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Highly Stereoselective Ring Expansion Reactions Mediated by Attractive, Non-Bonded Cation–*n* Interactions†

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Abstract

Electrostatic control of leaving group stereochemistry leads to superior diastereoselectivity in an asymmetric ring expansion reaction.

Keywords

ring expansion; non-bonded interactions; azides; Schmidt reaction; stereoselectivity

†Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author. CDCD Correspondence to: Jennifer L. Poutsma; Jeffrey Aubé.

Most stereoselective reactions are ruled by steric effects. In particular, kinetically controlled asymmetric transformations utilizing chiral reagent, auxiliaries, or catalysts succeed due to energy differences in transition states that most often arise by the minimization of repulsive, non-bonded 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 non-bonding or *n* electrons of a nearby alkoxy group. In recent years, alkoxy group control of stereoselective reactions via 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 non-bonded interactions between an alkoxy or alkylthio group and a positively charged leaving group.

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 alkyl groups originally adjacent to the ketone carbonyl. 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 azide relative to the *tert*-butyl group. Intermediates **A** and **B** can interconvert through conformational reorganization or by reversion to the initially formed oxonium ion followed by reclosure. In this scenario, selectivity is attained by stabilization of **A** over **B** due to traditional minimization of 1,3-diaxial interactions by placement of the R^1 or R^3 into equatorial positions in the former.

2-Substituted 1,3-azidopropanols present a special case that is unusually susceptible to stereoelectronic control due to 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 oxygen ether or an $N–N_2^+$ group in a 1,3 relationship to the R group means that 1,3-diaxial steric interactions will be minimized, and (3) the 1,3 relationship between axial R and N_2^+ groups 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, non-bonded 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 small-molecule stereoselective reactions.[7]

A computational study[8] and analogy to the well-known ability of ether groups to bind cations suggested that intermediates like **B** should be even more enhanced in compounds where R = alkoxy. As shown in Figure 1, isomer **B** containing a diaxial relationship between methoxy group and leaving group was calculated to be ca. 3.8 kcal/mol more stable than the equatorial isomer for which no interaction between methoxy and N_2^+ groups are possible. To test this, 1-azido-2-methoxypropanol **3** was prepared and reacted with 4-*tert*-butylcyclohexanone using BF_3•OEt_2 as 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, due to 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 opposite direction of 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 >98:2 dr was obtained for this system, favoring **3d**. *The selectivities obtained with both methoxy and methylthio, 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]

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 via 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 high 97:3 ratio of **5** over **6**, in which the major product goes through an intermediate in which a *syn* relationship between the methoxy group and the leaving N_2+ substituent is possible (Scheme 2). A computational investigation showed that the cation–*n* intermediate **C** is stabilized by 3.9 kcal/mol. Notably, the O–N_2^+ distances, energy differences, and ratios are similar between systems **B** and **C**. Previous work in the reactions of substituted 1,2-azidoethanols has shown the predominant steric feature affecting stereochemistry to exist between the migrating carbon and substituents on the five-membered heterocyclic ring.[4,5b] In cases where the alkyl group is adjacent to oxygen (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 reaction stereochemistry, as clearly demonstrated by the non-selective cyclohexyl case shown in Scheme 2b.

The opposite situation occurs when the methoxymethyl group is placed adjacent to the azido group. In this case, there is no substantial difference in distance between the methoxy group and 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 computationally. Instead, the usual steric course of the reaction leads to the same product observed for the analogous example to **14** (Scheme 3).

