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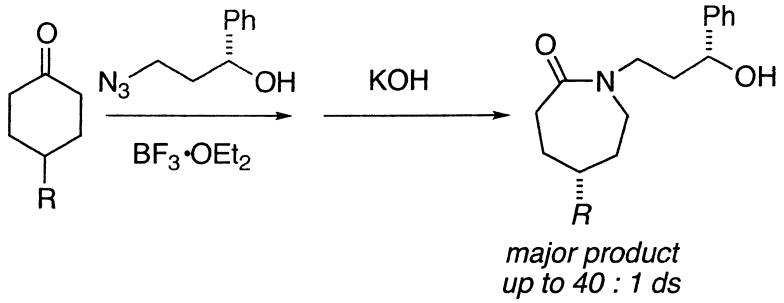

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Asymmetric Schmidt Reaction of Hydroxyalkyl Azides with Ketones

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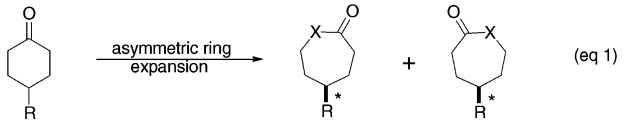
Abstract: An asymmetric equivalent of the Schmidt reaction permits stereocontrol in ring expansions of symmetrical cyclohexanones. The procedure involves the reaction of chiral 1,2- and 1,3-hydroxyalkyl azides with ketones under acid catalysis; the initial reaction affords an iminium ether that can be subsequently opened with base. A systematic study of this reaction is reported, in which ketone substrates, chiral hydroxyalkyl azides, and reaction conditions are varied. Selectivities as high as ca. 98:2 are possible for the synthesis of substituted caprolactams, with up to 1,7-stereoselection involved in the overall process. The fact that either possible migrating carbon is electronically identical provides an unusual opportunity to study a ring-expansion reaction controlled entirely by stereoelectronic factors. The mechanism of the reaction and the source of its stereoselectivity are also discussed.

Achiral ketones can be subjected to group-selective asymmetric transformations leading to a variety of usefully functionalized derivatives. Such reactions are of particular synthetic utility because they provide ready access to medium-ring compounds, many of which are only made with difficulty using other methods.[1] Much recent attention in this field has focused on asymmetric deprotonation[2] and ring-expansion processes. In the latter, the formal insertion of a group X between the carbonyl and one of the enantiotopic methylene groups in a ketone such as 4-methylcyclohexanone can afford an asymmetric synthesis of a seven-membered hetero- or carbocyclic product (eq 1).



(eq 1)

Asymmetric Baeyer−Villiger processes using enzymatic reactions,[3] metal-promoted catalysis,[4] or multistep equivalents thereof[5] have received the greatest share of attention in this regard. In contrast, very few carbon-based versions of this chemistry have been introduced to date.[6]

Likewise, only a few methods for the asymmetric conversion of ketones to lactams exist. Previously described methods that furnish enantiomerically enriched nitrogen-insertion products include the rearrangement of chiral oximes via the Beckmann rearrangement[7] and the photochemical rearrangement of chiral oxaziridines.[8] The paucity of methods available for the stereospecific synthesis of enantiopure oximes[9] limits the utility of the Beckmann rearrangement for this purpose. Unlike oximes, oxaziridines can be prepared easily in diastereo- and enantio-

(1) Reviews of medium rings and their synthesis: (a) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10 749−10 784. (b) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777−2849. (c) Tochtermann, W.; Kraft, P. *Synlett* **1996**, 1029−1035. (d) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603−609. (e) Yet, L. *Tetrahedron* **1999**, *55*, 9349−9403. (f) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073−2077. (g) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007. (h) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125−196.

(2) For representative examples, see: (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymm.* **1991**, *2*, 1−26. (b) Izawa, H.; Shirai, R.; Kawasaki, H.; Kim, H.-d.; Koga, K. *Tetrahedron Lett.* **1992**, *30*, 7221−7224. (c) Coggins, P.; Gaur, S.; Simpkins, N. S. *Tetrahedron Lett.* **1995**, *36*, 1545−1548. (d) Majewski, M.; Lazny, R. *J. Org. Chem.* **1995**, *60*, 5825−5830. (e) Toriyama, M.; Sugasawa, K.; Shindo, M.; Tokutake, N.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 567−570. (f) Lee, J. C.; Lee, K.; Cha, J. K. *J. Org. Chem.* **2000**, *65*, 4773−4775. (g) A number of papers on this topic have appeared in a Symposium-in-Print on lithium amide base chemistry. O'Brien, P., Guest Ed., *Tetrahedron*, **2002**, *58*, 4657−4727.

(3) (a) Taschner, M. J.; Black, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 6892−6893. (b) Taschner, M. J.; Chen, Q.-Z. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 535−538. (c) Taschner, M. J.; Black, D. J.; Chen, Q.-Z. *Tetrahedron: Asymm.* **1993**, *4*, 1387−1390. (d) Lopp, M.; Paju, A.; Kanger, T.; Pehk, T. *Tetrahedron Lett.* **1996**, *37*, 7583−7586. (e) Stewart, J. D.; Reed, K. W.; Zhu, J.; Chen, G.; Kayser, M. M. *J. Org. Chem.* **1996**, *61*, 7652−7653. (f) Bolm, C.; Luong, T. K. K.; Schlingloff, G. *Synlett* **1997**, 1151−1152. (g) Kayser, M. M.; Chen, G.; Stewart, J. D. *J. Org. Chem.* **1998**, *63*, 7103−7106. (h) Stewart, J. D.; Reed, K. W.; Martinez, C. A.; Zhu, J.; Chen, G.; Kayser, M. M. *J. Am. Chem. Soc.* **1998**, *120*, 3541−3548. (i) Stewart, J. D. *Curr. Org. Chem* **1998**, *2*, 195−216. (j) Mihovilovic, M. D.; Chen, G.; Wang, S.; Kyte, B.; Rochon, F.; Kayser, M. M.; Stewart, J. D. *J. Org. Chem.* **2001**, *66*, 733−738.

(4) (a) Bolm, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1848−1849. (b) Bolm, C.; Luong, T. K. K.; Schlingloff, G. *Synlett* **1997**, 1151−1152. (c) Paneghetti, C.; Gavagnin, R.; Pinna, F.; Strukul, G. *Organometallics* **1999**, *18*, 5057−5065.

(5) (a) Honda, T.; Kimura, N.; Tsubuki, M. *Tetrahedron: Asymm.* **1993**, *4*, 1475−1478. (b) Sugimura, T.; Fujiwara, Y.; Tai, A. *Tetrahedron Lett.* **1997**, *38*, 6019−6022.

(6) (a) Nemoto, H.; Tanabe, T.; Fukumoto, K. *Tetrahedron Lett.* **1994**, *35*, 6499−6502. (b) Nemoto, H.; Tanabe, T.; Fukimoto, K. *J. Org. Chem.* **1995**, *60*, 6785−6790.

