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Ring Expansion by in situ Tethering of Hydroxy Azides to Ketones: The Boyer Reaction

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Abstract: Although alkyl azides can react with ketones to form ring-expanded lactams, the reaction suffers from poor generality and the need to use powerful Lewis acid promotion. The reactions of 1,2- and 1,3-hydroxyalkyl azides with ketones yield *N*-hydroxyalkyl lactams in high yields under the action of protic or Lewis acids such as BF_3•OEt_2. The reaction appears to succeed due to the initial formation of a hemiketal, which then renders the attack of azide on an oxonium ion intramolecular. The scope of this reaction vis à vis ketone and hydroxyalkyl azide structure is discussed.
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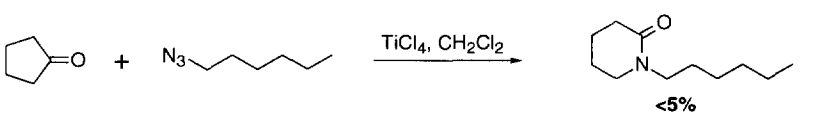
The Schmidt reaction between a cyclic ketone and hydrazoic acid is commonly used for the preparation of lactams.[1] Replacement of hydrazoic acid with an alkyl azide would provide a direct route to *N*-substituted lactams, but the development of this transformation has been problematic. In the 1940s, attempts to insert methyl azide in ketones under classical conditions were unsuccessful.[2] However, in the early 1990s, we reported that $TiCl_4$ (and only $TiCl_4$) could promote Schmidt-type reactions between *n*-hexyl or benzyl azide and certain ketone partners.[3] To wit, although the reactions of unhindered cyclohexanones and cyclobutanones were reasonably efficient, very poor results were obtained with cyclopentanone or 2-methylcyclohexanone (Scheme 1a). In contrast, the *intramolecular* Schmidt reaction – which first sparked our interest in the nucleophilic chemistry of alkyl azides[4] – is quite immune to differences in substitution or ketone ring size, and works under protic or Lewis acid promotion.

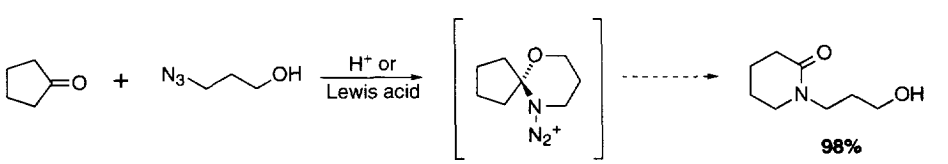
We recently disclosed a functional equivalent of an intermolecular ring-expansion process that nonetheless benefits from intramolecularity in an unusual way.[5] In this paper, we disclose some key features of the "Boyer reaction" of hydroxyalkyl azides and ketones (Scheme 1), which affords *N*-hydroxyalkyl lactams with vastly superior yields and scope relative to the reaction involving simple alkyl azides.

Scheme 1

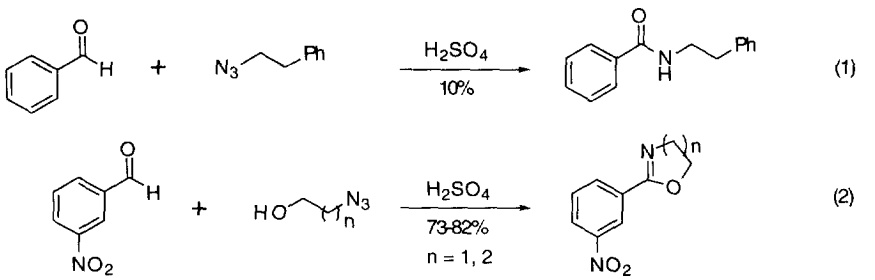
(a) Intermolecular addition of a simple alkyl azide



(b) Intramolecular delivery of a hydroxyalkyl azide



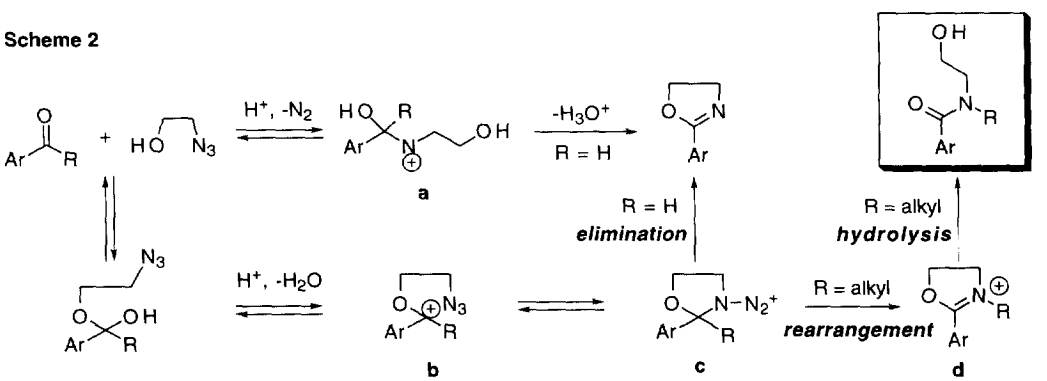
The first realization that placement of a hydroxy group β or γ to an azide would facilitate addition to carbonyl compounds was due to Boyer and coworkers.[6] Reminiscent of our own experience with simple alkyl azides, this group obtained Schmidt-type products from the addition of alkyl azides to electron-poor aromatic aldehydes in the presence of H_2SO_4 (classical Schmidt conditions, eq 1). In contrast, the reactions of 1,2-azidoethanol or 1,3-azidopropanol with aromatic aldehydes under similar conditions gave masked amides (oxazolines or dihydrooxazines) in much higher yields (eq 2). Although attempts to extend this synthesis to aliphatic or electron-rich aromatic aldehydes were reported to fail, we have since reinvestigated this process and found it to work on these substrates using modified reaction conditions.[7]



