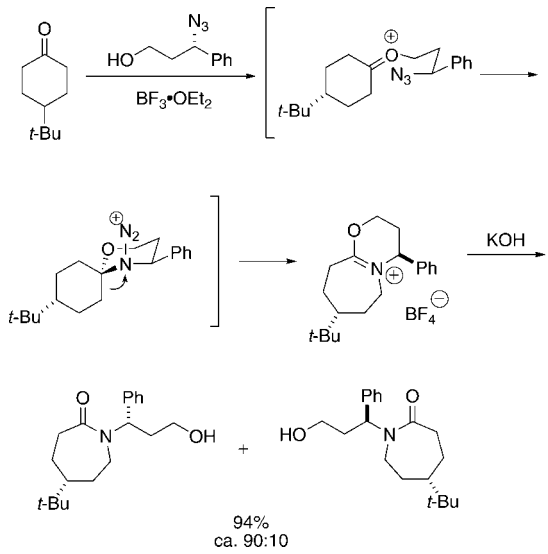
**SCHEME 1**




laboratory involves connection of the tether under the same conditions used to effect the reaction of interest.[4] We have examined this "in situ tethering" strategy in the context of hydroxyalkyl azide-mediated ring expansions of cyclic ketones.[5,6] The use of chiral hydroxyalkyl azides in this reaction provides an efficient asymmetric route to lactams from appropriately substituted cyclohexanones (Scheme 1).[7] In this case, the key stereochemistry-determining feature is the conformation of the azide-containing tether: the chairlike ring containing an equatorial phenyl substituent leads selectively to a spirocyclic intermediate that rearranges to afford an iminium ether. This latter intermediate is converted into product by treatment with aqueous base or by reaction with other nucleophiles.[8]

In exploring the scope of this process, it soon became clear that results using certain phenyl-containing hydroxyalkyl azides could not be readily explained solely by analysis of steric interactions. Specifically, we proposed that the stereoselectivity of some of the reactions could be affected by attractive, nonbonded interactions of a substituted aromatic group with the cationic $N_2^+$ leaving group when both moieties were in a 1,3-diaxial relationship to one another (Figure 1). Preliminary results that supported this view were communicated in 2003, including experiments that showed the dependence of stereoselectivity on the electronic nature of the phenyl group and conformational constraints.[9] In this account, the full details of this work are disclosed along with a detailed theoretical treatment of the substituent effects on the 1,3 cation-phenyl interaction. In addition, the possible role of these effects in the analogous reactions of 1,2-hydroxyalkyl azides will be discussed.

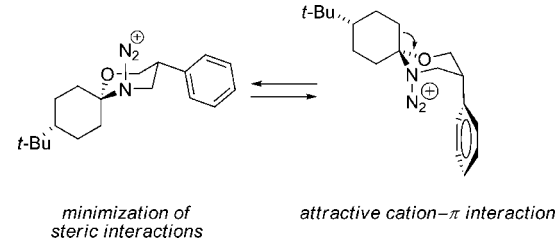



**FIGURE 1.** Two possible intermediates in the ring-expansion reaction of hydroxyalkyl azides, one in which steric interactions are minimized by placing the phenyl group in an equatorial position (left) and one with the potential for an attractive cation−π interaction between the leaving group and a phenyl group (right).

## Results and Discussion

**Initial Observations.** Our current view of the mechanism of the in situ tethered hydroxyalkyl azide Schmidt reaction, indicated in Scheme 2, is supported by considerable experimental evidence[5,9] and computational studies.[10] We propose that the stereoselectivity of the sequence is controlled by the equilibrium between intermediates **A** and **B**, each of which features equatorial addition of azide to the oxonium ion derived from the ketone substrate (i.e., formation of a spirocycle having nitrogen trans to the 4-*tert*-butyl group) but that differ in which chairlike conformation of the intermediate is involved. Each intermediate undergoes rearrangement to an iminium ether through migration of a methylene group antiperiplanar to the leaving $N_2^+$ group. Two aspects of this step are noteworthy. First, the system is set up in such a way that the only reactive conformations have a 1,2-diaxial relationship between the migrating carbon and leaving group (equatorial $N_2^+$would be antiperiplanar to a nonmigratable C−O bond). Second, we propose, based on theory[10] and on the absence of reasonable alternatives, that the rates of migration from **A** or **B** are comparable, leaving the sole source of stereoselectivity to be the relative stability of these intermediates.[11] **A** and **B** can equilibrate by conformational interconversion or by reversion to an oxonium ion followed by reformation; which one occurs is not relevant to this analysis, provided that interconversion is fast relative to migration. In any event, the stereochemistry-determining step is completed by formation of the iminium ethers, which are hydrolyzed to afford lactams.

Initial observations that suggested something might be interesting about intermediates bearing a phenyl group placed

(3) Reviews of disposable tethers in synthetic organic synthesis: (a) Ford, W. T. *CHEMTECH* **1987**, *17*, 246–250. (b) Fensterbank, L.; Malacria, M.; McN. Sieburth, S. *Synthesis* **1997**, 813–854. (c) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289–2338. (d) Knapp, S. *Chem. Soc. Rev.* **1999**, *28*, 61–72. (e) Cox, L. R.; Ley, S. V. In *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1 pp 275–395. (f) Breslow, R. In *Templated Organic Synthesis*; Diederich, F., Stang, P. J.; Eds., Wiley-VCH: Weinheim, 2000; Vol. 1 pp 159–188. (g) Zachary, A. D.; Overman Larry, E. *Chem. Commun.* **2004**, *253*, 65. (h) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912–1915.

(4) For other examples of "in situ" tethering in synthesis, see: (a) Sammakia, T.; Berliner, M. A. *J. Org. Chem.* **1995**, *60*, 6652–6653. (b) Haynes, R. K.; King, G. R.; Vonwiller, S. C. *J. Org. Chem.* **1994**, *59*, 4743–4748. (c) Greico, P. A.; Kaufman, M. D.; Daeuble, J. F.; Saito, N. *J. Am. Chem. Soc.* **1996**, *118*, 2095–2096. (d) Suginome, M.; Iwanami, T.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 6096–6097. (e) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092–1093.

(5) (a) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 8047–8048. (b) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aubé, J. *Tetrahedron* **1997**, *53*, 16241–16252.

(6) See also Haynes, R. K.; King, G. R.; Vonwiller, S. C. *J. Org. Chem.* **1994**, *59*, 4743–4748.

(7) For asymmetric versions of the hydroxyalkyl azide-mediated Schmidt reaction, see ref 5a and: (a) Vidari, G.; Tripolini, M.; Novella, P.; Allegraucci, P.; Garlaschelli, L. *Tetrahedron: Asymmetry* **1997**, *8*, 2893–2903. (b) Furness, K.; Aubé, J. *Org. Lett.* **1999**, *1*, 495–497. (c) Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B. T.; Katz, C. E.; Reddy, D. S.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 7914–7922.

(8) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 10–11.

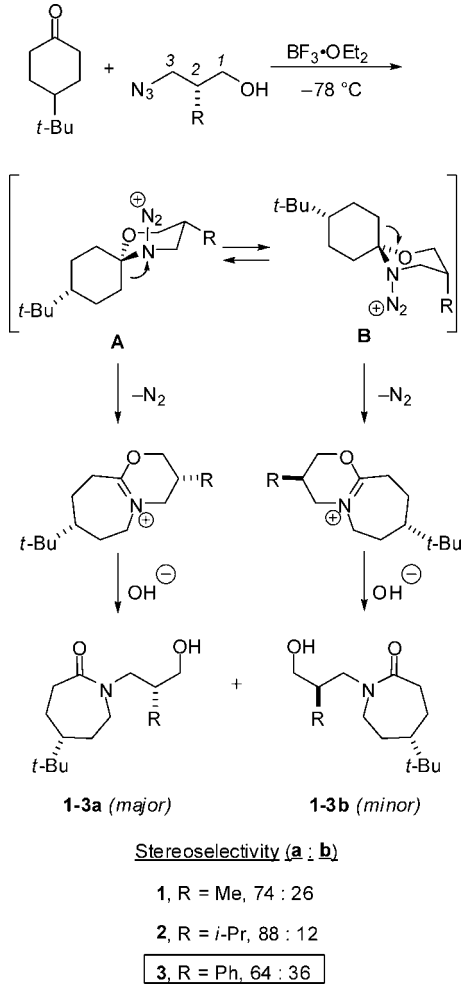
(9) Katz, C. E.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 13948–13949.