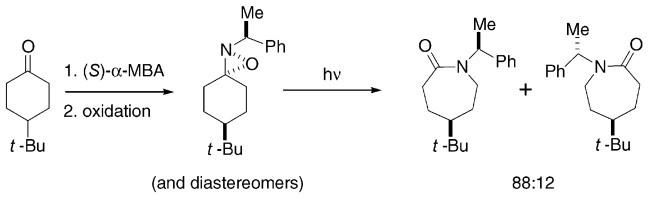
(7) (a) Lyle, R. E.; Lyle, G. G. *J. Org. Chem.* **1959**, *24*, 1679−1684. (b) Lyle, G. G.; Barrera, R. M. *J. Org. Chem.* **1964**, *29*, 3311−3314. (c) Toda, F.; Akai, H. *J. Org. Chem.* **1990**, *55*, 4973−4974.

(8) (a) Lattes, A.; Oliveros, E.; Rivière, M.; Belzecki, C.; Mostowicz, D.; Abramskj, W.; Piccinni-Leopardi, C.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *104*, 3929−3934. (b) Aubé, J.; Burgett, P. M.; Wang, Y. *Tetrahedron Lett.* **1988**, *29*, 151−154. (c) Aubé, J. *Tetrahedron Lett.* **1988**, *29*, 4509−4512. (d) Aubé, J.; Wang, Y.; Hammond, M.; Tanol, M.; Takusagawa, F.; Vander Velde, D. *J. Am. Chem. Soc.* **1990**, *112*, 4879−4891. (e) Aubé, J. *Chem. Soc. Rev.* **1997**, *26*, 269−277.

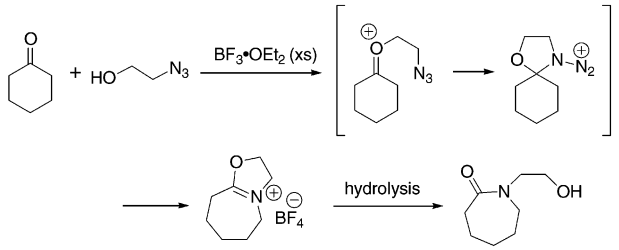
(9) Adamczyk, M.; Chen, Y.-Y.; Fishpaugh, J. R.; Gebler, J. C. Tetrahedron: Asymm. **1993**, *4*, 1467−1468.

10.1021/ja0348896 CCC: $25.00

Scheme 1



Scheme 2



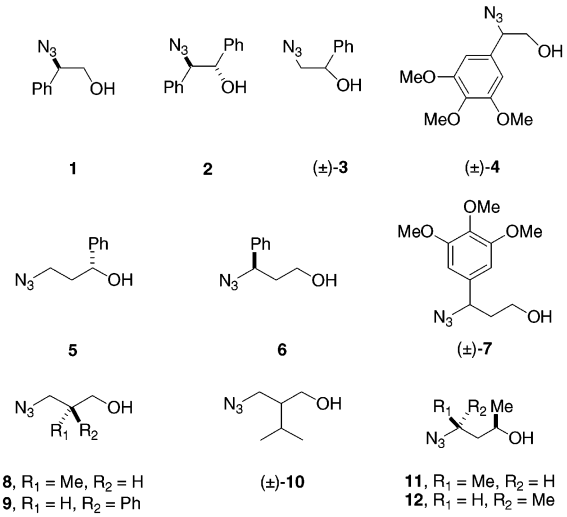
merically enriched form; once made, they undergo photochemically induced, regioselective ring expansion reactions. A typical reaction sequence is shown in Scheme 1. Using α-methylbenzylamine as a stereocontrolling group, the overall selectivity for the conversion of ketones to lactams reached a maximum of ca. 88% ds.[8d] Enantiomerically pure lactams were obtained by separation of the diastereomers and removal of the chiral group on the nitrogen. Besides the relatively low stereoselectivity, this methodology suffered from the need to carry out three discrete chemical steps and moderate overall yields.

Recent work in this laboratory has circumvented these issues by using alkyl azides in nitrogen ring-expansion reactions. In particular, 1,2- and 1,3-hydroxyalkyl azides have proven especially useful for the conversion of ketones to lactams via an "in situ-tethering" strategy.[10] Activation of the carbonyl group by a protic or Lewis acid promotes the initial formation of a hemiketal and dehydration to the oxenium ion shown (Scheme 2). Intramolecular attack by the azido group followed by rearrangement and the loss of N_2 yields an intermediate iminium ether that can be purified or subjected to hydrolysis in a one-pot process. This overall process is dubbed "in situ-tethering" because alkyl azides are poor nucleophiles in intermolecular reactions with ketones[11b,d] and because the tethering step can be carried out under the same conditions used for the rearrangement reaction. These reactions are very closely related to azido-Schmidt reactions with ketone equivalents[11] and carbocations.[12]

In preliminary work, we reported that chiral hydroxy alkyl azides can lead to highly selective nitrogen asymmetric ring expansion reactions as shown in eq 1 above.[10a,13] In this paper, we report studies on the scope and utility of this process focusing on the effects of structural variation in both the ketone and hydroxyalkyl azide reaction partners. The origin of the stereoselectivity of the reaction will also be discussed.

Results

Selection and Synthesis of Hydroxyalkyl Azides. Previous work[10] had shown that the in-situ tethering process worked best with 1,2- and 1,3-hydroxyalkyl azides, so a representative series of mono- and disubstituted reagents **1**−**12** were targeted for study. These specific derivatives represent a selection of variously substituted compounds bearing substituents of differing steric demands. In some cases, diastereomers or constitutional isomers were separately prepared to test specific mechanistic issues. Although most of these compounds were prepared in enantiomerically enriched form, some reagents were used as racemates and are so indicated.



An attractive aspect of the proposed ring-expansion protocol was the ready availability of chiral hydroxyalkyl azides from commercial starting materials using simple chemical transformations. In general, 1,2-azido alcohols were made by ring opening of epoxides or via analogous reactions using activated diols (Scheme 3). In some cases, a Mitsunobu procedure carried out on the diol directly afforded the azido alcohol without the need for protecting groups or additional activation. This procedure was more convenient for providing **1** in high ee relative to the known ring opening of styrene oxide, in part because the desired regioisomer is formed in high yield as the major product (cf., the synthesis of **3**). Bittman and co-workers have reported a related method for the stereoselective azidation of 1,2- and 1,3-diols using Mitsunobu chemistry.[14] The ready synthesis of highly enantiomerically enriched 1,2-diols by asymmetric dihydroxylation chemistry[15] ensures that a wide structural variety of chiral 1,2-azido alcohols is available.

(10) (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*, 16 241−16 252. (c) Forsee, J. E.; Smith, B. T.; Frank, K. E.; Aubé, J. *Synlett* **1998**, 1258−1260. (d) Smith, B. T.; Gracias, V.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 3771−3774.

(11) (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966. (b) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635−1637. (c) Mossman, C. J.; Aubé, J. *Tetrahedron* **1995**, *52*, 3403−3408. (d) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449−10459. (e) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226−7232. (f) Wrobleski, A.; Aubé, J. *J. Org. Chem.* **2001**, *66*, 886−889.