Mechanistically, the higher yields embodied in eq 2 were attributed to the presumably higher stability of hydroxyalkyl azides in acidic medium, possibly due to hydrogen bonding. The mechanism proposed by Boyer for product formation involved initial attack of the activated aldehyde by the azide, accompanied by loss of N_2 and H_2O to afford product (Scheme 2, via intermediate **a**). However, an alternative route involving initial *hydroxyl group attack* followed by formation of cation **b**, azide addition, and finally elimination from intermediate **c** (where R = H) seems more reasonable in light of the recent appreciation of intramolecularity as a beneficent force in Schmidt chemistry.[4,8] The application of this mechanistic scheme to bona fide insertion, rather than elimination, chemistry was contingent on the ability to perform chemistry like that shown in Scheme 2 where both Ar and R are replaced by alkyl substituents. Specifically, the ability of intermediate **c** to undergo rearrangement to iminium ether **d** was not addressed by Boyer, except to state that no tractable products were obtained when acetophenone was treated with 2-azidoethanol and sulfuric acid. Once formed, hydrolysis of **d** should readily provide an *N*-(ω-hydroxyalkyl) amide.

This paper will discuss the extension of our previously communicated extension of the Boyer reaction to ketones,[5] with special emphasis placed on the effects of Lewis acid, ring size, and N–O tether length.

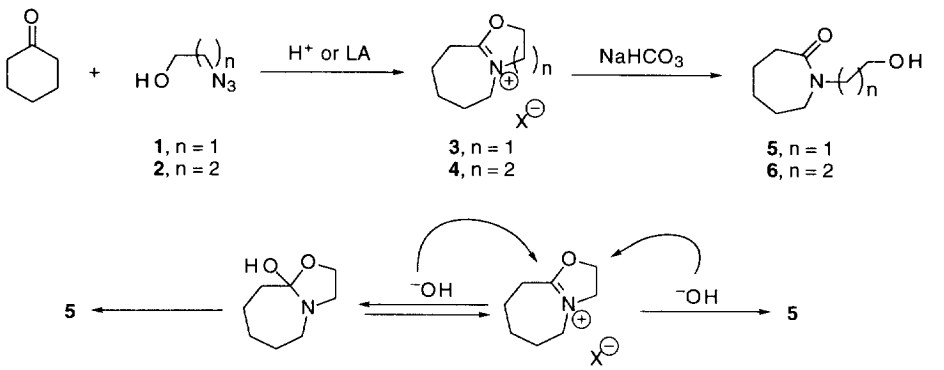
Scheme 2



Results

The initial experiments were carried out with cyclohexanone and, taking the lead of Boyer,[6] 2-azidoethanol (**1**) and 3-azidopropanol (**2**) as the alkyl azide reaction partners (Scheme 3). Thus, when **1** or **2** was added to a solution of cyclohexanone in trifluoroacetic acid at 0 °C, vigorous gas evolution was immediately observed. Taking this as a sign of successful iminium ether formation, we reasoned that simple addition of base should result in hydrolysis and formation of the desired *N*-hydroxyalkyl lactams. Accordingly, quenching the reaction with a saturated solution of aqueous $NaHCO_3$ followed by a standard workup gave lactam **5** or **6**, respectively. As shown in Scheme 3, iminium ethers **3** and **4** can react with hydroxide by either of the two mechanisms shown;[9,10] both routes afford the same product and so the hydrolysis mechanism operating cannot be stated with certainty at the present time.

Scheme 3



Early experiments gave "yields" in excess of 100% due to difficulties in completely removing trifluoroacetate salts from the product lactams. Having settled on an effective hydrolysis procedure, we decided to examine a variety of Lewis acids. The yields of scrupulously purified lactam **6** from the reactions of cyclohexanone and **2** are shown in Table 1. Of the several Lewis and protic acids found effective, $BF_3{\bullet}OEt_2$ proved most convenient in terms of efficiency and ease of workup. However, other conditions are also effective and may have advantages in particular applications.

Table 1. Effect of Acid on the Formation of Lactam **6**

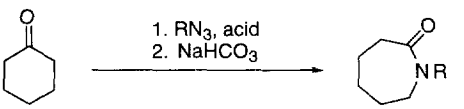
entry	Lewis acid	yield (%)	entry	Lewis acid	yield (%)
1	TFA	64	4	$TiCl_4$	86
2	TfOH	82	5	$SnCl_4$	85
3	$BF_3{\bullet}OEt_2$	90	6	TMSOTf	64

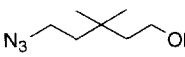
It was later determined that a white powder precipitated from the reaction mixture after the addition of cold THF. These materials were identified as the tetrafluoroborate salts of **3** and **4**; the BF_4^- counterion presumably results from the disproportionation[11] of $BF_3{\bullet}OEt_2$, which is used in excess. This assignment was consistent with the observed ^1H-, ^{13}C-, and ^{11}B-NMR spectra (^{11}B $\delta = -1.11$ ppm), IR ($\nu_{C=N} = 1660$ cm^{-1}), MS, and elemental analysis. We have described the reactions of the isolated salts with nucleophiles other than hydroxide elsewhere.[10] This provides additional circumstantial evidence for the structural assignments of **3** and

4 and sets the stage for the extension of this ring-expansion protocol to the general synthesis of otherwise functionalized *N*-alkyl lactams.