(10) Hewlett, N. D.; Aubé, J.; Radkiewicz-Poutsma, J. L. *J. Org. Chem.* **2004**, *69*, 3439–3446.

(11) Hoye, T. R.; Ryba, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 8256–8257.

(12) An outstanding collection of A values for substituted cyclohexanes can be found in: (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994, pp 696–697; see also the numerous references cited. For determination of equatorial/axial preferences in substituted 1,3-dioxanes, see: (b) Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444–3458. (c) Eliel, E. L. *Acc. Chem. Res.* **1970**, *3*, 1–8. (d) Shea, K. J.; Dougherty, T. K. *J. Org. Chem.* **1985**, *50*, 4439–4442.

**SCHEME 2**




in a 1,3-diaxial relationship to the leaving group are summarized in Scheme 2.[7c] Thus, the selectivity observed upon modifying the nature of a substituent placed at carbon 2 in a series of 1,3-hydroxyalkyl azides did not follow the steric demands of the substituents, with selectivity increasing in the order Ph (**A** value[12a] 2.8) < Me (1.74) < *i*-Pr (2.21). Furthermore, the low selectivity seen for the 2-phenyl reactant was unique to this series, with high selectivities observed for 1,3-hydroxyalkyl azides bearing a phenyl substituent in either the 1 position (95:5 ratio) or in the 3 position (90:10 ratio; see Scheme 1). On one hand, lower selectivity compared to 1- or 3-substituted azides was not surprising in that the axial R group in intermediate **B** only experiences a single 1,3-diaxial interaction with a relatively small $N_2^+$ group. C-5 substituents in 1,3-dioxanes (the closest model for which detailed conformational benchmarks are readily available) have lower equatorial/axial biases than in cyclohexanes but they generally follow the same order. Thus, the $-\Delta G°_{25}$ values for Me, *i*-Pr, and Ph in 5-alkyl-2-*tert*-butyl-1,3-dioxanes are 0.80, 0.98, and 1.03 kcal/mol, respectively.[12b–d] 1,3-Diaxial interactions between the R group and the $N_2^+$ leaving group clearly play some role given the higher selectivity of R = *i*-Pr v. Me en route to **2** and **1**, respectively. The fact that the C-2 phenyl group was an outlier - giving much lower selectivity than even the smaller methyl-containing analog - suggested an electronic component. In particular, the transition structure leading to the minor product series **b** in Scheme 2 might be stabilized by nonbonded interactions between the

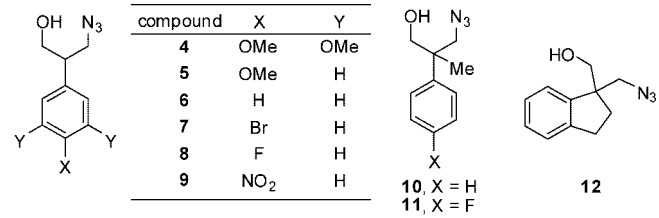



**FIGURE 2.** 2-Aryl-1-hydroxyalkyl-3-azides used in this work.

electron-rich phenyl group and the $N_2^+$ leaving group. Cation−$\pi$ interactions are commonly invoked in bioorganic chemistry as features of protein structure and have also been cited as components of host–guest interactions.[13] In contrast, such interactions have only rarely been invoked as stereocontrolling elements in selective organic reactions.[14,15] We decided to probe this effect by examining related substrates designed to vary both the electronic and conformational aspects of the reaction.

**Substituted Aryl-Containing 1,3-Hydroxyalkyl Azides.** A series of 2-aryl-1-hydroxyalkyl-3-azides were initially prepared following the hypothesis that lactam stereoisomer **b** would be predominant with more electron-rich systems (Figure 2; see Cubero[16] for a theoretical treatment of the effect of substituents and polarizability on cation−$\pi$ interactions). Most of the reactants were prepared and used in racemic form, although downstream problems in assessing the stereochemical outcome of several examples necessitated some asymmetric syntheses. Throughout, compounds will be depicted in a single enantiomeric series to simplify comparison of various examples. Synthetic details and particulars of which stereochemical series were used are provided in the Supporting Information.

With a series of electronically tuned hydroxyalkyl azides in hand, the compounds were reacted with 4-*tert*-butylcyclohexanone in the presence of $BF_3 \cdot OEt_2$, followed by hydrolysis of the intermediate iminium ethers using aqueous KOH. Selectivities were determined by HPLC or gas chromatographic analysis of the crude reaction mixtures (Table 1). Subsequently, the product lactams were purified by chromatography to afford the yields shown; these reactions were generally high yielding. Product stereostructures were determined by X-ray crystallography and retention times of crystalline samples were compared to those taken from crude reaction mixtures.

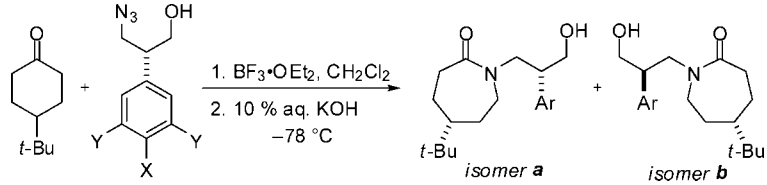
(13) For literature of cation−$\pi$ interactions in macromolecular structure and molecular recognition, see:(a) Dougherty, D. A. *Science* **1996**, *271*, 163168(b) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303–1324. (d) Gokel, G. W.; De Wall, S. L.; Meadows, E. S. *Eur. J. Org. Chem.* **2000**, 2967–2978. (e) Shi, Z.; Olson, C. A.; Bell, A. J., Jr.; Kallenbach, N. R. *Biopolymers* **2001**, *60*, 366–380. (f) Gokel, G. W.; Barbour, L. J.; Ferdani, R.; Hu, J. *Acc. Chem. Res.* **2002**, *35*, 878–886. (g) Zacharias, N.; Dougherty, D. A. *Trends Pharmacol. Sci.* **2002**, *23*, 281–287.

(14) Cation−$\pi$ interactions in organic synthesis have been recently reviewed: (a) Yamada, S. *Org. Biomol. Chem* **2007**, *5*, 2903–2912. For lead references, see: (b) Lakshminarasimhan, P.; Sunoj, R. B.; Chandrasekhar, J.; Ramamurthy, V. *J. Am. Chem. Soc.* **2000**, *122*, 4815–4816. (c) Stratakis, M.; Froudakis, G. *Org. Lett.* **2000**, *2*, 1369–1372. (d) Yamada, S.; Morita, C. *J. Am. Chem. Soc.* **2002**, *124*, 8184–8185. (e) Yamada, S.; Saitoh, M.; Misono, T. *Tetrahedron Lett.* **2002**, *43*, 5853–5857. (f) Ramamurthy, V.; Shailaja, J.; Kaanumalle, L. S.; Sunoj, R. B.; Chandrasekhar, J. *Chem. Commun.* **2003**, 1987–1999. (g) Chiavarino, B.; Crestoni, M. E.; Fornarini, S. *Int. J. Mass Spectrom.* **2004**, *235*, 145–154. (h) Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2007**, *129*, 2766–2767.

(15) For literature in which cation−$\pi$ interactions play a role in asymmetric catalysis, see: (a) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226–12227. (b) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445–3447. (c) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536–6537. (d) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351–1354. (e) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859–4861.

(16) Cubero, E.; Luque, F. J.; Orozco, M. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 5976–5980.

