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Asymmetric Ring Expansion

Highly Stereoselective Ring Expansion Reactions Mediated by Attractive Cation–n Interactions**

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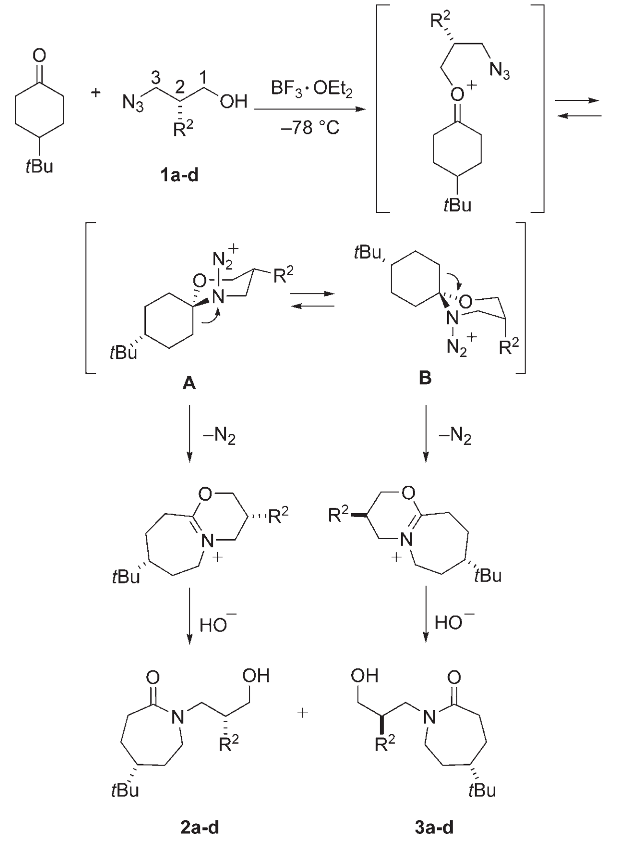
Most stereoselective reactions are ruled by steric effects. In particular, kinetically controlled asymmetric transformations utilizing chiral reagents, auxiliaries, or catalysts succeed because of energy differences in the transition states that most often arise by the minimization of repulsive, nonbonded interactions. Stereoelectronic considerations, which arise when the alignment of particular orbitals are necessary for a successful reaction, can also play a role.[1] An iconic stereoelectronic effect in organic chemistry is the anomeric effect.[2] Reactions controlled by the anomeric effect, such as glycosidations, largely depend on the relative orientation of the nonbonding or *n* electrons of a nearby alkoxy group. In recent years, alkoxy group control of stereoselective reactions by electrostatic interactions has received renewed scrutiny, led by the Woerpel group.[3] In this communication, we report an alternative and highly effective approach to stereocontrol through the maximization of attractive nonbonded interactions between an alkoxy or alkylthio group and a positively charged leaving group.



Scheme 1. Origin of selectivity in asymmetric Schmidt reactions.

The Lewis acid promoted reaction of a symmetrically substituted cyclic ketone with a chiral hydroxyalkyl azide provides a stereoselective route to lactams (Scheme 1).[4] In this reaction, initial formation of a spirocyclic intermediate sets up the selective migration of one of the methylene groups, originally adjacent to the ketone carbonyl group. Migration of a C–C bond antiperiplanar to the N_2^+ leaving group (only possible when the latter is in an axial position as shown) affords an iminium ether that is converted into lactam by workup with aqueous base. For 1- or 3-substituted azidopropanols (not shown), 10:1 selectivities are obtained, corresponding to preferential reaction through the most stable chairlike heterocyclic ring (**A** or **B**) resulting from equatorial addition of the azide group relative to the *tert*-butyl group. Intermediates **A** and **B** can interconvert through conformational reorganization or by reversion to the initially formed oxonium ion and then reclosure. In this scenario, selectivity has been generally attributed to the stabilization of one intermediate over the other owing to traditional minimization of 1,3-diaxial interactions (for example, favoring **A** when R^2 = alkyl).

2-Substituted 1,3-azidopropanols present a special case that is unusually susceptible to stereoelectronic control because of three factors: 1) the methylene groups near the spiro linkage are locally isoelectronic, so the reaction cannot be controlled by migratory aptitude, 2) the presence of either an ether oxygen atom or an N-N_2^+ group in a 1,3 relationship to the R^2 group means that 1,3-diaxial steric interactions will be minimized, and 3) the 1,3 relationship between the axial R^2

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Table 1: Selectivity of reactions of substituted 1,3-hydroxyalkyl azides (see Scheme 1 a).