Investigation of Azide Tether Length. Having established the viability of the Boyer reaction on cyclohexanone using hydroxyalkyl azides **1** and **2**, other azide reactants were examined. These experiments were pursued to help establish the scope of the reaction vis à vis N–O tether length and oxygen functionality, and to obtain additional evidence for the reaction course depicted in Scheme 2. The results of this survey are shown in Table 2; once again, cyclohexanone was used as a prototypical ketone substrate. In general, the hydroxyalkyl azides were synthesized from commercially available halides by nucleophilic displacement with NaN_3 in DMF.

Table 2. Acid-Promoted Insertion Reactions of Cyclohexanone and Various Azide Reactants



entry	hydroxyalkyl azide, RN_3	acid	product[a]	yield (%)
1	$HO(CH_2)_2N_3$ (**1**)	BF_3•OEt_2	**5**	90
2	$HO(CH_2)_3N_3$ (**2**)	BF_3•OEt_2	**6**	98
3	$TMSO(CH_2)_3N_3$ (**7**)	TMSOTf (0.2 equiv)	**6**[b]	20
4		TMSOTf (1.0 equiv)	**6**[b]	92
5	$CH_3O(CH_2)_3N_3$ (**8**)	BF_3•OEt_2	–	–[c]
6		TfOH	**9**	19
7	$HO(CH_2)_4N_3$ (**10**)	BF_3•OEt_2	–	–[c]
8		TfOH	**11**	34
9		$TiCl_4$	**11**	14
10	$HO(CH_2)_5N_3$ (**12**)	BF_3•OEt_2	–	–[c]
11		TfOH	**13**	33
12		$TiCl_4$	**13**	7
13	 (**14**)	BF_3•OEt_2	–	–[c]
14	$CH_3(CH_2)_5N_3$	BF_3•OEt_2	–	–[c,d]
15		TfOH	**15**[d]	30
16		$Ti(O\text{-}i\text{-}Pr)_4$	–	–[c]
17		$TiCl_4$	**15**[d]	80[d]

Notes: (a) Except where noted, the substituent R in the product lactam is the same as in the starting alkyl azide. (b) In this case, the trimethylsilyl ether is lost during the reaction, so the product is the same as that obtained in entry 2. (c) No lactam product was isolated in this experiment. (d) As reported in reference 3.

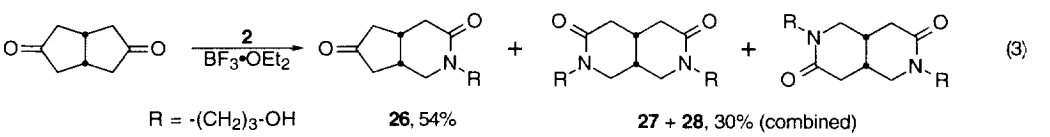
As expected, a two or three carbon span between the hydroxy group and azide is optimal (Table 2, entries 1 and 2). Increasing this distance by one or two additional methylene units (entries 7-13) gave no reaction with cyclohexanone using BF_3•OEt_2 as the Lewis acid, but was moderately successful under TfOH promotion, with yields topping out at about 30-35%. This result is consistent with a shift in mechanism from the hydroxyl group-assisted paradigm shown in Scheme 2 for cases requiring the transient formation of a seven- or higher-membered ring in the azide addition step (i.e., **b** → **c** in Scheme 2). In these examples, it seems likelier

that the azide group in the longer hydroxyalkyl azides undergoes direct addition to the activated carbonyl group, followed by rearrangement. Similar behavior supporting this interpretation was observed when the hydroxy group in **2** was capped by methylation (entries 5 and 6). Finally, TfOH promotion also afforded a thirtysomething yield of lactam in the reaction of cyclohexanone with *n*-hexyl azide; a similar result was previously reported using cyclohexanone methyl enol ether.[12]

It appears, for the time being, that hydroxyl-group assistance is limited to hydroxyalkyl azides in which the two functionalities are separated by two or three atoms, with other hydroxyalkyl azides behaving more like simple alkyl azides.[3] However, a key difference is $TiCl_4$ is not an acceptable activator for the hydroxyalkyl azides with a separation of four or more atoms, whereas this is the *only* Lewis acid that has been found to work well for simple alkyl azides (cf. entries 9 and 12 with entry 17). It is likely that the hydroxyalkyl azide displaces the chlorides on titanium and dissipates the power of this reagent to effect an insertion reaction (note that titanium tetraisopropoxide is not an effective promoter for the reaction of *n*-hexyl azide with cyclohexanone (entry 16)).