**TABLE 1. Reactions of 2-Aryl-1,3-hydroxyalkyl Azide with 4-*tert*-Butylcyclohexanone**




| entry | hydroxyalkyl azide | X | Y | lactam | yield (%) | diastereomeric ratio[a] | |
|---|---|---|---|---|---|---|---|
| | | | | | | **a** | **b** |
| 1 | **4** | OMe | OMe | **13** | 99 | 43 | 57 |
| 2 | **5** | OMe | H | **14** | 99 | 47 | 53 |
| 3 | **6** | H | H | **3** | 85 | 64 | 36 |
| 4 | **7** | Br | H | **15** | 90 | 68 | 32 |
| 5 | **8** | F | H | **16** | 73 | 69 | 31 |
| 6 | **9** | $NO_2$ | H | **17** | 86 | 76 | 24 |

[a] See Supporting Information for methods used to determine structures and ratios.

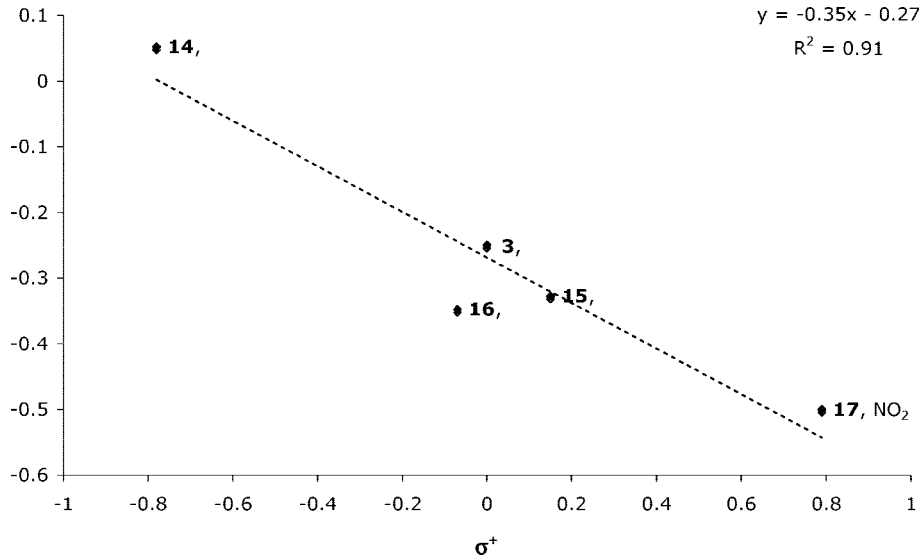



**FIGURE 3.** Hammett plot of the stereoselectivities of the reactions from Table 1 versus $\sigma^+$ parameters. The results from hydroxyalkyl azide **4** are not included due to the unavailability of an appropriate $\sigma^+$ value.

The data indicate a correlation between the electronic nature of the 2-aryl substituent and the stereoselectivity of the ring-expansion reaction, consistent with greater stabilization of the intermediate leading to isomer **b** via nonbonded cation−π interactions. A Hammett-like analysis of the data is shown in Figure 3. Although its application to nonbonded interactions constitutes a stretch of the linear free energy concept,[17] the reasonable correlation ($r = 0.91$) obtained between $\sigma^+$ and the −log(**a**/**b**) values supports the hypothesis that increased electron density in the aryl substituent assists in the formation of isomer **b**.

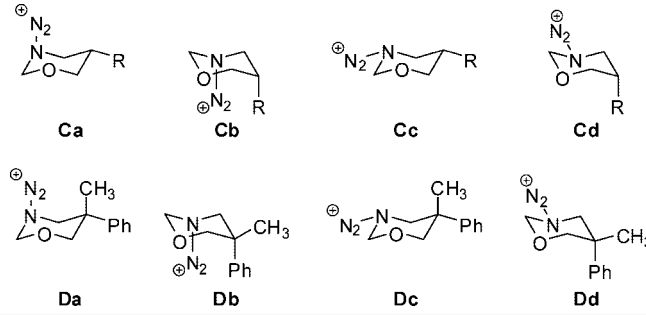
To gain greater understanding of this phenomenon, a series of ab initio calculations was performed. In previous work, intermediates **a** and **b** were calculated along with the transition structures leading to iminium ether products.[10] These calculations supported our overall view of the reaction mechanism and additionally provided preliminary evidence in favor of the nonbonded stabilization of the $N_2^+$ leaving group by an appropriately positioned phenyl group. In the present work, this approach was applied to the intermediates associated with the reactions of hydroxyalkyl azides bearing phenyl substitution.

Energies were calculated using the MP2/6–311+G**//MP2/6–31G* level of theory and focused on the *N*-diazonium-1,3-oxazinane part of the intermediate **C** (Table 2). There are four possible versions of the intermediate: **Ca** ($N_2^+$ axial/R equatorial), **Cb** ($N_2^+$ axial/R axial), **Cc** ($N_2^+$ equatorial/R equatorial), and **Cd** ($N_2^+$ equatorial/R axial). In all cases, the $N_2^+$ axial conformers were lower in energy than the $N_2^+$ equatorial conformers. Thus, the energy differences between **Ca** and **Cb** were used to calculate the axial/equatorial preferences of the substituted phenyl groups. Energies were converted to $\Delta G$ values using standard methods and solvent was added via the CPCM method. For comparison between the experimental data and our calculations, the experimental ratios were converted to $\Delta G$ values using $\Delta G = -RT \ln K$.

The calculations show a surprising degree of correlation with the experimental results considering the small differences in the $\Delta G$'s between intermediates containing differently substituted phenyl rings. Both gas phase and solvent axial/equatorial free energy differences are provided in Table 2. Previously, the gas phase calculations overestimated the stability of the axial/axial conformer **Cb**,[10] and this was again observed for the substituted

(17) For recent examples of linear free energy treatments of nonbonded interactions, see: (a) Cockroft, S. L.; Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 8594–8595. (b) Thomas, K. M.; Naduthambi, D.; Zondlo, N. J. *J. Am. Chem. Soc.* **2006**, *128*, 2216–2217. (c) Hodges, J. A.; Raines, R. T. *Org. Lett.* **2006**, *8*, 4695–4697.

**TABLE 2. Comparison of Calculated Free Energy Differences and Experimental Diastereoselectivities**[a]



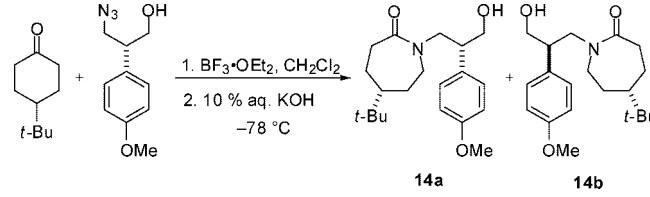

| entry | model system | lactam | **a:b**[b] | $\Delta G_{expt}$[c] | $\Delta G_{gas}$[c] | $\Delta G_{solv}$[c] |
|---|---|---|---|---|---|---|
| 1 | **C**, R = $(MeO)_3C_6H_2$ | **13** | 43:57 | −0.1 | −3.5 | −0.5 |
| 2 | **C**, R = 4-$MeOC_6H_4$ | **14** | 47:53 | 0.0 | −2.8 | −0.2 |
| 3 | **C**, R = $C_6H_5$ | **3** | 64:36 | 0.2 | −2.0 | −0.3 |
| 4 | **C**, R = 4-$BrC_6H_4$ | **15** | 68:32 | 0.3 | −2.2 | −0.2 |
| 5 | **C**, R = 4-$NO_2C_6H_4$ | **16** | 76:24 | 0.4 | −1.8 | 0.2 |
| 6 | **D** | **18** | 5:95 | −1.1 | −5.8 | −4.3 (−1.4)[d] |

[a] Calculations for the solvent (CPCM, $\epsilon$ = 8.93) free energy differences were performed at the MP2/6–311+G**//MP2/6–31G* level of theory. [b] Experimental ratios. [c] Differences between **Cb/Ca** or **Db/Da**. [d] The number in parentheses is the selectivity for equatorial versus axial attack of the azide on the carbonyl carbon.

examples. Despite this, the experimental trend was reproduced by the theoretical data ($R^2 = 0.89$), aside from a slight difference in the relationship between the unsubstituted phenyl and bromophenyl. This is consistent with the view that the selectivities are a direct result of the axial/equatorial preference and the strength of the cation−$\pi$ interaction. Inclusion of solvent gives free energies that are in very good agreement with the experimental selectivities with errors of only ± 0.5 kcal/mol. Although the CPCM method correctly reproduces the shielding effect of the solvent, the overall accuracy of these types of calculations is reduced compared to gas phase. Thus, the trend present in the experimental data and gas phase results is not as obvious for the solvent results ($R^2 = 0.65$).