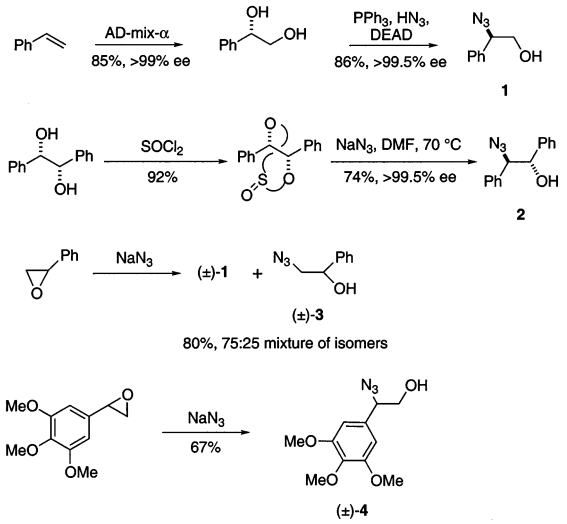
(12) (a) Pearson, W. H.; Schkeryantz, J. M. *Tetrahedron Lett.* **1992**, *33*, 5291−5294. (b) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.-k.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10 183−10 194. (c) Pearson, W. H.; Fang, W.-k.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682−2684. (d) Pearson, W. H.; Fang, W.-k. *J. Org. Chem.* **1995**, *60*, 4960−4961. (e) Pearson, W. H. *J. Het. Chem.* **1996**, *33*, 1489−1496. (f) Pearson, W. H.; Gallagher, B. M. *Tetrahedron* **1996**, *52*, 12 039−12 048. (g) Pearson, W. H.; Fang, W.-k. *Isr. J. Chem.* **1997**, *37*, 39−46. (h) Pearson, W. H.; Fang, W.-k. *J. Org. Chem.* **2000**, *65*, 7158−7174.

(13) Furness, K.; Aubé, J. *Org. Lett.* **1999**, *1*, 495−497.

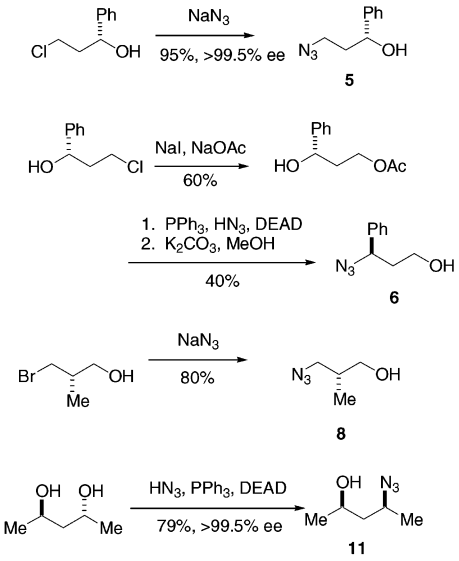
(14) He, L.; Wanunu, M.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **1999**, *64*, 6049−6055.

(15) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

Scheme 3



Scheme 4

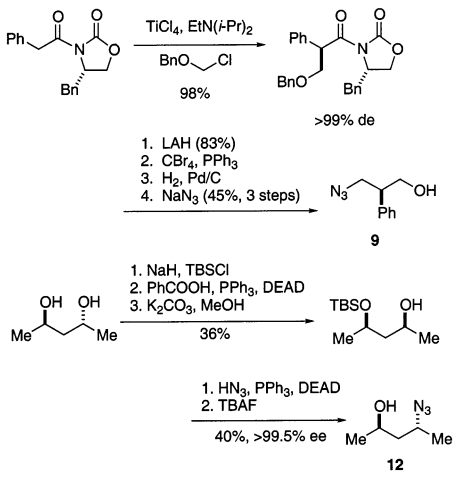


The 1,3-azido alcohols were synthesized by a variety of techniques (Scheme 4). In some cases, simple azide displacement of an alkyl halide provided the desired reagent in a single step. For example, treatment of commercially available (*R*)-3-chloro-1-phenyl-1-propanol and (*S*)-3-bromo-2-methyl-1-propanol with NaN_3 directly led to enantiomerically pure **5** and **8**, respectively. (*S*)-3-Chloro-1-phenyl-1-propanol could also be converted to the phenyl-containing (*R*)-**6** by displacement of the chloride with acetate, hydrolysis, and Mitsunobu azidation (inversion) of the benzylic center. Conversion of the C_2-symmetrical chiral diol (*R*,*R*)-2,4-dihydroxypentane to the corresponding azide was accomplished by Mitsunobu inversion of one of the homotopic hydroxyl groups, affording **11**. Mitsunobu reactions were also used to prepare compounds **7** and **10** in racemic form (routes not shown; see the Supporting Information).

Compounds **9** and **12** were synthesized using the multistep pathways shown in Scheme 5. These reagents were needed for certain stereochemical assignments and for mechanistic studies.

Reactions of 1,2-Hydroxyalkyl Azides. Optimal solvent and temperature conditions were determined using the hydroxyalkyl azide **1** and 4-methylcyclohexanone (Scheme 6). Our initial studies with achiral hydroxyalkyl azide addition reactions established $BF_3{\cdot}Et_2O$ as a superior Lewis acid for the nitrogen-insertion reactions.[10] Thus, 1.5 equiv of **1** and 3.0 equiv of $BF_3{\cdot}Et_2O$ were added to ketone under the conditions shown in Table 1. Presumably, an excess of Lewis acid is needed to accommodate the disproportionation of the reagent into tetrafluoroborate; see below. After the reactions were carried out for the time noted, the intermediate iminium ether **13** was hydrolyzed by the addition of aqueous $NaHCO_3$ or KOH, affording **14a,b** as

Scheme 5



Scheme 6

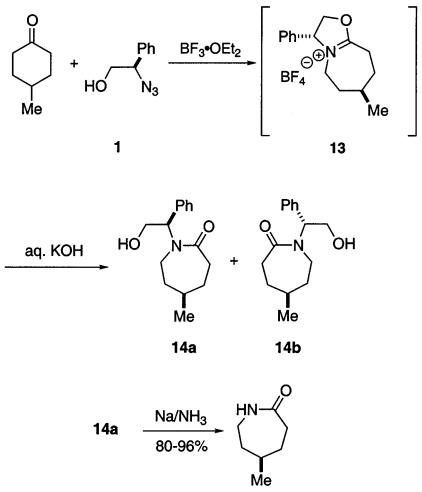


Table 1. Reactions of **1** with 4-Methylcyclohexanone

entry	solvent	*T* (°C)	time (h)	yield (%)[a]	ratio of **14a: 14b**[b]
1	THF	−78→ rt	36	0	−
2	Et_2O	0	21	3[c]	73:27
3	cyclohexane	3	18	74	73:27
4	CH_3CN	−30	18	41	69:31
5	CH_2Cl_2	−30	18	15[c]	83:17
6	CH_2Cl_2	−30	100	62	70:30
7	CH_2Cl_2	0	21	86	69:31
8	CCl_4	−20	18	97	78:22
9	*n*-pentane	−20	23	100	78:22

[a] Isolated yields except where noted. [b] Ratios determined by HPLC of crude reaction mixtures; see text and Supporting Information for stereostructure determinations. [c] Yield for this example estimated from HPLC trace.