One additionally useful result is that the requisite oxonium ion **b** (Scheme 2) can be generated directly from the ketone and trimethylsilyl ether of 3-azidopropanol (**7**) according Noyori/Markó conditions (entry 4).[13] Silyl ether **7** was previously used in this laboratory for the related Boyer reaction route to oxazolines.[7]

Survey of Ketones. The reactions of 2-azidoethanol (**1**) and 3-azidopropanol (**2**) with a variety of symmetrical cyclic ketones were examined (Table 3). In the simple cases examined ranging from four- to six-membered cycloalkanones, good overall results were observed. As mentioned at the outset of this paper, we were particularly keen to obtain good yields from five-membered ring ketones, as these substrates were not good partners in $TiCl_4$-promoted reactions with simple alkyl azides. Entries 2-5 in Table 3 contain promising evidence for the application of this reaction to five-membered ring systems. Both types of reactions are readily applied to cyclobutanones and cyclohexanones (entries 1, and 6-12).[3] The ability of the reaction to accommodate modest functionality was briefly examined using *N*-methyl-4-piperidone and the monoketal of 1,4-cyclohexanedione (entries 11 and 12). Both experiments gave good results. In comparison, the reaction of *cis*-bicyclo[3.3.0]octanedione with **2** gave a mixture of products, with the product of a single ring-expansion (**26**) nonetheless dominating (eq 3). An approximately equimolar mixture of regioisomeric products **27** and **28** were also obtained in this experiment.



We have only examined a few unsymmetrical ketones to date; some representative results are shown in Scheme 4. In our original communication, the reaction of 2-methylcyclopentanone and hydroxyalkyl azide **1** yielded a nearly equimolar mixture of regioisomers.[5] In contrast, 2-methoxy ketones appear to favor formation of the opposite isomer expected from normal Schmidt chemistry.[1] We are currently examining this issue in detail and the results of this study will be reported in due course.

Scheme 4

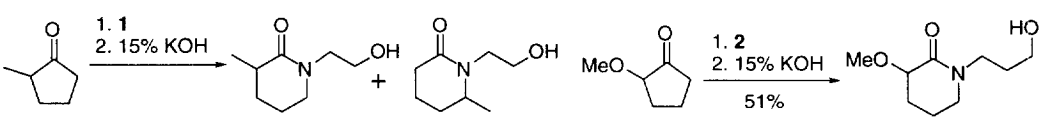
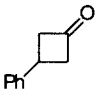
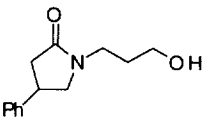
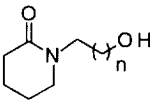
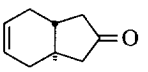
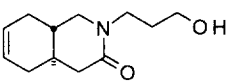
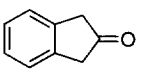
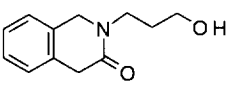
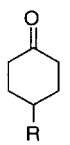
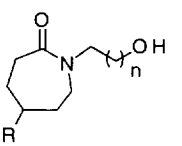
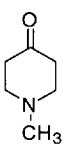
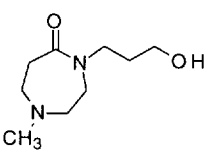
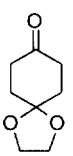
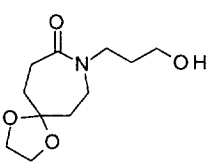


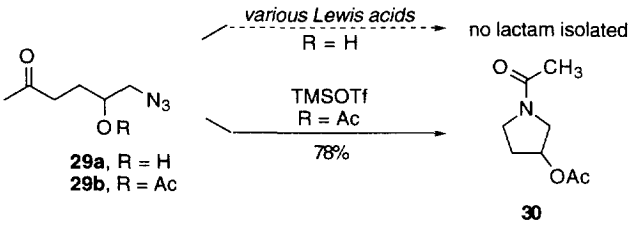
Table 3. Reactions of **1** and **2** with Various Ketones Using $BF_3 \cdot OEt_2$

entry	ketone	azide	product		yield (%)
1		**2**		**16**	73
2	cyclopentanone	**1**		**17**, n = 1	96
3		**2**		**18**, n = 2	98
4		**2**		**19**	88
5		**2**		**20**	80
					
6	R = H	**1**		**5**, n = 1	98
7		**2**		**6**, n = 2	90
8	$R = CH_3$	**2**		**21**, n = 2	83
9	R = Ph	**2**		**22**, n = 2	88
10	R = *t*-Bu	**2**		**23**, n = 2	82
11		**2**		**24**	73
12		**2**		**25**	79

An Intramolecular Example. Finally, the presence of a hydroxyl group proved deleterious in at least one case in which an intramolecular addition reaction was examined. Compound **29a** was prepared from 5-hexen-2-one by treatment with dimethyl dioxirane (85%) followed by opening of the derived epoxide with NaN_3 (51%). No Lewis acid conditions that we tried could convert this compound to lactam. We suspect that, in this case, facile hemiketal formation sets up a situation in which the azide cannot comfortably attack a derived cation; it is also possible that a complex reaction pathway afforded idiosyncratic (and possibly volatile) products that were not readily isolated. Simple acetylation afforded **29b**, which readily gave the standard intramolecular Schmidt reaction[4] product shown. There are obviously many cationic reaction partners that could be derived through variations of this strategy, however, and it would be premature to state that

an intramolecular Boyer reaction is impossible.