A brief survey of solvent effects was also carried out experimentally (Table 3). With one exception (entry 1), the effect was relatively flat across the small number of solvents that were examined (a greater range was not possible as the reaction fails in highly polar solvents).[5,9] In particular, neither a dependence on dielectric constant nor a strong effect of carrying out the reaction in an aromatic solvent could be gleaned from these data. This suggests that the equilibrium between intermediates **A** and **B** (Scheme 1), differing mainly in the axial v. equatorial orientation of the aromatic group, is not generally perturbed in the solvents examined. These data are in agreement with previous theoretical studies that demonstrated that going from gas phase to solvent has a large effect on cation−$\pi$ interactions, but that a change in the dielectric of the solvent has a much smaller effect.[18] It is possible that diglyme, which is the prime outlier in this series, is able to complex the $N_2^+$ group and thereby lead to product that arises from a greater flux through intermediate type **A** containing an equatorial phenyl group. It is also possible that solvent effects are minimized due to the closeness of the aryl and cationic moieties. (We thank anonymous reviewers for these last two suggestions.)

**TABLE 3. Solvent Study with Hydroxypropyl Azide 5 and 4-*tert*-Butylcyclohexanone**




| | | | | diastereomeric ratio[a] | |
|---|---|---|---|---|---|
| entry | solvent | $\epsilon_r$[b] | yield (%) | **a** | **b** |
| 1 | $n$-$C_5H_{12}/CH_2Cl_2$[c] | na | 78 | 47 | 53 |
| 2 | toluene | 2.379 | 97 | 47 | 53 |
| 3 | $(C_5H_5)_2O$ | 4.266 | 98 | 54 | 47 |
| 4 | diglyme | 7.23 | 99 | 72 | 28 |
| 5 | $CH_2Cl_2$ | 8.83 | 99 | 47 | 53 |

[a] Determined by HPLC. [b] Reichhardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinhein, 1988. [c] A 5/2 ratio of $n$-$C_5H_{12}/CH_2Cl_2$, in agreement with the experimental data (Table 4).

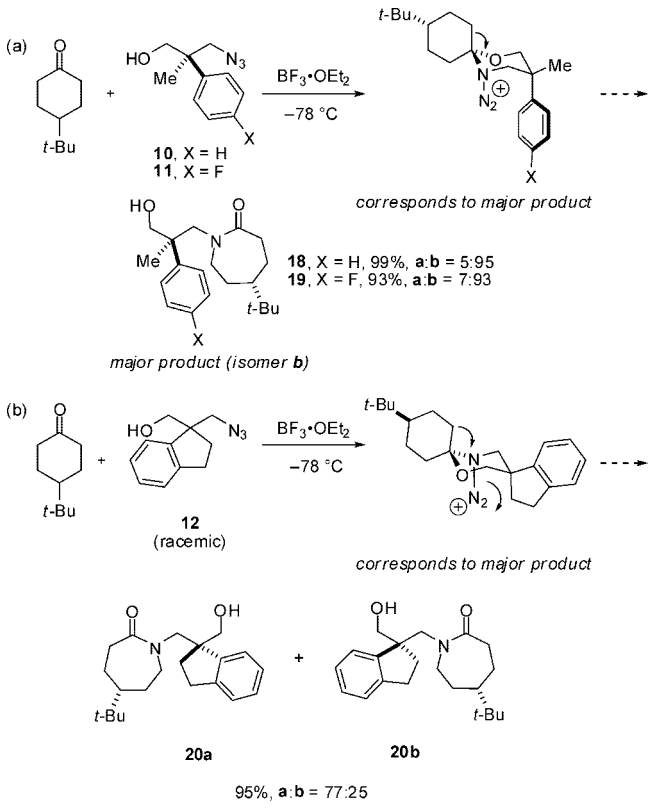
**Conformational Effects in the Reactions of 2-Aryl-1-Hydroxypropyl-3-Azides Containing Quaternary Stereocenters.** It has been established that 1-methyl-1-phenylcyclohexane exists as a ca. 2.5:1 mixture of conformers at −100 °C, favoring the isomer with an axial phenyl group and corresponding to an energy difference of ca. 0.32 kcal/mol at −78 °C.[19a] The conformation with axial phenyl is favored because it can avoid, through rotation, steric interactions with adjacent equatorial or methyl group hydrogens that are unavoidable when the phenyl is equatorial. The situation is complicated when *gem*-aryl,Me disubstitution is studied at C-5 in various 1,3 dioxanes, where conformers favoring either equatorial or axial aromatic rings have been observed, depending on electron donating or withdrawing C-5 aryl substitution (an effect that is absent in 1-aryl-1-methylcyclohexanes).[19b] Interestingly, although tethers containing quaternary nonstereogenic carbons are well-known to accelerate intramolecular reactions,[20] examples of stereogenic,

(18) (a) Gallivan, J. P.; Dougherty, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 870–874. (b) Biot, C.; Buisine, E.; Rooman, M. *J. Am. Chem. Soc.* **2003**, *125*, 13988–13994.

(19) (a) Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959–1962. For an excellent discussion of nonadditivity of cyclohexane-centric conformational analysis, see: (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 695–706. (c) Cook, M. J.; Nasri, K.; Vather, S. M. *Tetrahedron Lett.* **1986**, *27*, 3853–3854.

(20) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.

**SCHEME 3**




quaternary carbons appearing as a stereocontrolling feature of an intramolecular process are rare.[21]

Strikingly, the reaction of the geminally disubstituted hydroxyalkyl azide **10** was extremely selective, affording only the single isomer **18b** as determined through inspection of the crude NMR spectrum (Scheme 3a; the stereostructure of **18b** was secured by X-ray crystallographic analysis). Conservatively estimating the ratio at ≥95:5, this highly selective example suggests that either the eq-Me/ax-Ph conformation is highly favored in the reactive intermediate or that this conformation is considerably more reactive than the alternative bearing an axial Me group and equatorial phenyl (not shown). It is likely that the eq-Me/ax-Ph preference arises from both steric and electronic interactions. In contrast, for the systems examined in Table 1, these two considerations work against one another.

Calculations support the greater stability of this intermediate with the free energy preference for the axial/axial conformer predicted to be −5.8 kcal/mol in the gas phase and −4.3 kcal/mol in solvent. This is in contrast to the substituted aryl cases, which showed very small to no preferences in solvent. Converting the experimental ratio to a $\Delta G$ gives a value of −1.1 kcal/mol. This is significantly different from the calculated value of −4.1 kcal/mol. However, the observation of stereoselectivity also depends on equatorial attack of the azide to form the heterosubstituted cyclohexane intermediate. Our previous calculations have shown that the energy difference between equatorial and axial attack is −1.4 kcal/mol, giving a selectivity of 98:2. Thus, even if a large preference for the axial or equatorial conformation of the intermediate exists, the overall selectivity can never be greater than 98:2. Therefore, the

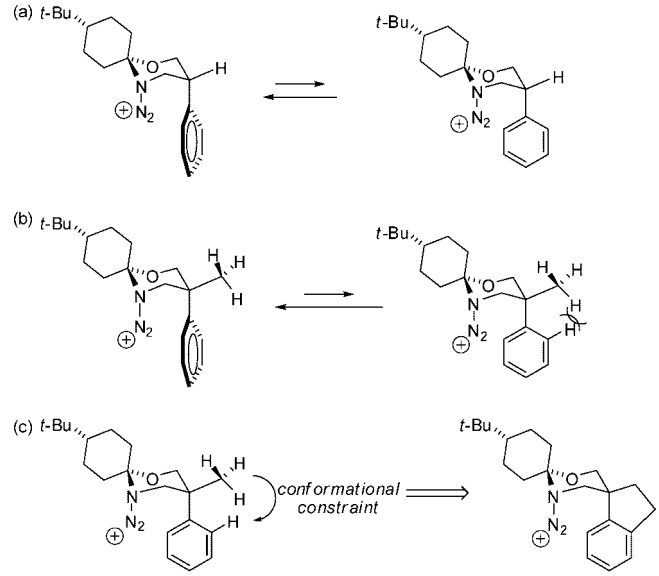



**FIGURE 4.** Conformational expectations for $C_{alkyl}-C_{aryl}$ bond rotamers in intermediates derived from (a) 2-phenyl-1-hydroxypropyl-3-azide and (b) 2-methyl-2-phenyl-1-hydroxypropyl-3-azide. (c) Conformational constraint that locks the phenyl group into a bisecting conformation.

experimental and theoretical predictions are in excellent agreement. We also examined the reaction of the fluoro-substituted hydroalkyl azide **11**; lactams **19a**,**b** were obtained in a comparable ratio to that for **18a**,**b** (Scheme 3a).