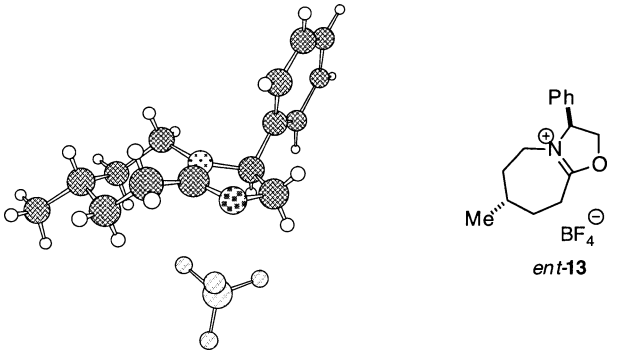
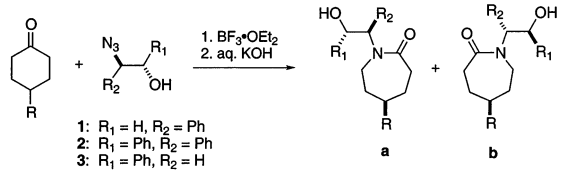


Figure 1. Ball-and-stick depiction of the X-ray crystallographic analysis of iminium ether **13**, showing the correct relative stereochemistry of the intermediate. Note that the enantiomeric series of the crystal structure was arbitrarily assigned and so this drawing depicts the enantiomer of **13** as synthesized from (*R*)-**1**.

Table 2. Reactions of 1,2-Hydroxyethyl Azides with 4-Substituted Ketones



entry	azide	ketone R	major product	yield (%)[a]	ratio **a**:**b**[b]
1	**1**	Me	**14a**	97	78:22
2	**1**	*t*-Bu	**15a**	83	85:15
3	**2**	Me	**16a**	51	87:13
4	**2**	*t*-Bu	**17a**	64	88:12
5	**3**[c]	*t*-Bu	**18a** or **18b**[d]	73	56:44

[a] Isolated yield. [b] Ratio determined by HPLC trace of the crude reaction mixture; see text and Supporting Information for stereostructure determinations. [c] This experiment was done using a racemic hydroxyalkyl azide. [d] Not assigned for this example.

a readily separated mixture of diastereomers (column chromatography). The products were assigned by removing the nitrogen substituent to afford the known 5-substituted caprolactam,[8b,d] and measuring its specific rotation. For the series of *N*-phenyl-(hydroxyethyl) derivatives examined, this step generally occurred in ≥80% yield and resulted in the convenient removal of the chiral induction moiety from the product.

Although crude solutions of the iminium ether were generally hydrolyzed by direct addition of base, in some cases the intermediate iminium ethers were isolated. Concentration of the reaction mixture of **1** and 4-methylcylohexanone followed by chromatography with CH_2Cl_2/MeOH afforded a solid that could be recrystallized from 3:1 hexane/EtOAc to afford X-ray quality crystals of **13** as the tetrafluoroborate salt (Figure 1). The intermediacy of iminium ethers in this chemistry had previously been proposed based on spectroscopic evidence, elemental analysis, and on their reactions with other nucleophiles.[10,16] This structure, which was the first we were able to obtain in this series, clearly indicates relative stereochemistry and the presence of the BF_4^- counterion. The latter was presumably formed by disproportionation of the Lewis acid, which is used in excess; however, neither the details of this disproportionation nor the presence of other boron species were explicitly examined.

A survey of reaction conditions showed that Et_2O and THF were inappropriate media for this reaction (Table 1). Methylene chloride and hydrocarbon solvents were considerably better, with less polar solvents such as *n*-pentane and CCl_4 affording the highest yields in the shortest time. The optimum temperature range for the reactions was determined to be between −30 °C and −20 °C, although it was necessary to allow the reaction to warm to room temperature and to carry out the iminium ether hydrolyses at room temperature to obtain the stated yields. Most importantly, the selectivities obtained using a hydroxyethyl azide were comparable to the best obtained using the multistep oxaziridine route (ratios ranging from 74:26 to 84:16 were obtained for 4-methylcyclohexanone using the latter[8d]), suggesting that the Schmidt-based technique would be competitive with earlier technology.

The reactions of 4-methylcyclohexanone and 4-*tert*-butylcyclohexanone with the hydroxyalkyl azides **1**, **2** and **3,** carried out under these optimized conditions (−20 °C, *n*-pentane or CCl_4 or 1:3 *n*-pentane/CCl_4), furnished lactams in the yields and selectivities shown in Table 2. The reactions of 4-methylcyclohexanone and 4-*tert*-butylcyclohexanone with azides **1** and **2** proceeded with high levels of stereoselectivity, whereas the reaction of azide **3** with 4-*tert*-butylcyclohexanone proceeded with poor selectivity.

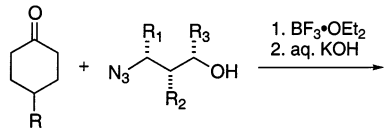
Reactions of 1,3-Hydroxyalkyl Azides. The reactions of 1,3-hydroxyalkyl azides with substituted cyclohexanones proved more facile than their 1,2-disubstituted cousins, taking place at lower temperatures. A brief optimization exercise allowed us to identify standard conditions of −82 °C to 25 °C, $BF_3{\cdot}Et_2O$, CH_2Cl_2, which were applied to various combinations of 4-methyl- or 4-*tert*-butylcyclohexanone and hydroxyalkyl azides **5**-**10** (Table 3). As before, reactions were allowed to warm to room temperature to ensure completion.

The stereoisomeric products were generally separable and the structures of major isomers determined by conversion to the known[8a,b,d] *N*-dealkylated lactams. For lactams **22** and **23**, this was accomplished by dissolving metal reduction (cf., Scheme 6). The removal of nonbenzylic lactam side chains was carried out by oxidation to the aldehyde or ketone followed by elimination of the lactam through treatment with base (Scheme 7). In the case of lactam **21a**, shown, it was additionally necessary to establish that hydrolysis did not occur by attack at the benzylic position (which has been observed with other nucleophiles[16] and would here lead to the enantiomeric form of **21b**; Scheme 7). This was established through X-ray crystallographic analysis of **21a**, which nailed down the relative stereochemistry of this lactam and, with the absolute chemistry as ascertained through degradation of **21**, fully established the stereochemical course of this reaction. Such precautions were not necessary for lactams **26** and **28** because the tether was terminated with a primary alcohol group. Since the stereoselectivity of each case derived from 4-methylcyclohexanone closely mirrored those obtained in the *tert*-butyl series, the directionality of the former reactions were assigned by analogy, as were lactams **24**, **29**, and **30**.

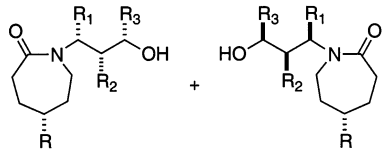
The reactions of chiral 1,3-hydroxyalkyl azides were generally more selective than those of their 1,2-disposed counterparts. For example, a 93:7 ratio of isomers was obtained from the reaction of hydroxyalkyl azide **5** with 4-methylcyclohexanone (Table 3, entry 1). Although results differed according to the structure

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

Table 3. Reactions of Monosubstituted 1,3-Hydroxyalkyl Azides with 4-Substituted Cyclohexanones