Scheme 5



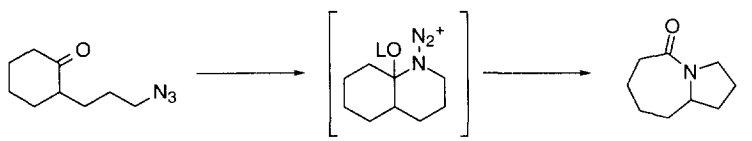
Discussion

The most noteworthy aspect of this new variation on alkyl azide chemistry is the use of a temporary tethering group to render the interaction of an azide and its electrophilic partner intramolecular. Although many intramolecular reactions have found wide utility, the present case differs from most in that the tethering device is not installed and removed in separate operations, but is passively formed under the reaction conditions used to trigger the insertion reaction of interest. A similar strategy has been used by Haynes for the formation of multicyclic ring systems using an ionic Diels-Alder reaction triggered by hemiketal formation between a hydroxyl group-containing diene and an enone.[14]

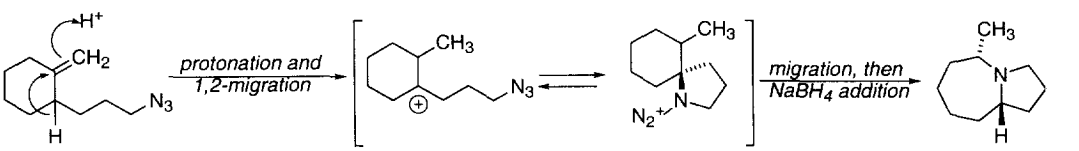
This mechanism is supported by the vastly improved yields obtained from 1,2- and 1,3-hydroxyalkyl azides compared to analogous reactions of simple alkyl azides and the observations that these improvements are largely lost when the distance between the hydroxyl group and the azide is increased or when the hydroxyl group is capped. It is also worth noting that the intermediate in the Boyer reaction differs from the azidohydrin observed in the previously reported intramolecular Schmidt reaction (Scheme 6).

Scheme 6

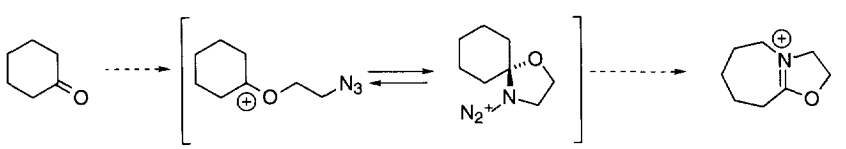
(a) Intramolecular Schmidt reaction of ketones



(b) Intramolecular Schmidt reaction of carbocations



(c) Boyer reaction



In the intramolecular Schmidt reaction, a fused azidohydrin intermediate (Scheme 6a) is encountered en route to the lactam product, but the Boyer reaction utilizes a spiro version as shown in Scheme 6c. Both fused and spiro modes are possible in the intramolecular Schmidt reaction of azides and carbocations as introduced by the Pearson group.[8,15] An interesting case, in which the spiro mode predominates in a system able to go through both intermediates thanks to 1,2-hydride shifts, is shown in Scheme 6b. The Boyer reaction can be considered an oxo analog of this reaction. An interesting contrast between the reactions of azides with ketones and their equivalents versus alkenes is that the intermolecular reaction of alkenes with azides proceeds in high yield under very nearly equivalent conditions to the intramolecular variant.[16] For carbonyls, either enhanced Lewis acid activation or recourse to tethering appears to be necessary for high yields. This is probably due to the higher reactivity of carbocations toward nucleophiles relative to activated ketones and their ilk.

From a practical viewpoint, the (1) success of the reaction for five-membered ring carbonyls, (2) ability to use a wider range of Lewis acids, and (3) utility of the iminium ether intermediates in obtaining functionalized lactams guarantee a place for the Boyer reaction of ketones in heterocyclic synthesis. We briefly touched on the extension of this reaction to asymmetric synthesis through the use of chiral hydroxyalkyl azides in our initial communication,[5] and are interested in the extension of the reaction to acyclic substrates and medium-to-large-ring synthesis. These investigations will be fully reported in due course.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded on a QE-300 (300 MHz and 76.5 MHz, respectively), a Bruker DRX-400 (400 MHz and 100.6 MHz), or a Bruker AM-500 (500 MHz and 125.7 MHz) instrument. All NMR samples were dissolved in $CDCl_3$, and the chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane with either TMS or residual chloroform as an internal reference. Abbreviations are s, singlet; d, doublet; t, triplet; q, quartet; br, broad. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Low resolution mass spectra (EI, electron impact, or CI, chemical ionization) were taken using a Ribermag R10-10 quadrapole instrument, and high resolution mass spectra (HRMS) were obtained using a VG Analytical ZAB double focusing spectrometer. Optical rotations were taken on a Perkin-Elmer 241 polarimeter at ambient temperature; the concentrations are reported in g/dL. Elemental analyses were performed in-house. All flash chromatography was performed using Fischer Scientific silica gel (32-63 mesh) with the indicated solvent mixtures. Tetrahydrofuran was distilled from sodium benzophenone ketyl, dichloromethane and triethylamine were distilled from calcium hydride, and all other solvents were used without further purification. Reaction flasks were oven-dried and cooled under argon, and all reactions were conducted under a positive pressure of dry nitrogen or argon.

Materials. The following compounds were prepared as previously disclosed: **1** and **2**,[7] 4-phenylcyclobutanone,[17] *trans*-1,3,3a,4,7,7a-hexahydro-2*H*-indene-2-one,[18] and 3,3-dimethyl-1,5-pentanediol.[19] All other starting materials were purchased from Aldrich, Fluka, or Fischer Chemical companies and used as received.