These results were also examined computationally (Table 2, entry 6; Figures 4 and 5). The most efficient cation−π interaction between a substituted phenyl group and a cationic species occurs when the flat face of the aromatic moiety is directed toward the positive charge.[22] In 2-monosubstituted cases, the aromatic groups are relatively mobile thanks to the presence of an oxygen atom in a 1,3 relationship to the stereogenic center (Figure 4a). Thus, calculations show that rotation about the $C-C_{phenyl}$ bond in 3-axial-phenyltetrahydropyran only costs ca. 1.4 kcal/mol over a range of 90°. In this case, one expects the phenyl group to occupy a range of conformations about the $C_{alkyl}-C_{aryl}$ bond. Of course, this ensemble is also in equilibrium with a set of conformations in which both rings have flipped and the phenyl group occupies an equatorial position; reactions through these conformations lead to isomeric lactams **a** (an example of these alternative conformations is given in Scheme 2). The situation changes when a methyl group is also attached to the carbon bearing the phenyl group (Figure 4b). As in 1-methyl-1-phenylcyclohexane,[19a] the phenyl group is unable to bisect the heterocyclic ring due to unfavorable steric interactions with the methyl group (i.e., the conformation shown to the right of the arrow in Figure 4b). This analysis was supported by ab initio calculations carried on the simplified system shown in Figure 5 (see Supporting Information for detailed results).

We wished to confirm the role of the $C_{alkyl}-C_{aryl}$ bond rotation in this reaction by synthesizing a conformationally constrained indane-containing hydroxyalkyl azide **12**. In this example, the phenyl group is forced to bisect the plane of the perhydroöxazine ring by connecting the geminal methyl and phenyl groups with a methylene bridge (see Scheme 3b). Upon submitting this

(21) (a) Gunther, H. J.; Jager, V.; Skell, P. S. *Tetrahedron Lett.* **1977**, *18*, 2538–2542. (b) Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636–644.

(22) Rashkin, M. J.; Hughes, R. M.; Calloway, N. T.; Waters, M. L. *J. Am. Chem. Soc.* **2004**, *126*, 13320–13325.

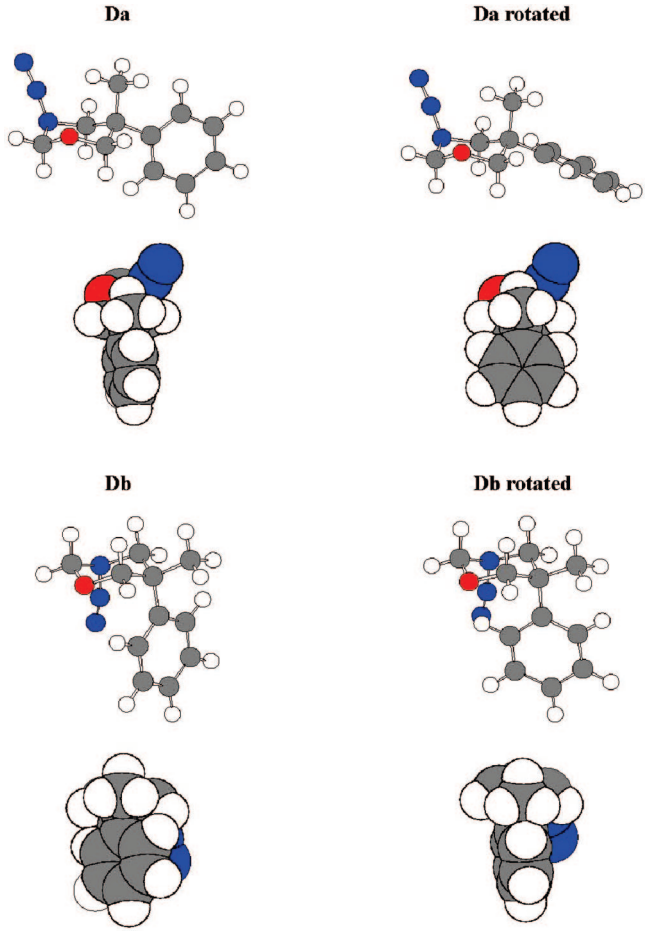
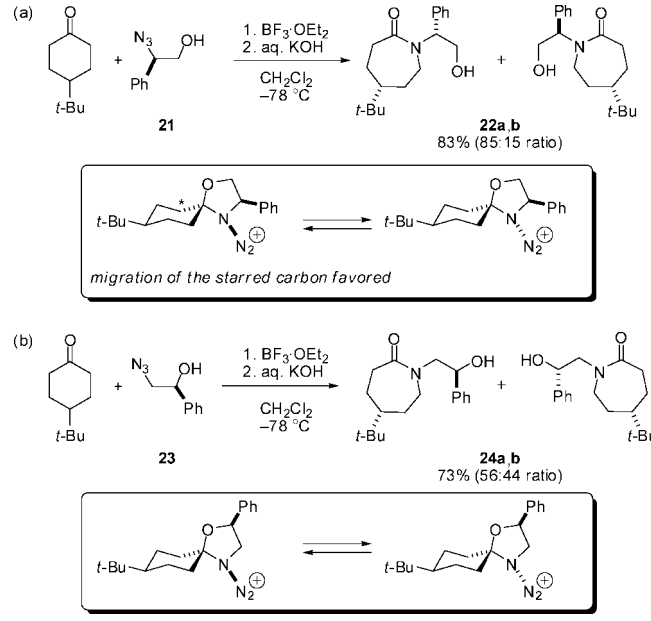



**FIGURE 5.** Possible conformers of the 3-methyl, 3-phenyl substituted intermediate **D**. The structures on the left are MP2/6–31G* optimized geometries. In the structures on the right, the phenyl ring has been rotated by 90°; in these structures, there are greater steric interactions with the adjacent methylenes on the six-membered ring (for **Da**) or the methyl group (for **Db**). In the space-filled pictures, some hydrogens have been deleted for clarity. Note that for **Da**, destabilizing steric interactions exist regardless of the orientation of the phenyl ring.

analogue to typical reaction conditions, a greatly diminished selectivity of ca. 3:1 was achieved. Furthermore, the major isomer obtained in this way resulted from an intermediate bearing an *equatorial* aryl group. The contrast between the behavior of **10** and **11** vs **12** clearly shows that aryl group rotation plays an important role in these reactions.

**Reactions of Azidoethanol Derivatives.** In the early development of this asymmetric Schmidt reaction, we had examined the reactions of 4-*tert*-butylcyclohexanone with two-carbon hydroxyalkyl azides bearing phenyl substitution (Scheme 4).[5a,7c] Thus, good selectivity was obtained for 2-azido-2-phenylethanol **21** (Scheme 4a), but the reaction of the isomer bearing a phenyl group next to the alcohol **23** (Scheme 4b) was essentially stereorandom. It was determined from analogy[7c] and calculation[10] that azide addition occurred from an equatorial direction in this system and that antiperiplanar migration relative to the departing $N_2^+$ group occurred here as well as in the azidopropanol-derived examples. Accordingly, analysis of the observed stereoselectivity of the reaction suggested intermediacy of a structure in which the $N_2^+$ group and the adjacent phenyl substituent were cis to one another and the bond antiperiplanar to the $N_2^+$ group migrates. We proposed that the minimization of steric interactions between the *migrating methylene group*

**SCHEME 4**




(starred in Scheme 4a) and the phenyl substituent could be responsible for this surprising result.