Entry	Series	R^2	**2**:**3** ratio	Yield [%]
1	**1a**	Me[a]	74:26	98
2	**1b**	Ph[b]	60:40	98
3	**1c**	OMe	4:96	98
4	**1d**	SMe	1.8:98.2	90

[a] Reference [4]. [b] References [4] and [5].

group and the N_2^+ group provides a strong opportunity for attractive electrostatic interactions to occur between these groups in intermediate **B**. In previous work, it was demonstrated that unusually low selectivities obtained in this system, when R = aryl, could be ascribed to preferential stabilization of intermediate **B** by attractive, nonbonded cation–π interactions between the aromatic group and the N_2^+ leaving group (Table 1).[5] Although such interactions are commonly proposed in biological systems,[6] they are rarely invoked as stereocontrolling features of stereoselective reactions of small molecules.[7]

A computational study[8] and analogy to the well-known ability of ether groups to bind to cations suggested that intermediates like **B** should be even more enhanced in compounds where R^2 = alkoxy. As shown in Figure 1, isomer **B** contains a diaxial relationship between a methoxy group and a leaving group, and was calculated to be approximately 3.8 kcal mol^{-1} more stable than the equatorial isomer for which no interaction between the methoxy and N_2^+ groups are possible. To test this, 1-azido-2-methoxypropanol (**1c**, R^2 = OMe) was prepared and reacted with 4-*tert*-butylcyclohexanone by using $BF_3{\cdot}OEt_2$ as the Lewis acid promoter. A striking 24:1 selectivity in favor of the isomer emanating from an axially disposed methoxy group was obtained in high yield (Table 1, entry 3).

This result suggests that the methoxy cation–n interaction is considerably stronger than the previously reported cation–π effect, because of the fact that the highest **3**:**2** ratio observed to date was 57:43 for the electron-rich 3,4,5-trimethoxyphenyl group (not shown).[5] The fact that the small MeO group (A value = 0.6[9]) pays a relatively small steric penalty in the axial orientation is a likely contributor to the high selectivity of this reaction as well. However, the much higher selectivity and the opposite direction of the stereocontrol obtained for the smaller MeO group as compared to alkyl or aryl substituents (Table 1, entries 1 and 2) is strong evidence for the proposed role of electrostatics in this reaction.

We proposed that a similar effect might be observed with a more polarizable heteroatom.[3m] Accordingly, **1d**, where R = SMe, was prepared and submitted to the asymmetric Schmidt reaction protocol. Remarkably, a greater than 98:2 d.r. was obtained for this system, favoring **3d**. The selectivities obtained with both the methoxy and methylthio groups, which depend mainly on electrostatics and feature axially disposed substituents, are higher than any previously reported, sterically based, example of this ring-expansion reaction.[4,5]

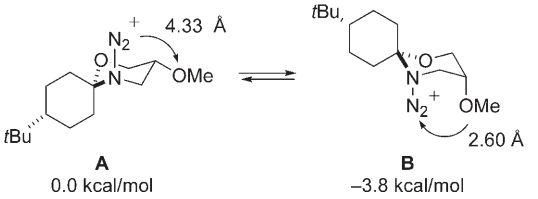
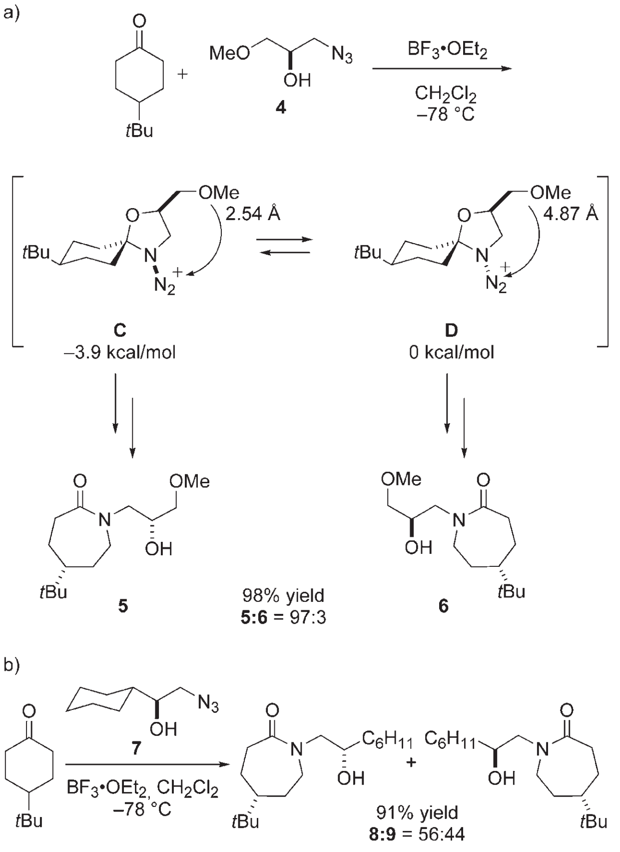