5-10



a **b**

		azide						
entry	ketone R	azide	R_1	R_2	R_3	products	ratio**a**:**b**[a]	yield (%)[b]
1	Me	**5**	H	H	Ph	**19**	93:7	98
2	Ph	**5**	H	H	Ph	**20**	96:4	99
3	*t*-Bu	**5**	H	H	Ph	**21**	95:5	100
4	Me	**6**[c]	Ph	H	H	**22**[c]	89:11	96
5	*t*-Bu	**6**[c]	Ph	H	H	**23**[c]	90:10	94
6	*t*-Bu	**7**[d]	$-C_6H(OMe)_3$	H	H	**24**[d]	90:10[d,e]	90
7	Me	**8**	H	Me	H	**25**	78:22	93
8	*t*-Bu	**8**	H	Me	H	**26**	74:26	98
9	Me	**9**[c]	H	Ph	H	**27**[c]	60:40	93
10	*t*-Bu	**9**[c]	H	Ph	H	**28**[c]	60:40	98
11	Me	**10**[d]	H	*i*-Pr	H	**29**[d]	88:12[d]	88
12	*t*-Bu	**10**[d]	H	*i*-Pr	H	**30**[d]	88:12[d]	85

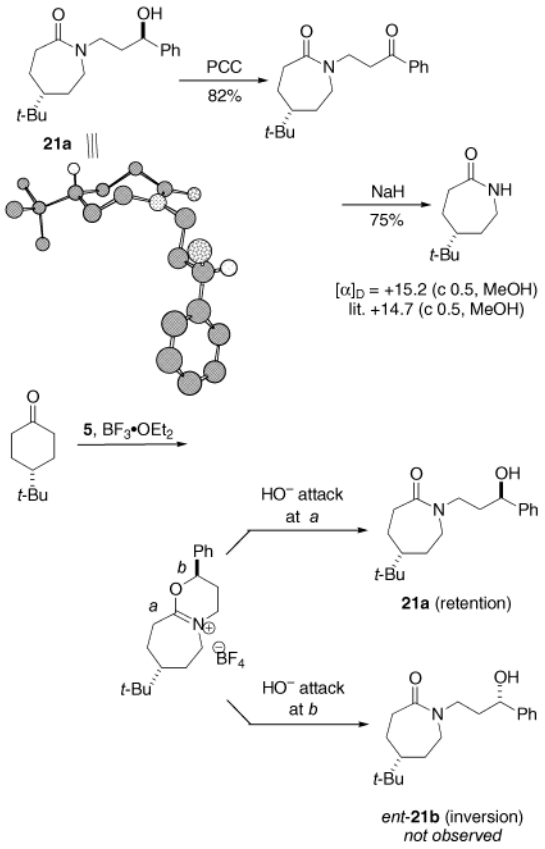
[a] Ratio determined by HPLC of crude reaction mixtures, except where noted. See text and Supporting Information for stereostructure determinations. [b] Total yields of isolated purified lactams. [c] This reaction was done in the enantiomeric series to that shown in this table. It is depicted in this manner to allow easy comparison between examples. See the text and Supporting Information for the correct enantiomers. [d] This experiment was done using a racemic hydroxyalkyl azide. [e] Ratio estimated by ^{1}H NMR examination of the crude reaction mixture.

of the hydroxy azide, very similar ratios were obtained in the reactions of a given hydroxyalkyl azide and either 4-methyl or 4-*tert*-butylcyclohexanone. The best ratios were obtained from reactions containing alkyl substitution at either the 1 or 3 position of the hydroxyalkyl side chain, with somewhat poorer results being obtained for 2-alkyl or (especially) 2-aryl examples. Overall yields for the entire sequence including iminium formation and hydrolysis were excellent throughout. It is noteworthy that outstanding levels of up to 1,7-stereoselection were observed in this series.

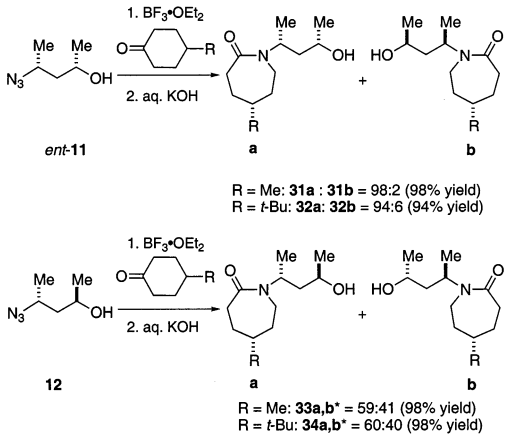
A particularly instructive pair of examples is shown in Scheme 8. The reactions of the disubstituted 3-carbon chain hydroxyalkyl azide **11** with 4-substituted ketones proceeded with high diastereoselectivity (≥49:1), whereas those using the epimeric azide **12** led to poor asymmetric induction for the same ketones (ca. 1.5:1). These results, among others, provide evidence for a chairlike transition structure for the heterocyclic ring generated in the azide addition step of the reaction (see below).

Additional opportunities for this reaction were briefly examined as shown in Scheme 9. As expected, the use of a meso-disubstituted cyclohexanone provided product in excellent yield and stereoselectivity, consistent with a hypothesis that selectivity partially depends on a reasonably conformationally fixed ketone (see below). Very good selectivity was also observed in the reaction of an unsymmetrical ketone, (*R*)-3-methylcyclohexanone, but in this case the reaction leads to constitutional isomers

Scheme 7



Scheme 8



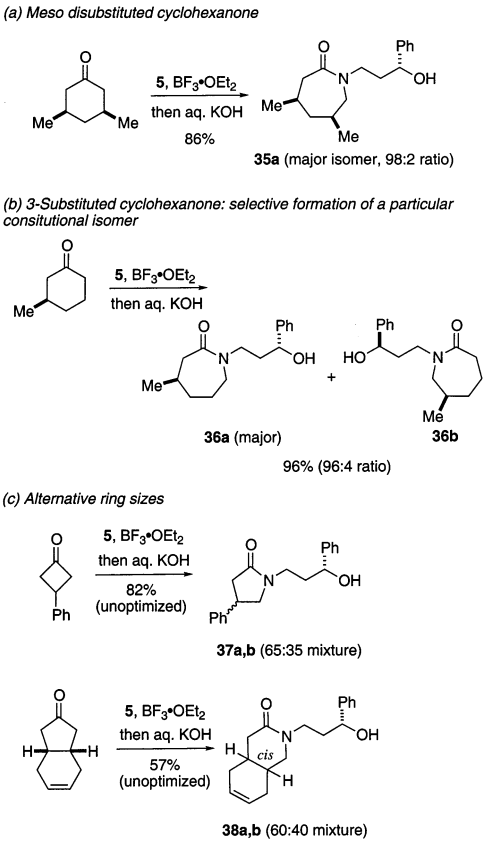
NOTE: The enantiomers of compounds **11**, **31a,b**, and **32a,b** are used in this scheme to allow easy comparison with examples given in Table 3. See Supporting Information for correct structures.

rather than stereoisomers (Scheme 9b). The fact that a stereocenter is already present in the starting material means that enantiomerically pure ketone must be used to avoid a 1:1 mixture of products (in this case, the enantiomeric (*S*)-3-methylcyclohexanone would react with **5** to give mostly the methyl epimer of compound **36b**).[17]

The reactions of additional ketones have also been found to proceed with good (unoptimized) yields but poor stereoselectivity (Scheme 9c). Thus, one cyclobutanone and a meso bicyclic

(17) Aubé, J.; Hammond, M. *Tetrahedron Lett.* **1990**, *31*, 2963−2966.