We considered the possibility that cation$-\pi$ interactions might also be relevant in these reactions. For example, it is possible that the intermediate containing vicinal cis $N_2^+$ and phenyl groups is stabilized over the alternative trans isomer and thereby leads to the observed product. Here, pathway divergence only requires nitrogen inversion as opposed to the change of ring conformations needed in the six-membered-ring containing cases discussed above. Thus, nitrogen inversion is sufficient to change which migratable bond is anti to the leaving group and thus which isomer is formed. In this model, the lack of stereoselectivity for the series in which the phenyl group is adjacent to oxygen could be due to the lack of preference for either $N_2^+$ epimer (Scheme 4b).

Ab initio calculations were first carried out for ground-state model systems **E** and **F** in which the two migrating carbons of the six-membered ring are replaced by methyl groups (Figure 6, Table 4). Since the five-membered ring can exist as a half-chair or envelope, extensive searches were performed to ensure that the lowest energy conformers were located for both cis and trans isomers. For the 1-phenyl compound, **E**, a significant gas-phase preference of 1.3 kcal/mol for the cis conformer was calculated, while only a small preference of 0.4 kcal/mol was observed for the 2-phenyl compound, **F**. In the cis epimer of **Ea**, the $N_2^+$ group and the phenyl ring are aligned for a potential cation$-\pi$ interaction, whereas a similar alignment is impossible in **Eb**. In **F**, a weaker cation$-\pi$ interaction due to the increased distance between the $N_2^+$ group and the phenyl ring is possible

**TABLE 4. Comparison of the gas-phase and solvated free energy differences between the R/$N_2^+$ cis (a) and R/$N_2^+$ trans (b) models to the experimental diastereoselectivities (kcal/mol)[a]**

| entry | model system | lactam | **a**:**b** | $\Delta G_{expt}$ | $\Delta G_{gas}$ | $\Delta G_{solv}$ |
|---|---|---|---|---|---|---|
| 1 | **E** | **22** | 85:15 | 0.7 | 1.3 | 0.6 |
| 2 | **F** | **24** | 56:44 | 0.1 | 0.4 | 0.2 |

[a] Calculations for the solvent (CPCM, $\epsilon = 8.93$) free energy differences were performed at the MP2/6–311+G**//MP2/6–31G* level of theory.

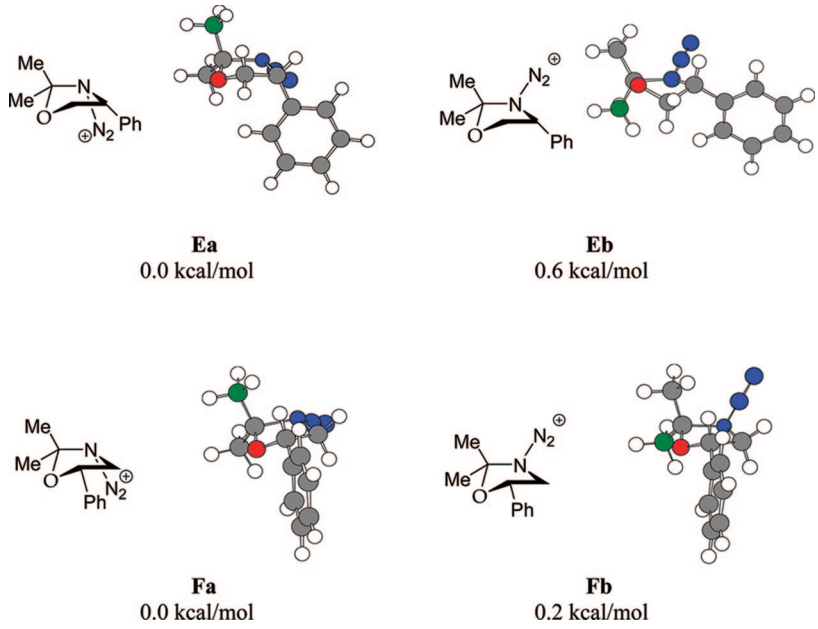
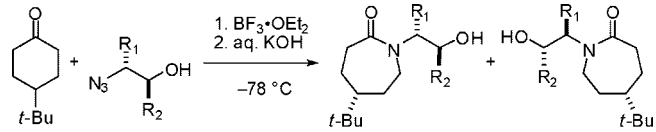



**FIGURE 6.** MP2/6–31G* optimized geometries and MP2/6–311+G**//MP2/6–31G* solvated energy differences of the cis (**a**) and trans (**b**) configured model systems **E** and **F**. The green atom indicates the carbon that is aligned for migration.

**TABLE 5. Reactions of 2-Substituted-2-azido-1-ethanols with 4-*tert*-Butylcyclohexanone**



**b**

| | | | | | | diastereomeric ratio[a] | |
|---|---|---|---|---|---|---|---|
| entry | hydroxyalkyl azide | $R_1$ | $R_2$ | lactam | yield (%) | **a** | **b** |
| 1 | **25** | 3,4,5-$(OMe)_3C_6H_2$− | H | **26** | 96 | 86 | 14 |
| 2[b] | **21** | $C_6H_5$− | H | **22** | 89 | 85 | 15 |
| 3 | **27** | 4-$(NO_2)$-$C_6H_4$− | H | **28** | 97 | 66 | 34 |
| 4 | **29** | $C_6H_{11}$ | H | **30** | 85 | 75 | 25 |
| 5 | **31** | H | $C_6H_{11}$ | **32** | 91 | 56 | 44 |

[a] See Supporting Information for methods used to determine structures and ratios. [b] This literature example[7c] was repeated for the present work to allow direct comparison with other cases.

in the cis conformer. However, this conformer is not the lowest energy structure due to destabilizing steric interactions between the methyl groups and the $N_2^+$ group. With the addition of solvent, a small preference is still observed for **Ea** over **Eb** (0.6 kcal/mol), but essentially no preference is seen for **Fa** over **Fb** (0.2 kcal/mol). The solvent numbers are in agreement with the experimental data.

The effect of substitution on the stereoselectivity of reactions of 2-aryl-2-azidoethanol derivatives with 4-*tert*-butylcyclohexanone was examined experimentally (Table 5). In this case, additional electron donation gave a ratio identical to that of the unsubstituted example (cf. entries 1 and 2, both about 5.6:1). In contrast, the electron-poor example shown in entry 3 resulted in a lower degree of selectivity favoring **28a** (ca. 1.9:1). However, the same direction of selectivity was obtained when the aryl group was replaced by a cyclohexyl substituent (entry 4, 3:1 selectivity), meaning that the source of the stereoselectivity in this system must have a strong steric component. In one final example, we also examined the stereoselectivity with 1-cyclohexyl-substituted hydroxyalkyl azide **31**, which verified that the nonselectivity of reactions of 1-substituted azidoethanols extended to alkyl as well as phenyl substitution (cf. Scheme 4b).


**FIGURE 7.** MP2/6–31G* optimized geometries and MP2/6–311+G**//MP2/6–31G* solvated energy differences of the cis (**a**) and trans (**b**) conformers of model systems **E** and **F**.

Calculations were performed on the syn/anti preferences on models for the 2-cyclohexyl substituted intermediate **G**. Not surprisingly, the anti conformer, **Gb**, is preferred by 1.9 kcal/mol in the gas phase and by 2.3 kcal/mol in dichloromethane at the MP2/6–311+G**//MP2/6–31G* level of theory (Figure 7). Because different ground-state configurations are favored for models **E** (phenyl) and **G** (cyclohexyl), the actual migration transition states for both the 2-phenyl and 2-cyclohexyl reactions were also examined theoretically. The barriers for methyl

**TABLE 6. Comparison of the Gas-Phase and Solvated Free Energy Barriers (kcal/mol) for Methyl Migration from the Minimum Intermediate Structure at the MP2/6-311+G**//MP2/6-31G* Level of Theory (CPCM, $\epsilon = 8.93$)**

| entry | model system | environment | $\Delta G^{\ddagger}$ (**a**−**a**$^{\ddagger}$) | $\Delta G^{\ddagger}$ (**b**−**b**$^{\ddagger}$) | $\Delta\Delta G^{\ddagger}$ (**b**−**a**) |
|---|---|---|---|---|---|
| 1 | **E** | gas | 20.4 | 23.7 | 3.3 |
| 2 | | solvent | 20.7 | 22.8 | 2.1 |
| 3 | **G** | gas | 18.5 | 20.7 | 2.2 |
| 4 | | solvent | 19.2 | 21.2 | 2.0 |

migration are given in Table 6. For both systems **E** and **G**, syn migration is preferred over anti migration by 2.1 and 2.0 kcal/mol, respectively. These energy differences, though, are much larger than expected based on the experimental results (where $\Delta G$ is ca. 0.7 kcal/mol). However, the computations do predict that the 2-phenyl and 2-cyclohexyl substituted systems should have similar selectivities, as was observed experimentally.