1-Azido-3-trimethylsilyloxypropane (7). A solution of 3-azido-1-propanol (1.0 g, 9.9 mmol) dissolved in Et_3N (80 mL) was treated with chlorotrimethylsilane (2.5 mL, 20 mmol) and the reaction mixture was stirred for 2 h. The reaction was poured into Et_2O (100 mL) and the organic layer was washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried (anhydrous Na_2SO_4), filtered and concentrated. Flash chromatography (10% Et_2O/*n*-pentane) gave 850 mg (50%) of **7** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 9H), 1.76 (pentet, J = 6.0 Hz, 2H), 3.36 (t, J = 6.0 Hz, 2H), 3.63 (t, J = 6.0 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 0.0, 32.4, 48.9, 59.8; IR (neat) 2960, 2875, 2100, 1250 cm^{-1}.

1-Azido-3-methoxypropane (8). 3-Azido-1-propanol (2.00 g, 19.8 mmol) in THF (5 mL) was added dropwise to NaH (60% dispersion in mineral oil, 1.58 g, 39.6 mmol) in THF (20 mL) at 0 °C, and the reaction mixture was stirred for 15 min. CH_3I (1.35 mL, 21.8 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 1 h, and was stirred at room temperature for an additional 14 h. The reaction was quenched by pouring into H_2O (10 mL) and extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (20 mL), dried (anhydrous Na_2SO_4), decanted, and concentrated. Flash chromatography (10% Et_2O/*n*-pentane) gave 1.25 g (55%) of **8** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (pentet, J = 6.0 Hz, 2H), 3.31 (s, 3H), 3.35 (t, J = 6.0 Hz, 2H), 3.42 (t, J = 6.0 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 29.1, 48.4, 58.6, 69.2; IR (neat) 2910, 2860, 2090, 1110 cm^{-1}.

4-Azido-1-butanol (10). To a solution of 4-chloro-1-butanol (85%, 5.45 g, 42.6 mmol) in DMF (50 mL) was added sodium azide (11.1g, 171 mmol). The reaction mixture was heated to 70 °C for 16 h, after which time it was cooled and diluted with Et_2O (250 mL). After washing with H_2O (150 mL) and brine (150 mL), the organic layer was dried (anhydrous Na_2SO_4), decanted, and concentrated. Flash chromatography (50% Et_2O/pentane) gave 2.76 g (56%) of **10** as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.62-1.70 (m, 4H), 2.40 (s, 1H), 3.33 (t, *J* = 6.5 Hz, 2H), 3.66 (t, *J* = 6.1 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.3, 29.6, 51.2, 61.9; IR (neat) 3340 (br), 2930, 2860, 2090 cm^{-1}.

5-Azido-1-pentanol (12). Prepared by the same general procedure as 4-azido-1-butanol from 5-chloro-1-pentanol (3.00 g, 24.5 mmol). Flash chromatography (33% EtOAc/hexanes) gave 2.47 g (78%) of **12** as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.35-1.42 (m, 2H), 1.49-1.61 (m, 4H), 2.84 (s,1H), 3.23 (t, *J* = 6.6 Hz, 2H), 3.56 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.6, 28.4, 31.8, 51.1, 62.0; IR (neat) 3330 (br), 2930, 2860, 2090 cm^{-1}.

3,3-Dimethyl-5-azido-1-pentanol (14). To a solution of 3,3-dimethyl-1,5-pentanediol[19] (2.00 g, 15.2 mmol) and triethylamine (1.69 g, 16.7 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added methanesulfonyl chloride (1.74 g, 15.2 mmol) dropwise. After 10 min, the reaction was quenched with saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (66% EtOAc/hexanes) gave 1.07 g (33%) of 3,3-dimethyl-5-methanesulfonyloxy-1-pentanol as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 6H), 1.54 (t, *J* = 7.4 Hz, 2H), 1.72 (t, *J* = 7.4 Hz, 2H), 2.99 (s, 1H), 3.69 (t, *J* = 7.5 Hz, 2H), 4.28 (t, *J* = 7.4 Hz, 2H).

To a solution of 3,3-dimethyl-5-methanesulfonyloxy-1-pentanol (1.00 g, 4.76 mmol) in DMF (15 mL) was added sodium azide (1.20 g, 18.5 mmol). The reaction mixture was heated to 80 °C for 8 h, after which time it was cooled to room temperature and diluted with Et_2O (50 mL). After washing with H_2O (30 mL) and brine (30 mL), the organic layer was dried (anhydrous Na_2SO_4), decanted, and concentrated. Flash chromatography (50% EtOAc/hexanes) gave 265 mg (35%) of **14** as a clear oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 6H), 1.35 (br s, 1H), 1.52-1.58 (m, 4H), 3.29 (t, *J* = 8.0 Hz, 2H), 3.71 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.4, 31.7, 40.4, 44.2, 47.6, 59.4; IR (neat) 3330 (br), 2950, 2085 cm^{-1}.