Figure 1. Calculations for proposed intermediates **A** and **B** performed at the MP2/6-311 + G**//MP2/6-31G* level of theory.[8]

Although the first example of an asymmetric azido-Schmidt reaction reported utilized an azidoethanol reagent, that series has typically provided lower selectivities relative to the three-carbon-containing reagents like **1**, and has more recently been shown to occur by predominant steric control, even when a phenyl group is in a position to participate in a cation–π interaction.[5] In sharp contrast to these previous results, the reaction using reagent **4** afforded a 97:3 ratio of **5** over **6**; the major product is derived from an intermediate in which a *syn* relationship between the methoxy group and the leaving N_2+ substituent is possible (Scheme 2 a). A computational investigation showed that cation–n intermediate **C** is stabilized by 3.9 kcal mol^{-1}. Notably, the O–N_2^+ distances, energy differences, and ratios are similar between systems **B** and **C**. Previous work on the reactions of substituted 1,2-azidoethanols has shown the predominant steric feature affecting stereochemistry to exist between the migrating carbon center and the substituents on the five-membered heterocyclic ring.[4,5b] In cases where the alkyl group is

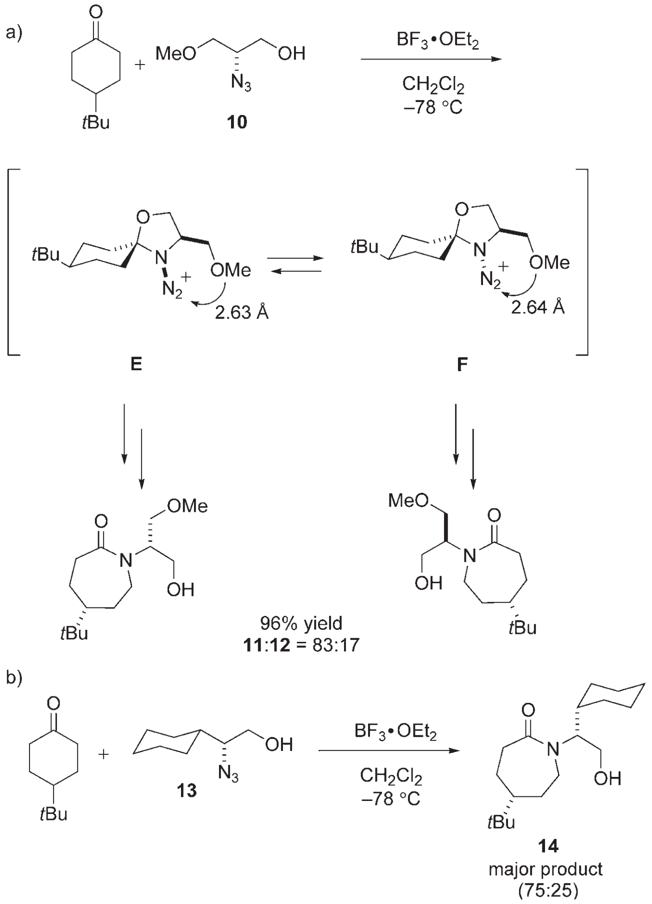


Scheme 2. a) Electrostatically controlled reaction of 1-azidoethanol derivative **4** with 4-*tert*-butylcyclohexanone (including calculated energies of proposed, minimized intermediates **C** and **D**[8]) and b) a cyclohexyl-containing control compound.[5b] The model systems used for the calculations are given in the Supporting Information (Figure S1).

adjacent to an oxygen atom (i.e. across the ring from the migrating methylene group and the N_2^+ leaving group), steric effects do not play an important role in determining the reaction stereochemistry, as clearly demonstrated by the nonselective cyclohexyl case shown in Scheme 2b.

The opposite situation occurs when the methoxymethyl group is placed adjacent to the azido group (Scheme 3). In this case, there is no substantial difference in distance between the methoxy group and the N_2^+ group in either isomeric intermediate, so electrostatic considerations cannot play a role, and the preference for syn **E** over anti **F** drops to 0.6 kcal mol^{-1} computationally. Instead, the usual steric course of the reaction leads to the same product observed for the analogous example to **14**.

The most interesting elements of this approach are that: 1) intermediates are subject to nonbonded, attractive interactions that are able to strongly favor one stereoisomeric form over the other, 2) these intermediates lead to the corresponding products in a process entirely controlled by stereoelectronic considerations, and 3) the overall stereoselectivity ultimately depends on the control of leaving group stereoslectivity at an epimerizable nitrogen atom. The high yields of these reactions combined with the utility of the lactam products suggests a high level of utility of the present ring expansion. Of perhaps greater long-term interest will be the attempted utilization of cation nonbonding electron stabilization in other stereoselective processes.[10]



Scheme 3. Sterically controlled reactions of a) **10** and b) a previously reported cyclohexane-containing substrate example.[5] The model systems used for the calculations are given in the Supporting Information (Figure S1).