These results are consistent with our original explanation for stereoselectivity in this system.[7c] Thus, the migrating methyl group and cyclohexyl group are syn to each other when reaction takes place from the $N_2^+$/cyclohexyl anti conformer (**Gb**) and this creates a large steric clash. Accordingly, the barrier to migration from the less populated ground state **Ga** is lower and leads to the major product. Although the same effect is also operative in the phenyl-substituted cases, here the reactive conformer and the more stable conformer are the same (**Ea**) due to the ability of the phenyl group to rotate and reflecting stabilization of the ground state by nonbonded attractive cation−$\pi$ interactions. Comparison of the gas phase and solvent results for the phenyl vs cyclohexyl cases shows that the difference in barrier heights is reduced by the inclusion of solvent more significantly for **E**. This is because the syn transition structure is stabilized by a cation−$\pi$ interaction, which is reduced in solvent. Solvent plays a lesser role for system **G**, in which the difference in barrier heights is strictly the result of steric effects. The selectivity differences observed for substituted phenyl cases are consistent with a cation−$\pi$ contribution to the selectivity in this reaction as well, but the relative contributions of this effect vs strict steric control cannot be determined.

These results are also consistent with the lack of selectivity in reactions using 2-azido-1-phenylethanol (Scheme 4b). In this case, little opportunity exists for steric clashes between the migrating group and the phenyl substituent in the transition state because the two groups are not adjacent on the five-membered heterocyclic ring (see model structures **F** in Figure 6). This fact, combined with the nearly equal stability of the two epimeric intermediates (Table 4), leads to a nonselective outcome for this case.

## Summary

Although most stereoselective reactions that depend on the conformation of a tether connecting two reactive groups may be understood on the basis of size, these results demonstrate that maximization of attractive nonbonded interactions can also play a role. At present, it is evident that steric effects are dominant in most of the ring-expansion reactions we have studied. For example, previous work unveiled no unusual trends in the reactions of 1,3-azidopropanol derivatives when a substituent was placed on either the 1- or the 3-position.[7c] However, attractive nonbonded interactions appear to be quite significant in reactions of 2-substituted hydroxypropyl azides. For the 2-substituted azidopropanol derivatives, cation−$\pi$ effects are consistent with the following observations: (1) the poor selectivity of the 2-phenyl version compared to an alkyl control (**2** v. **3**; Scheme 2), (2) the dependence of selectivity on the electronic density of a substituted aryl group (Table 1), (3) ab initio calculations that are able to reproduce the observed selectivities, and (4) the requirement that the phenyl group be able to present its flat face to the leaving $N_2^+$ group as ascertained through geminal substitution (Scheme 3). With respect to this last point, it must be remembered that there is a steric component to the preference for an ax-Ph/eq-Me conformation.

An interesting point concerns the presence of an axial $N_2^+$ group in all of the proposed six-membered transition states. Although this is the low energy N-configuration in this series due to an electrostatic effect between the $N_2^+$ group and the C−O lone pair in the 1,3-oxazinane ring,[10] this point is not relevant to stereochemical analysis because only chairlike rings containing an axial leaving group are capable of attaining the necessary trans-antiperiplanar arrangement between the leaving group and the migrating carbon. Thus, 1,3-oxazinanes containing an equatorial $N_2^+$ group cannot contribute to product formation at all.

The results obtained from substituted 2-azidoethanol reagents show that steric considerations dominate these reactions. Accordingly, our hypothesis[7c] that minimization of nonbonded interactions between a migrating methylene and an alkyl or aryl group adjacent to nitrogen is still valid. Even here, however, calculations show that the phenyl group is close enough for a conceivable cation−$\pi$ effect that may explain differences in the selectivities noted in Table 5.

## Experimental Section

**General Procedure for the Synthesis of Lactams.** A solution of 4-*tert*-butylcyclohexanone in anhydrous $CH_2Cl_2$ (0.04 M) was cooled to −78 °C and $BF_3 \cdot OEt_2$ (5.0 equiv) was added. After 30 min, a solution of hydroxyalkyl azide (1.2 equiv) in anhydrous $CH_2Cl_2$ (0.04 M) was added to the cooled solution dropwise via a cannula. The reaction mixture was allowed to warm to room temperature slowly over 18–24 h at which time it was concentrated under reduced pressure and excess 15% KOH was added slowly to the residual oil. The reaction mixture was stirred vigorously at room temperature for 30 min and then partitioned between $CH_2Cl_2$ and $H_2O$. The organic layer was washed with water, brine, and dried ($Na_2SO_4$) and concentrated to an oil.

**5-*tert*-Butyl-1-(2′-(4″-fluorophenyl)-3-hydroxy-2-methylpropyl)-azepan-2-one.** Isolated as a mixture of diastereomers (yellow oil, 0.48 g, 93%). $R_f = 0.25$ (50/50 EtOAc/hex). **Compound** (±)-**19b**: Mp 117–119 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.28 (m, 2H), 6.99 (m, 2H), 4.94 (m, 1H), 3.85 (dd, $J = 4.7$, 11.6 Hz, 1H), 3.38 (t, $J = 10.5$ Hz, 1H), 2.91 (m, 2H), 2.51 (m, 2H), 2.41 (dd, $J = 6.6$, 15.5 Hz, 1H), 1.89 (m, 1H), 1.60 (m, 1H), 1.32 (s, 3H), 1.15–1.25 (m, 4H), 0.85 (s, 9H). $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 178.7, 161.8 (d, $J = 241.4$ Hz) 140.8, 128.2, 115.7, 115.5, 65.4, 57.2, 51.8, 51.6, 43.7, 36.4, 33.4, 28.9, 27.8, 24.5, 22.2. IR (neat) 3360, 1624 cm$^{-1}$. MS (CI) *m*/*z* 336 $[M+1]^+$; HRMS (FAB) calcd for $C_{20}H_{31}FNO_2$ $[M+1]^+$ 336.2339, found 336.2339.

**5-*tert*-Butyl-1-(2′-hydroxy-1′-(3″,4″,5″-trimethoxyphenyl)ethyl)-azepan-2-one. Compound** (±)-**26a:** White solid (0.61 g, 86%). Mp 148.2–152.1 °C. $R_f = 0.46$ (10% MeOH/EtOAc). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.50 (s, 2H), 5.70 (dd, $J = 8.0$, 5.8 Hz, 1H), 4.05 (m, 1H), 3.95 (m, 1H), 3.80 (s, 9H), 3.21 (m, 2H), 2.61 (m, 1H), 2.52 (m, 1H), 2.01 (m, 1H), 1.94 (m, 1H), 1.56 (m, 2H), 1.16 (m, 2H), 0.73 (s, 9H), 0.61 (m, 1H). $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 177.5, 153.1, 137.5, 133.1, 105.4, 61.6, 60.8, 58.6, 56.2, 51.2, 44.2,

36.7, 32.9, 29.1, 27.3, 24.1. IR (neat) 3400, 2980, 1600 $cm^{-1}$. MS (ES+) *m*/*z* 380.2 $[M+1]^+$; HRMS (ES+) calcd for $C_{21}H_{34}NO_5$ $[M+1]^+$ 380.2437, found 380.2427.