General Procedure for the Synthesis and Isolation of Iminium Ethers. Synthesis of Iminium Ether 3. A solution of cyclohexanone (100 mg, 1.02 mmol) and 2-azido-1-ethanol (106 mg, 1.22 mmol) in CH_2Cl_2 (4 mL) was cooled to 0 °C. BF_3•OEt_2 (0.26 mL, 2.04 mmol) was added dropwise over 5 min. Immediate gas evolution was noted upon addition. The reaction mixture was allowed to warm to room temperature and stirred for 17 h before concentrating to afford a colorless oil. The oil was precipitated by the dropwise addition of cold THF (ca -20 °C, 50 mL). The white precipitate was filtered and the solid was washed with additional cold THF (ca 0 °C, 50 mL), before the residual solvent was removed under vacuum to afford 197 mg (85%) of **4** as a white crystalline solid: mp 60-63 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.76-1.98 (m, 6H), 2.88 (m, 2H), 3.79 (br s, 2H), 4.35 (t, *J* = 9.9 Hz, 2H), 5.00 (t, *J* = 9.9 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 20.8, 24.6, 27.2, 28.3, 48.3, 52.8, 71.8, 180.0; ^{11}B NMR ($CDCl_3$) -1.11 ppm, referenced to external BF_3•OEt_2 in $CDCl_3$; IR ($CHCl_3$) 3025, 2940, 1660 cm^{-1}; MS (EI) *m/e* 140 (M^+), 139, 124, 110; Anal. calcd for $C_8H_{14}NOBF_4$: C, 42.32; H, 6.22; N, 6.17, found C, 42.34; H, 6.60; N, 6.11.

Iminium Ether 4. White crystalline solid (477 mg, 78%); mp 87-89 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73-1.92 (m, 6H), 2.32 (pentet, *J* = 5.7 Hz, 2H), 2.88 (m, 2H), 3.77-3.85 (m, 4H), 4.62 (t, *J* = 5.4 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 19.5, 21.4, 24.4, 28.6, 33.4, 48.1, 56.0, 68.2, 177.9; ^{11}B NMR ($CDCl_3$) -1.15 ppm, referenced to external BF_3•OEt_2 in $CDCl_3$; IR ($CDCl_3$) 3020, 1650 cm^{-1}; MS (EI) *m/e* 154 (M^+), 138, 110, 84, 70, 55; Anal. calcd for $C_9H_{16}NOBF_4$: C, 44.80; H, 6.69; N, 5.81, found: C, 44.65; H, 6.78; N, 5.71.

General Procedure for the Synthesis of *N*-Hydroxyalkyl Lactams Using BF_3•OEt_2. 1-(2'-hydroxyethyl)azepan-2-one (5). A solution of cyclohexanone (112 mg, 1.14 mmol) and 2-azido-1-ethanol (132 mg, 1.52 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C. BF_3•OEt_2 (0.28 mL, 2.3 mmol) was added dropwise over 5 min. Immediate gas evolution was noted upon addition. The reaction was allowed to warm to room temperature over 30 min and was stirred at room temperature for an additional 17 h. The solution was concentrated and saturated $NaHCO_3$ (5 mL) was added to the residual oil. The reaction mixture was stirred for 30 min at room temperature. After concentration of the aqueous layer, additional CH_2Cl_2 (100 mL) was added and the organic layer was dried (anhydrous Na_2SO_4), filtered, and concentrated to afford a residual oil. Flash chromatography (EtOAc) gave 176 mg (98%) of **5** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.62-1.82 (m, 6H), 2.55 (m, 2H), 3.21 (br s, 1H), 3.43 (m, 2H), 3.57 (t, *J* = 4.9 Hz, 2H), 3.76 (t, *J* = 4.9 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 22.9, 27.9, 29.5, 36.7, 50.7, 51.2, 60.8, 176.9; IR (neat) 3480, 2920, 1620 cm^{-1}; MS (EI) *m/e* 157 (M^+), 139, 126, 84, 69; HRMS calcd for $C_8H_{16}NO_2$ (M^++1): 158.1181, found 158.1178.

1-(3'-Hydroxypropyl)azepan-2-one (6). Oil (312 mg, 90%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.60-1.80 (m, 8H), 2.56 (m, 2H), 3.20 (br s, 1H), 3.35 (m, 2H), 3.50-3.55 (m, 4H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 23.2, 28.1, 29.7, 29.9, 36.7, 44.4, 49.7, 57.8, 177.1; IR (CCl_4) 3380, 2920, 1610 cm^{-1}; MS (EI)

m/e 172 (M^++1), 171 (M^+), 153, 140, 126, 69, 44; HMRS calcd for $C_9H_{18}NO_2$ (M^++1): 172.1337, found 172.1331.

1-(3'-Methoxypropyl)azepan-2-one (9). Synthesized by the general procedure except that TfOH and 15% NaOH were used in place of BF_3•OEt_2 and saturated $NaHCO_3$, respectively. Dark yellow oil (89 mg, 19%); ^1H NMR (400 MHz, $CDCl_3$) δ 1.56-1.69 (m, 6H), 1.73 (m, 2H), 2.48 (m, 2H), 3.27 (s, 3H), 3.29-3.40 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.3, 28.2, 28.6, 29.9, 37.2, 45.6, 49.8, 58.5, 70.2, 175.6; IR (neat) 2920, 2840, 1630 cm^{-1}; MS (CI) *m/e* 186 (M^++1), 154, 126, 98; HRMS calcd for $C_{10}H_{20}NO_2$ (M^++1): 186.1494, found 186.1485.