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[1] P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Oxford, **1983**.

[2] For reviews, see: a) E. Juaristi, G. Cuevas, *Tetrahedron* **1992**, *48*, 5019–5087; b) P. P. Graczyk, M. Mikolajczyk, *Top. Stereochem.* **1994**, *21*, 159–349.

[3] For a review on electrostatic interactions between ethers and oxocarbenium ions, see: a) D. M. Smith, K. A. Woerpel, *Org. Biomol. Chem.* **2006**, *4*, 1195–1201. For selected examples from the recent literature, see: b) I. R. Dunkin, A. J. Paul, C. J. Suckling, E. Valente, H. C. Wood, *J. Chem. Soc. Perkin Trans. 1* **1985**, 1323–1326; c) D. R. Mootoo, B. Fraser-Reid, *J. Chem. Soc. Chem. Commun.* **1986**, 1570–1571; d) S. P. Elvey, D. R. Mootoo, *J. Am. Chem. Soc.* **1992**, *114*, 9685–9686; e) G. A. Molander, K. O. Cameron, *J. Org. Chem.* **1993**, *58*, 5931–5943; f) W. Shan, P. Wilson, W. Liang, D. R. Mootoo, *J. Org. Chem.* **1994**, *59*, 7986–7993; g) P. G. Andersson, *J. Org. Chem.* **1996**, *61*, 4154–4156; h) S. Suga, S. Suzuki, J.-i. Yoshida, *Org. Lett.* **2005**, *7*, 4717–4720; i) M. Fujita, H. J. Lee, T. Okuyama, *Org. Lett.* **2006**, *8*, 1399–1401; j) W. R. Judd, S. Ban, J. Aubé, *J. Am. Chem. Soc.* **2006**, *128*, 13736–13741; k) G. Baghdasarian, K. A. Woerpel, *J. Org. Chem.* **2006**, *71*, 6851–6858; l) S. R. Shenoy, D. M. Smith, K. A. Woerpel, *J. Am. Chem. Soc.* **2006**, *128*, 8671–8677; m) M. G. Beaver, S. B. Billings, K. A. Woerpel, *J. Am. Chem. Soc.* **2008**, *130*, 2082–2086.

[4] a) V. Gracias, K. E. Frank, G. L. Milligan, J. Aubé, *Tetrahedron* **1997**, *53*, 16241–16252; b) K. Sahasrabudhe, V. Gracias, K. Furness, B. T. Smith, C. E. Katz, D. S. Reddy, J. Aube, *J. Am. Chem. Soc.* **2003**, *125*, 7914–7922.

[5] a) C. E. Katz, J. Aubé, *J. Am. Chem. Soc.* **2003**, *125*, 13948–13949; b) C. E. Katz, T. Ribelin, D. Withrow, Y. Basseri, A. K. Manukyan, A. Bermudez, C. G. Nuera, V. W. Day, D. R. Powell, J. L. Poutsma, J. Aubé, *J. Org. Chem.* **2008**, in press.

[6] a) D. A. Dougherty, *Science* **1996**, *271*, 163–168; b) J. C. Ma, D. A. Dougherty, *Chem. Rev.* **1997**, *97*, 1303–1324.

[7] For a review, see: a) S. Yamada, *Org. Biomol. Chem.* **2007**, *5*, 2903–2912. For some leading references, see: b) P. Lakshminarasimhan, R. B. Sunoj, J. Chandrasekhar, V. Ramamurthy, *J. Am. Chem. Soc.* **2000**, *122*, 4815–4816; c) M. Stratakis, G. Froudakis, *Org. Lett.* **2000**, *2*, 1369–1372; d) S. Yamada, T. Misono, M. Ichikawa, C. Morita, *Tetrahedron* **2001**, *57*, 8939–8949; e) S. Yamada, C. Morita, *J. Am. Chem. Soc.* **2002**, *124*, 8184–8185; f) V. Ramamurthy, J. Shailaja, L. S. Kaanumalle, R. B. Sunoj, J. Chandrasekhar, *Chem. Commun.* **2003**, 1987–1999; g) B. Chiavarino, M. E. Crestoni, S. Fornarini, *Int. J. Mass Spectrom.* **2004**, *235*, 145–154.

[8] All calculations reported utilize MP2/6-311+G(d,p)//MP2/6-31G(d) free energies with CPCM dichloromethane solvent-optimized geometries.

[9] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, pp. 696–697, and references therein.

[10] All experimental details and stereochemical assignments are described in the Supporting Information. CCDC-647651 (**3c**), 647652 (*O*-benzyl derivative of **5**), 647654 (*O*-*p*-nitrobenzoyl derivative of **11**), and 683831 (**3d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.