Scheme 9

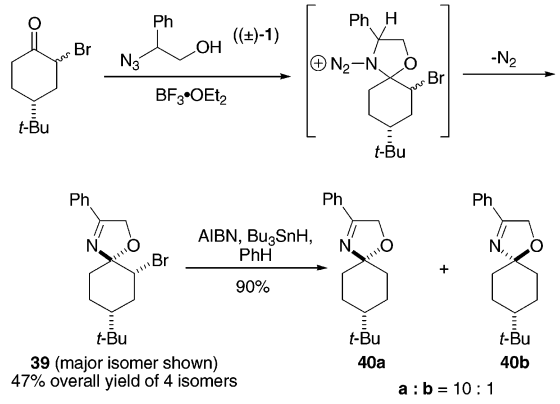


cyclopentanone were examined but gave unpromising results. An analogous reaction of a bicyclic cyclopentanone with **5** has been reported by Vidari et al. with similar results.[18] We propose that such substrates have a poor level of diastereofacial selectivity with respect to the plane of the ketone and that this leads to the observed results.

Elimination Products from 2-Bromo-4-*tert*-Butylcyclohexanone. In previous work, we had learned that 2-phenyl-2-azidoethanol reacted with 2-bromocyclohexanone to afford modest yields of spirocyclic oxazoline products in place of the usual ring-expanded lactams.[10d] As both reactions presumably go through the same *N*-diazonium intermediate, it occurred to us that this process could provide evidence for equatorial or axial addition of azide leading to formation of the spirocyclic stereogenic center (Scheme 10).

Thus, 2-bromo-4-*tert*-butylcyclohexanone was prepared as a mixture of isomers and subjected to reaction with racemic **1** to give a modest yield of four isomeric spirocyclic oxazolines, of which the major isomeric compound **39** could be isolated by crystallization. X-ray crystallography showed **39** to have the structure shown in Scheme 10, in which the azide has attacked the conformationally biased substrate from an equatorial direction. Alternatively, a thermodynamic equilibrium of isomeric *N*-diazoniumoxazolidines could selectively undergo reaction to predominantly afford elimination product containing equatorial nitrogen. It was difficult to accurately determine the ratio of isomers present at this stage, but removal of the bromide group under radical conditions smoothly led to a ca. 10:1 mixture of **40a,b**. The structure of **40a** was confirmed by separately

Scheme 10



preparing it through debromination of pure **39**. Although these results could be complicated by a variety of factors (such as instability of the alternative axial addition product or stereochemical direction by the bromine group), they are at least consistent with equatorial addition of azide in the 1,2-azido alcohol series.

Discussion

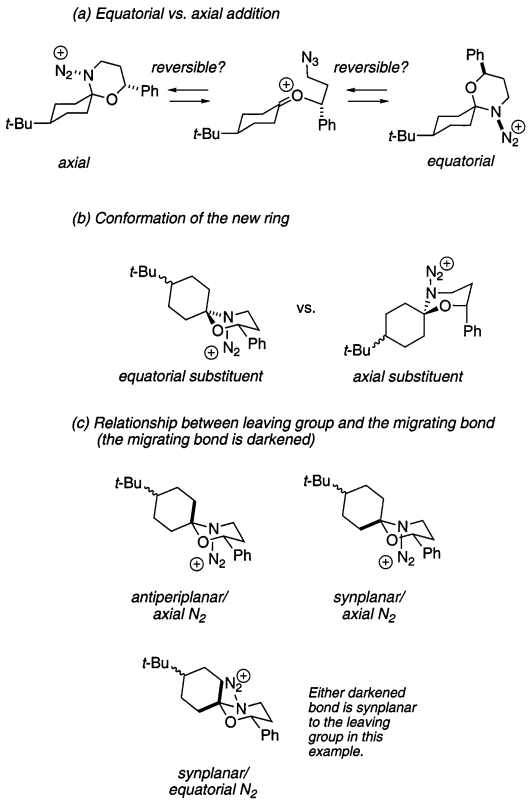
The advantages of the in situ tethering method for the stereoselective ring expansion of ketones to lactams are severalfold. (1) It is a one-pot, one-workup procedure that provides diastereomers that can generally be separated on a preparative scale by nonheroic means. The removal of the chiral group can be accomplished via several methods depending on structure. By comparison, the oxaziridine method[8] (Scheme 1) requires three chemical steps to get to the diastereomeric lactam products. (2) In the best cases, the selectivity is considerably greater than previous methods; this is especially true for propane-derived hydroxyalkyl azides (which also react more readily and at a lower temperature). (3) Although limited, for the time being, to substituted cyclohexanones, the reaction reliably provides extremely easy access to a variety of chiral caprolactams with up to 98% 1,7-selectivity being obtained.

Mechanistic Hypotheses: Three-Carbon Tethers. The overall stereochemical course of the reaction has been determined for most of the examples examined, but of course only two products are possible from the reaction of a chiral hydroxyalkyl azide with a symmetrical ketone. We believe that the stereochemistry depends on three independent variables, illustrated for the specific example of 4-*tert*-butylcyclohexanone with hydroxyalkyl azide **5**: (1) addition of the azide onto the oxenium ion from an equatorial direction or an axial direction relative to resident ketone substitution (Scheme 11a), (2) the reactive orientation of the newly formed heterocyclic ring (Scheme 11b), and (3) the relationship between the leaving N_2^+ group and the migrating carbon (Scheme 11c). These variables will be discussed in reverse order in the context of the substituted azidopropanol reagents, with the two-carbon case to be discussed in the following section. One interesting point is that each potentially migratory carbon is identically substituted, so that electronic influences on migratory aptitude are absent, allowing a purely stereoelectronic analysis of the rearrangement reaction.[19] Another interesting point is that the reactive oxenium

(18) Vidari, G.; Tripolini, M.; Novella, P.; Allegraucci, P.; Garlaschelli, L. *Tetrahedron: Asymm.* **1997**, *8*, 2893−2903.

(19) The proposed transition state in our original communication[10a] was incorrectly depicted and should be replaced by the following arguments.

Scheme 11



ion could, in principle, exist as two geometrical isomers with the alkyl group coplanar to one or another of the adjacent methylene groups. It is likely that these two forms are interconvertible through rapid bond rotation and this point is not considered in the analysis below.

Theoretical studies have characterized the aminodiazonium group involved in this process as pyramidal and having a very small barrier (ca. 1 kcal/mol) to stereochemical inversion.[20] Numerous 1,2-migration reactions are believed to involve antiperiplanar rearrangements of leaving group relative to the migrating bond,[21] including the Beckmann[22] and classical Schmidt[23] rearrangements. Additionally, Pearson has invoked antiperiplanar migration in studies in the closely analogous reactions of alkyl azides with unstabilized carbocations[12b,h] and Hoffman has also proposed this relationship in rearrangements of *N*-(arylsulfonoxy)amines.[24] Antiperiplanar migration has also recently been supported experimentally for the Criegee and Baeyer−Villiger reactions by Kishi, by Chandrasekar, and by Crudden.[25]

It seems very reasonable to propose synchronous migration of carbon antiperiplanar to the leaving N_2^+ moiety based on the above precedent. In addition, the observation of high selectivity in a number of examples examined suggests that prior ionization of the aminodiazonium group followed by carbon migration to a resulting nitrenium ion is less likely as there is no clear way of rationalizing selective migration in such a process. In the present case, antiperiplanar C → N migration requires an axial orientation of the departing diazonium ion (Scheme 11c). An equatorial N_2^+ group would only have synplanar migrating groups available to it, both of which would have nearly the same dihedral angle between either migrating group. Again, this situation would make it difficult to rationalize the high stereoselectivity observed in this reaction. Thus, although we do not have direct evidence of antiperiplanar and synchronous migration in this step, such a postulate is strongly in accord with previous work, theoretical considerations, and our observations of highly stereoselective migration in the absence of electronically differentiable migrating groups.