**Compound (±)-26b:** Brown oil (0.10 g, 14%). $R_f = 0.60$ 10% MeOH/EtOAc). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.53 (s, 2H), 5.68 (dd, $J = 8.4$, 5.4 Hz, 1H), 4.07 (m, 2H), 3.87 (m, 10 H), 3.66 (s, 1H), 3.25 (m, 2H), 2.67 (m, 1H), 2.56 (m, 1H), 1.99 (m, 1H), 1.60 (m, 1H), 1.21 (m, 3H), 0.77 (s, 9H). $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 177.7, 153.2, 137.6, 132.9, 105.5, 62.1, 60.8, 59.2, 56.2, 51.2, 44.5, 36.8, 33.0, 29.2, 27.4, 24.2. IR (neat) 3400, 2980, 1600 $cm^{-1}$. MS (ES+) *m*/*z* 380.2 $[M+1]^+$; HRMS (ES+) calcd for $C_{21}H_{34}NO_5$ $[M+1]^+$ 380.2437, found 380.2419.

**5-*tert*-Butyl-1-(−2′-hydroxy-1′-(4″-nitrophenyl)ethyl)azepan-2-one. Compound (±)-28a:** White solid (0.07 g, 62%). Mp 164.4–168.5 °C. $R_f = 0.10$ (80% EtOAc/hex). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, $J = 8.8$ Hz, 2H), 7.52 (d, $J = 8.5$ Hz, 2H), 5.70 (t, $J = 7.2$ Hz, 1H), 4.11 (m, 2H), 3.56 (br s, 1H), 3.34 (dd, $J = 15.3$, 10.6 Hz, 1H), 3.18 (m, 1H), 2.69 (dd, $J = 14.5$, 6.9 Hz, 1H), 2.56 (m, 1H), 2.01 (m, 1H), 1.68 (m, 1H), 1.24 (m, 2H), 0.79 (s, 9H), 0.68 (m, 1H). $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 177.6, 147.4, 145.3, 129.1, 123.7, 61.7, 59.5, 51.2, 45.6, 36.7, 33.0, 29.3, 27.4, 24.0. IR (neat) 3400, 2995, 1630, 1530, 1350 $cm^{-1}$. MS (ES+) *m*/*z* 335.2 $[M+1]^+$; HRMS (ES+) calcd for $C_{18}H_{27}N_2O_4$ $[M+1]^+$ 335.1971, found 335.1963.

**Compound (±)-28b:** White solid (0.04 g, 35%). Mp 160.4–167.5 °C. $R_f = 0.30$ (80% EtOAc/hexanes). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.21 (m, 2H), 7.52 (d, $J = 8.0$ Hz, 2H), 5.87 (dd, $J = 7.6$, 5.9 Hz, 1H), 4.23 (dd, $J = 11.5$, 5.6 Hz, 1H), 4.08 (m, 1H), 3.15 (s, 3H), 2.70 (dd, $J = 14.1$, 8.0 Hz, 1H), 2.56 (m, 1H), 2.02 (m, 1H), 1.92 (m, 1H), 1.30 (m, 3H), 0.86 (s, 9H). $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 177.4, 147.3, 145.5, 128.7, 123.7, 61.9, 58.5, 51.5, 45.5, 36.5, 33.0, 29.7, 27.5, 24.0 IR (neat) 3390, 2990, 1630, 1530 $cm^{-1}$. MS (ES+) *m*/*z* 335.2 $[M+1]^+$; HRMS (ES+) calcd for $C_{18}H_{27}N_2O_4$ $[M+1]^+$ 335.1971, found 335.1962.

**5-*tert*-Butyl-1-(1′-cyclohexyl-2′-hydroxyethyl)azepan-2-one. Compound (±)-30a:** Pink solid (0.35 g). Mp 105.6–106.4 °C. $R_f = 0.26$ (70% EtOAc/hexanes). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.80 (m, 4H), 3.34 (dd, $J = 15.2$, 9.2 Hz, 1H), 3.30 (dd, $J = 14.4$, 6.0, 1H), 2.54 (m, 2H), 1.96 (m, 2H), 1.70 (m, 6H), 1.22 (m, 6H), 0.97 (m, 2H), 0.85 (s, 9H). $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 177.6, 62.3, 51.2, 36.9, 36.4, 33.0, 30.9, 29.8, 29.5, 27.4, 26.3, 25.9, 25.8, 24.1. IR (neat) 3400, 2980, 1640 $cm^{-1}$. MS (ES+) *m*/*z* 296.25 $[M+1]^+$; HRMS (ES+) calcd for $C_{18}H_{34}NO_2$ $[M+1]^+$ 296.2590, found 296.2587.

**Compound (±)-30b:** White solid (0.08 g). Mp 126.4–129.8 °C. $R_f = 0.40$ (70% EtOAc/hexanes). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.14 (s, 1H), 3.83 (d, $J = 11.2$ Hz, 1H), 3.63 (m, 1H), 3.33 (m, 2H), 2.79 (br s, 1H), 2.55 (m, 2H), 1.96 (m, 2H), 1.62 (m, 6H), 1.24 (m, 6H), 1.13 (m, 7H), 0.86 (s, 10H). $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 177.6, 62.0, 51.7, 44.9, 36.7, 35.9, 33.0, 30.5, 30.1, 29.3, 27.5, 26.2, 25.9, 24.1. IR (neat) 3410, 2960, 1630 $cm^{-1}$. MS (ES+) *m*/*z* 296.2 $[M+1]^+$; HRMS (ES+) calcd for $C_{18}H_{34}NO_2$ $[M+1]^+$ 296.2590, found 296.2587.

**5-*tert*-Butyl-1-(2′-cyclohexyl-2′-hydroxyethyl)azepan-2-one. Compound (±)-32a:** White solid (0.47 g). Mp 133.0–135.8 °C. $R_f = 0.68$ (70% EtOAc/hexanes). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.70 (dd, $J = 14.0$, 9.2 Hz, 1H), 3.56 (m, 2H), 3.26 (m, 2H), 2.23 (dd, $J = 14.0$, 7.6 Hz, 1H), 2.60 (dd, $J = 14.0$, 7.6 Hz, 2H), 1.99 (m, 2H), 1.88 (d, $J = 12.8$ Hz, 1H), 1.75 (m, 2H), 1.37 (m, 3H), 1.21 (m, 5H), 1.08 (m, 3H), 0.87 (s, 9H). $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 178.0, 76.1, 54.3, 51.6, 51.4, 42.5, 36.3, 33.1, 29.8, 29.1, 27.9, 27.6, 26.5, 26.25, 26.11, 24.0, IR (neat) 3400, 2970, 1630 $cm^{-1}$. MS (ES+) *m*/*z* 318.2 $[M+Na]^+$; HRMS (ES+) calcd for $C_{18}H_{33}NO_2Na$ $[M+Na]^+$ 318.2409, found 318.2401.

**Compound (±)-32b:** White solid (0.461 g). Mp 110.4–111.9 °C. $R_f = 0.51$ (70% EtOAc/hexanes). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.80 (dd, $J = 14.4$, 9.6 Hz, 1H), 3.51 (m, 3H), 3.23 (dd, $J = 15.2$, 6.0 Hz, 1H), 3.06 (dd, $J = 14.0$, 2.0 Hz, 1H), 2.57 (dd, $J = 14.4$, 7.2 Hz, 1H), 2.52 (m, 1H), 1.97 (m, 2H), 1.75 (m, 5H), 1.37 (m, 1H), 1.19 (m, 5H), 1.07 (m, 3H), 0.88 (s, 9H). $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 178.4, 75.9, 54.0, 51.6, 50.3, 42.6, 36.3, 33.2, 29.8, 28.9, 28,8, 27.9, 27.6, 26.5, 26.3, 26.1, 24.2. IR (neat) 3410, 2980, 1635 $cm^{-1}$. MS (ES+) *m*/*z* 318.2 $[M+Na]^+$; HRMS (ES+) calcd for $C_{18}H_{33}NO_2$ $[M+Na]^+$ 318.2409, found 318.2402.

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**Supporting Information Available:** Calculation methodology and results, experimental details (including starting material preparations, characterization of new compounds, and stereochemical determinations), copies of $^1H$ and $^{13}C$ spectra of new compounds, and CIFs for compounds **19b**, **26a**, **28b**, **30b**, and **32a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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