The most interesting elements of this approach are that: (1) intermediates are subject to non-bonded, 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 reaction. Of perhaps greater long-term interest will be the attempted utilization of cation nonbonding electron stabilization in other stereoselective processes.[10]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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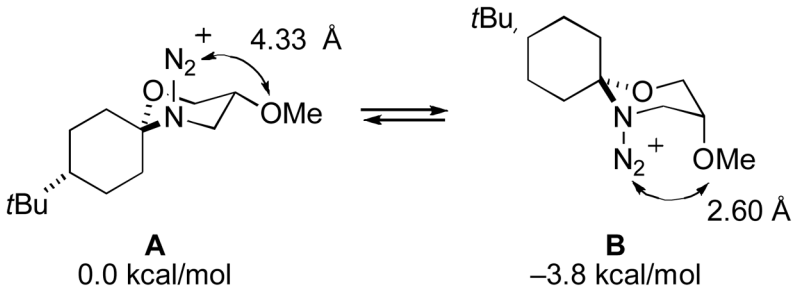
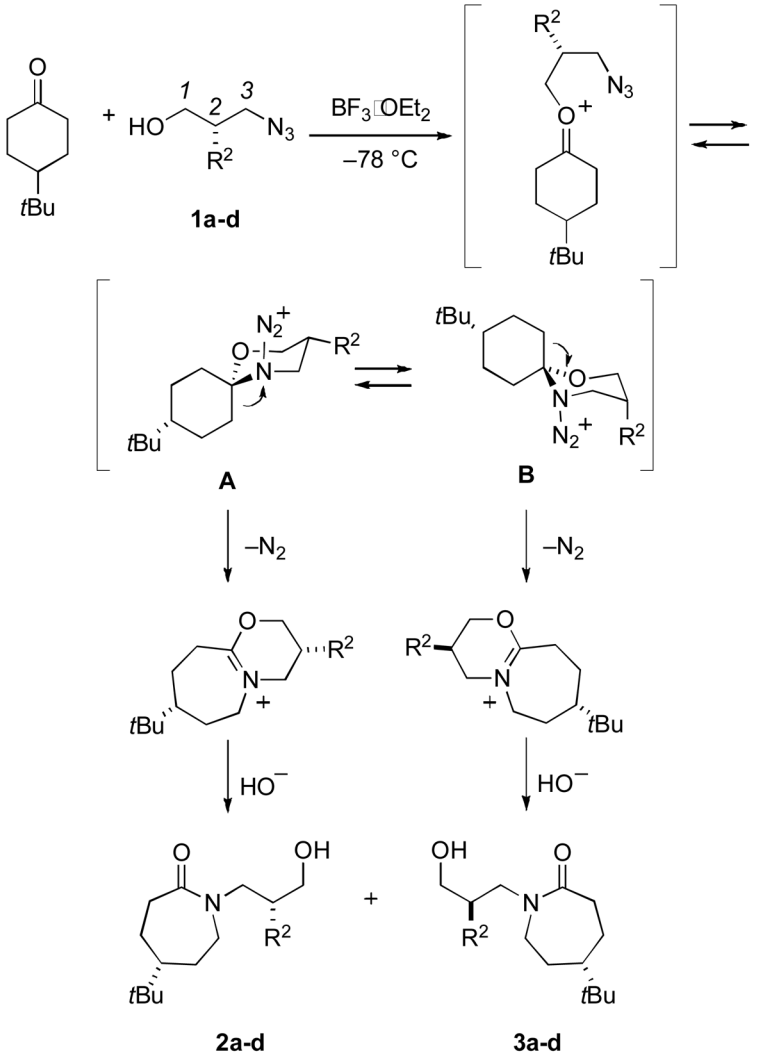
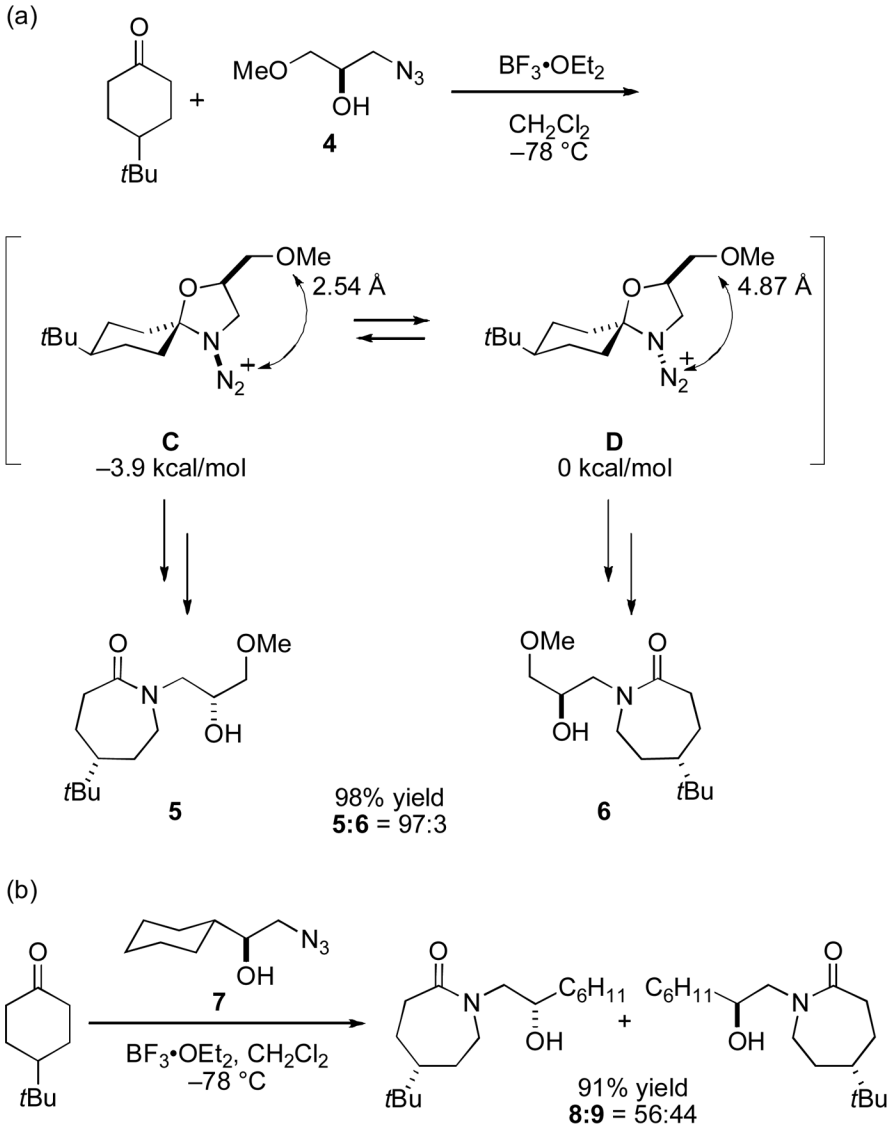