The analysis of the other two variables, shown in Scheme 11 (parts a and b), is complicated by the lack of evidence regarding the reversibility of the azide addition to the oxenium ion. It is likely, though, that similar steric interactions predominate in either eventuality and this principle will form the basis for the following discussion.

A structure/selectivity analysis of the variously substituted hydroxyalkyl azides is strongly supportive of the intermediacy of a chairlike *N*-diazoniumtetrahydrooxazine ring. As shown in Scheme 11b, the intermediacy of the two different chair forms would lead to different isomers, provided that no other mechanistic step were changed at the same time. Thus, better selectivity should correlate with the stability of a given chair form over its alternative. For monosubstituted hydroxyalkyl azides, one presumes that the single substituent will occupy the equatorial position (Scheme 11b). A particularly relevant comparison is that between the reactions of *syn*- vs *anti*- 1,3-dimethylazidopropanol, in which outstanding selectivity was observed in the former but essentially disappeared in the latter (Scheme 8). In the anti case, at least one of the methyl groups must occupy an axial position and each chairlike form would be expected to have nearly equal energy.

The series of 2-substituted azidopropanols is also instructive. As expected, the size of the substituent has a profound effect on the selectivity of the reaction (Table 3, cf. entries 7/9/11 or 8/10/12). The low selectivity observed with azide **9** relative to either **8** or **10** was somewhat surprising in that the phenyl group is generally thought to be nearly isosteric with an isopropyl group. This is a matter for further exploration, but for the moment it is worth mentioning that phenyl groups are sometimes more stable in an axial orientation relative to their aliphatic counterparts.[26] Also, the lower selectivity for each of the 2-substituted azidopropanols relative to the 1- or 3-monosubstituted analogues makes sense because an axial group in this position is in a 1,3-relationship to an oxygen and an aminodiazonium group, which should provide relatively small 1,3-diaxial effects compared to the other two monosubstitution types (see Scheme 11b for an example).

Finally, two ways of gaining entry into the two conformers are possible. In one, each chair form could kinetically form in

(20) (a) Glaser, R.; Choy, G. S.-C. *J. Phys. Chem.* **1991**, *95*, 7682−7693. (b) Glaser, R.; Choy, G. S.-C. *J. Org. Chem.* **1992**, *57*, 4976−4986. (c) Cacase, F.; Attinà, M.; Speranza, M.; de Petris, G.; Grandinetti, F. *J. Org. Chem.* **1993**, *58*, 3639−3642. (d) Glaser, R.; Choy, G. S.-C. *J. Am. Chem. Soc.* **1993**, *115*, 2340−2347.
(21) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.
(22) Gawley, R. E. *Org. React.* **1988**, *35*, 1−420.
(23) (a) Wolff, H. *Org. React.* **1946**, *3*, 307−336. (b) Banthorpe, D. V. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley & Sons: London, 1971; pp 397−440. (c) Smith, P. A. S. In *Molecular Rearrangements*; de Mayo, P., Ed.; John Wiley & Sons: New York, 1963; Vol. 1, pp 457−591.
(24) Hoffman, R. V.; Kumar, A. *J. Org. Chem.* **1985**, *50*, 1859−1863.
(25) (a) Chandrasekhar, S.; Roy, C. D. *Tetrahedron Lett.* **1987**, *28*, 6371−6372. (b) Chandrasekhar, S.; Roy, C. D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2141−2143. (c) Goodman, R. M.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9392−9393. (d) Crudden, C. M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2851−2855.
(26) Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959−1962.

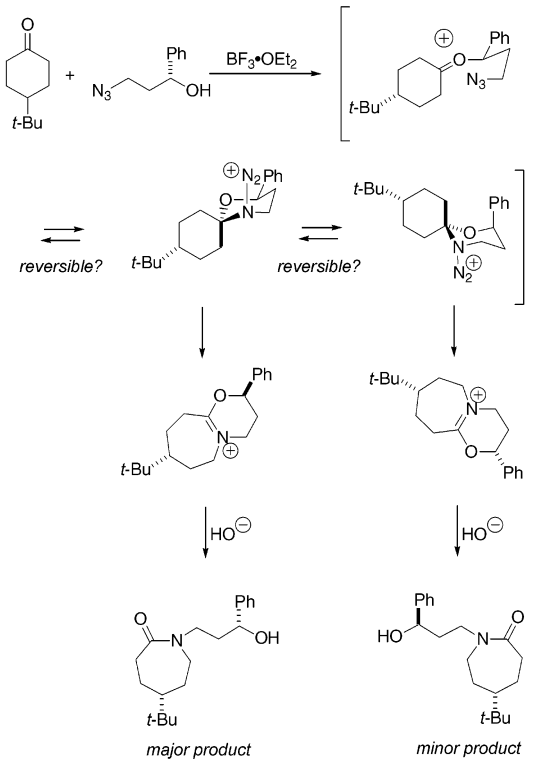
the course of azide attack onto the oxenium ion. In this case, selectivity would result from the minimization of nonbonded interactions in the course of this step. Alternative, the two conformers could equilibrate following ring closure; if this equilibrium is rapid, selectivity would arise by minimizing steric interactions in the migration step itself. (This kind of equilibrium could involve one of two distinct mechanisms: simple conformational equilibrium or, alternatively, retroaddition of the azide species to regenerate the oxenium ion followed by readdition of azide.) We have no experimental evidence to favor either view at this point, but note once again that either mechanism would be subject to a similar analysis of conformer stability.

Related arguments can be used to address the third issue, i.e., the relative stereochemistry of azide addition relative to the preexisting 4-substituent on the original cyclohexanone ring (Scheme 11a). There is no direct precedence to indicate whether a kinetic azide attack should occur from an equatorial or an axial orientation onto a relatively fixed cyclohexanone-based oxenium ion. In either case, spirocyclization would occur with one group in the usually disfavored axial position; a simplistic analysis would indicate that the smaller oxygen group might prefer to emerge in this position relative to the substituted nitrogen atom. Again, the azide addition might be reversible, in which case the relative stability of the two spirocyclic products would determine the overall stereoselectivity of the process (thermodynamic control). (Here, equilibrium between the two forms could only occur through a retroaddition/readdition mechanism and not simple conformational equilibrium).

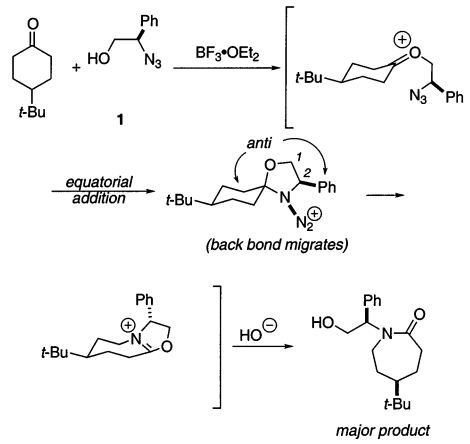
Initially, we settled on a favored equatorial addition (either kinetic or thermodynamic) by (1) assuming antiperiplanar migration, (2) assuming formation of the more stable chairlike tetrahydrooxazine ring, and (3) correlating the absolute configurations with the starting materials and products. Gathering confidence in assumptions (1) and (2) for the reasons noted above, we have additional circumstantial evidence for equatorial addition in spirocyclizations of *two-carbon-chain* hydroxyalkyl azides step through the experiments shown in Scheme 10. Again, we take comfort from the relatively high stereoselectivity of the overall process: if a change in equatorial/axial addition were to occur, it would have to be dramatic to account for the relatively high selectivities observed throughout.