Figure 1.
Calculations for proposed intermediates **A** and **B** performed at the MP2/6-311+G**// MP2/6-31G* level of theory.[8]

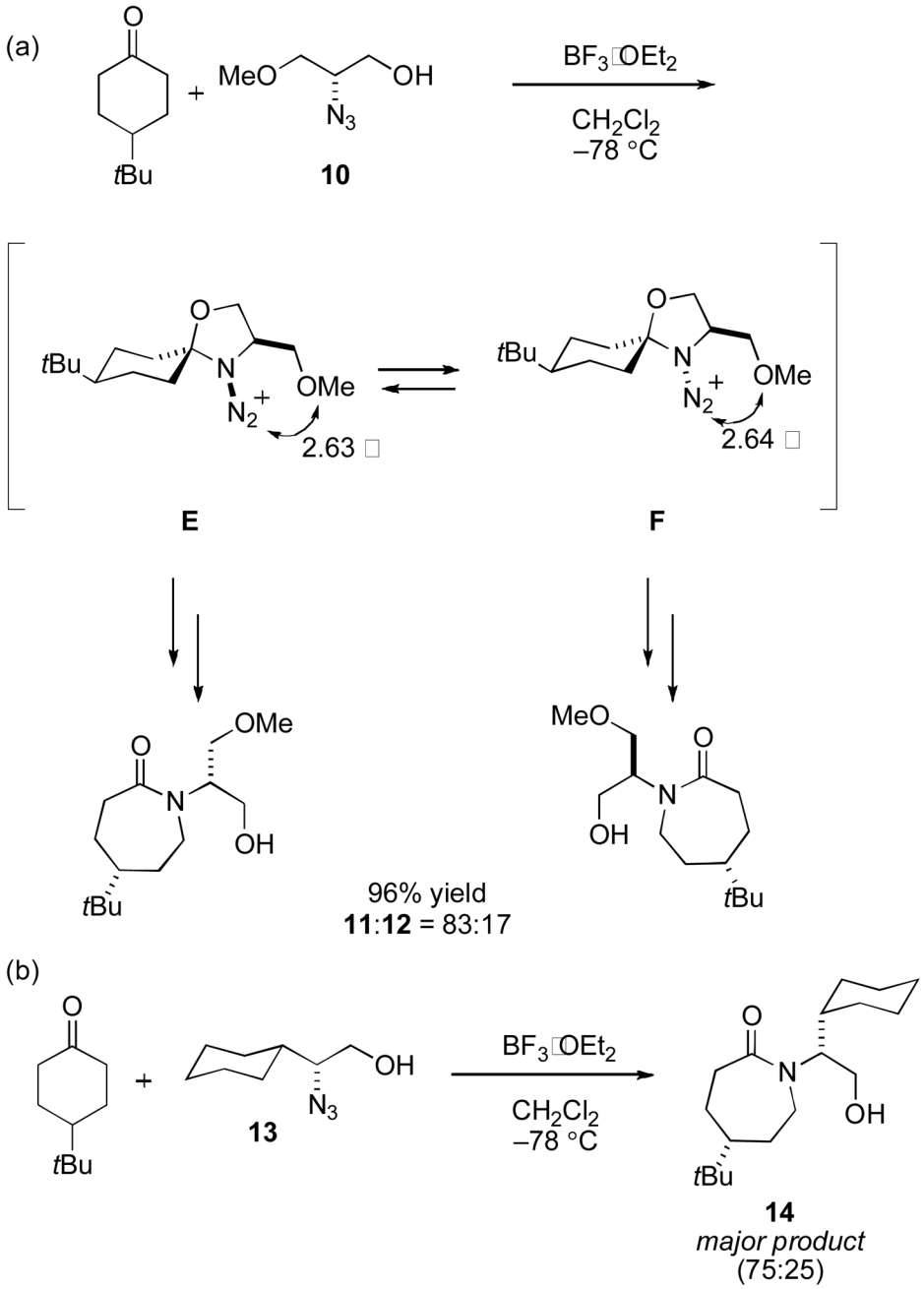


Scheme 1.
Origin of selectivity in asymmetric Schmidt reactions.



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.[5b] The model systems used for the calculations are given in the Supporting Information (Figure S1).



Scheme 3.

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

Table 1

Selectivity of reactions of substituted 1,3-hydroxyalkyl azides.

entry	series	R^2	2:3 ratio	yield (%)
1	**a**	Me[a]	74:26	98
2	**b**	Ph[b]	60:40	98
3	**c**	OMe	4:96	98
4	**d**	SMe	1.8:98.2	90

[a] Reference 4.

[b] References 4 and 5.