Taken together, these considerations lead to the overall pathway summarized in Scheme 12.[19] Addition of the azide onto the oxenium ion sets up an equilibrium between two chairlike heterocycles (as discussed above but not shown in the scheme, this equilibrium may be set via various mechanisms). The above-noted arguments suggest that the predominant isomer of these processes is that shown to the left in Scheme 12, resulting from equatorial addition and formation of a tetrahydrooxazine ring in which the phenyl substituent occupies the more stable equatorial position. Antiperiplanar migration of carbon to nitrogen proceeds predominantly from this intermediate to yield the observed major product. The minor product is depicted as resulting from the less-favored heterocyclic chair. This is proposed based on the observations that there is little, if any, dependence of selectivity on the substitution of the starting ketone (see Table 3, and cf. entries 1/2/3, 4/5, 7/8, etc.) but changes in substitution on the hydroxyalkyl azide have a significantly larger effect.

Scheme 12



Scheme 13



Mechanistic Hypotheses: Two-Carbon Tethers. Although somewhat less selective than their three-carbon-chain counterparts, the azidoethanol derivatives still provide some caprolactams in ratios rivaling the previous-best oxaziridine technology.[8] In this case, some circumstantial evidence supports equatorial addition of azide (Scheme 10), whereas the relationship of the *N*-diazonium group and the existing tetrahydrooxazine's stereocenter is less certain due to their presence on a five-membered ring. Accordingly, the mechanism shown in Scheme 13 is proposed, wherein the key source of stereoselectivity is the minimization of steric interactions between the phenyl group present on the hydroxyalkyl azide *and the migrating carbon.* This hypothesis, which results in a reactive conformation in which the diazonium ion is on the same face as the phenyl group, arises because of the need to correlate the structures of starting materials and products while still assuming antiperiplanar migration. The cis N_2^+/Ph relationship is reasonable because

of the small size of the azido group compared to the steric repulsion between the phenyl group and the migrating carbon, which increases as the reaction proceeds. Finally, we note that this hypothesis is consistent with the steep drop in selectivity incurred when moving the phenyl group from its position next to the azido group (C-2) to C-1 (Table 2, entry 5).

Summary

An asymmetric equivalent of the Schmidt reaction is presented, in which in situ tethering permits stereocontrol in ring expansions of symmetrical cyclohexanones. Selectivities as high as ca. 98:2 are possible for the synthesis of substituted caprolactams, with up to 1,7-stereoselection involved in the overall process. The synthetic utility of this reaction derives from the lack of comparably useful methods to accomplish this sort of asymmetric nitrogen ring expansion. Both 1,2- and 1,3-azido alcohols are useful and bring complementary advantages and liabilities to the experimentalist. The 1,3-azido alcohols are generally more reactive and provide superior selectivities. However, the lactams arising from 1-azidophenylethanol are easier to *N*-dealkylate.

The fact that either possible migrating carbon is electronically identical provided an unusual opportunity to study a ring-expansion controlled entirely by stereoelectronic factors. Although there is much to learn about the details of this process, a stereochemical analysis has allowed us to make some initial suggestions as to how the selectivity obtained in the overall process might be achieved.

Experimental Section

Representative Procedure: Synthesis of 19a,b. A solution of (*R*)-3-azido-1-phenylpropanol **5** (205 mg, 1.15 mmol) and 4-methylcyclohexanone (188 mg, 1.68 mmol) in 3 mL of CH_2Cl_2 was cooled to −82 °C (ether/dry ice bath), and $BF_3{\cdot}OEt_2$ (0.56 mL, 4.48 mmol) was added dropwise. The reaction was gradually warmed to room temperature over a period of 48 h. The resulting crude iminium ether was diluted with Et_2O (5 mL) and hydrolyzed with 50% KOH (1 mL) added dropwise over 5 min. The solution was stirred for 30 min, and partitioned between CH_2Cl_2 (20 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with NH_4Cl (5 mL), dried ($MgSO_4$), filtered and concentrated. HPLC analysis of the crude reaction mixture showed a 93:7 ratio of diastereomeric lactams. Flash chromatography (1:1→9:1 EtOAc/hexane) gave **19a** and **19b** as transparent oils in a combined yield of 296 mg (98%). TLC (1:1 hexane/EtOAc): R_f (**19a**) = 0.15, R_f (**19b**) = 0.20; HPLC: t_R major (**19a**) = 19.9 min, t_R minor (**19b**) = 18.2 min (Chirobotic T; 90% hexane/EtOH; flow rate 1 mL/min; UV 254 nm). Major diastereomer (**19a**): $[\alpha]_D = -4.2$ (*c* 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J = 6.6 Hz, 3H), 1.12−1.31 (m, 3H), 1.62−1.75 (m, 1H), 1.76−1.98 (m, 4H), 2.42−2.61 (m, 2H), 3.12 (dt, J = 14.2, 4.4 Hz, 1H), 3.24 (dd, J = 6.5, 15.2 Hz, 1H), 3.51 (dd, J = 10.9, 15.2 Hz, 1H), 4.09−4.19 (m, 1H), 4.62 (m, 1H), 7.23−7.38 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.6, 31.4, 35.7, 36.1, 37.2, 37.7, 45.7, 49.3, 69.8, 125.5, 127.0, 128.3, 144.1, 177.1. MS (EI) *m*/*e* 262 (M^++1), 244 (100); HRMS *m*/*e* calcd for $C_{16}H_{24}NO_2$: (M^++1) 262.1807, found: (M^++1) 262.1798. Minor diastereomer (**19b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 6.5 Hz, 3H), 1.18−1.30 (m, 2H), 1.65−1.95 (m, 5H), 2.50−2.56 (m, 2H), 3.01 (m, 1H), 3.32 (dd, J = 15.1, 5.9 Hz, 1H), 3.47 (J = 15.1, 11.0 Hz, 1H), 4.10−4.25 (m, 1H), 4.53 (br d, J = 10.4 Hz, 1H), 4.75−4.85 (m, 1H), 7.21−7.39 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.6, 31.3, 35.7, 35.8, 36.3, 37.5, 44.9, 48.4, 69.6, 125.7, 127.0, 128.2, 144.1, 177.2. MS (EI) *m*/*e* 262 (M^+ + 1), 244; HRMS *m*/*e* calcd for $C_{16}H_{24}NO_2$: (M^++1) 262.1807, found: (M^++1) 262.1797.

Acknowledgment. Financial support was provided by the National Institutes of Health (GM-49093). The authors also thank Lawrence Seib and Doug Powell for crystallographic data, and Robie Lucas for carrying out some early experiments. We thank the referees of the paper for helpful comments.

Supporting Information Available: Characterization data for new compounds and additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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