1-(4'-Hydroxybutyl)azepan-2-one (11). Synthesized by the general procedure except that TfOH and 15% NaOH were used in place of BF_3•OEt_2 and saturated $NaHCO_3$, respectively. Clear oil (158 mg, 34%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.53-1.73 (m, 10H), 2.51 (m, 2H), 3.16 (br s, 1H), 3.33-3.42 (m, 4H), 3.65 (t, J = 6.0 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 23.4, 24.6, 28.6, 29.5, 29.9, 37.2, 48.0, 49.6, 62.2, 176.0; IR (neat) 3380 (br), 2920, 2850, 1620 cm^{-1}; MS (EI) *m/e* 186 (M^++1), 168, 140, 126, 98, 44; HRMS calcd for $C_{10}H_{19}NO_2$ (M^+): 185.1416, found 185.1403.

1-(5'-Hydroxypentyl)azepan-2-one (13). Synthesized by the general procedure except that TfOH and 15% NaOH were used in place of BF_3•OEt_2 and saturated $NaHCO_3$, respectively. Pale yellow oil (152 mg, 33%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.32-1.42 (m, 2H), 1.49-1.73 (m, 10H), 2.51 (m, 3H), 3.32-3.39 (m, 4H), 3.62 (t, J = 6.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.8, 23.2, 27.6, 28.4, 29.7, 32.1, 37.0, 47.9, 49.4, 62.0, 175.7; IR (neat) 3400 (br), 2930, 2855, 1620 cm^{-1}; MS (EI) *m/e* 200 (M^++1), 182, 169, 154, 126, 98, 44; HRMS calcd for $C_{11}H_{22}NO_2$ (M^++1): 200.1650, found 200.1662.

1-(3'-Hydroxypropyl)-4-phenylpyrrolidin-2-one (16). Oil (106 mg, 71%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (pentet J = 5.8 Hz, 2H), 2.63 (dd, J = 8.4, 17.1 Hz, 1H), 2.85 (br s, 1H), 2.88 (dd, J = 9.0, 16.8 Hz, 1H), 3.40-3.65 (m, 6H), 3.75 (dd, J = 8.4, 9.3 Hz, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 29.4, 37.1, 38.6, 38.8, 54.7, 58.3, 126.5, 127.0, 128.7, 142.0, 174.8; IR (CCl_4) 3380, 2920, 2840, 1650, 690 cm^{-1}; MS (EI) *m/e* 220 (M^++1), 219 (M^+), 201, 175, 117, 104, 44; HRMS calcd for $C_{13}H_{18}NO_2$ (M^++1): 220.1338, found 220.1312.

1-(2'-Hydroxyethyl)piperidin-2-one (17). Oil (409 mg, 96%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.75-1.90 (m, 4H), 2.41 (m, 2H), 3.37 (m, 2H), 3.54 (t, J = 5.1 Hz, 2H), 3.59 (br s, 1H), 3.75-3.85 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 20.7, 22.8, 31.8, 49.1, 50.3, 60.4, 171.1; IR (neat) 3350, 2390, 2850, 1610 cm^{-1}; MS (EI) *m/e* 143 (M^+), 112, 100, 84, 44; HRMS calcd for $C_7H_{13}NO_2$ (M^+): 143.0946, found 143.0944.

1-(3'-Hydroxypropyl)piperidin-2-one (18). Oil (430 mg, 97%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-1.90 (m, 6H), 2.42 (m, 2H), 3.24 (m, 2H), 3.44-3.52 (m, 4H), 3.70 (br s, 1H), 3.75-3.85 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 20.5, 22.4, 28.8, 31.3, 42.9, 47.3, 57.7, 170.3; IR (neat) 3390, 2940, 1610 cm^{-1}; MS (EI) *m/e* 158 (M^++1), 139, 124, 44; HRMS calcd for $C_8H_{16}NO_2$ (M^++1): 158.1181, found 158.1185.

(4a*S*,8a*R*)-2-(3'-Hydroxypropyl)-1,4,4a,5,8,8a-hexahydroisoquinolin-3-one (19). White crystalline solid (70 mg, 88%); $[\alpha]_D$ -15.4 (*c* 0.68, EtOH); mp 82-84 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.62-1.87 (m, 6H), 2.05 (m, 1H), 2.20 (m, 2H), 2.60 (m, 1H), 2.96 (t, J = 10.5 Hz, 1H), 3.28 (dd, J = 3.1, 12.2 Hz, 1H), 3.37-3.50 (m, 3H), 3.60 (m, 1H), 4.05 (m, 1H), 5.65 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 28.5, 29.1, 31.7, 32.5, 33.5, 38.6, 43.0, 53.6, 57.8, 124.7, 125.6, 170.8; IR (CCl_4) 3400, 2900, 1620, 1490, 1130 cm^{-1}; MS (EI) *m/e* 210 (M^++1), 209 (M^+), 191, 178, 176, 165, 136, 44; HRMS calcd for $C_{12}H_{20}NO_2$ (M^++1): 210.1494, found 210.1484.

2-(3'-Hydroxypropyl)-2,4-dihydroisoquinolin-3-one (20). Oil (124 mg, 80%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (m, 2H), 3.47-3.53 (m, 2H), 3.65 (s, 2H), 3.69 (t, J = 6.2 Hz, 2H), 3.78 (br t, J = 6.0 Hz, 1H), 4.47 (s, 2H), 7.16-7.28 (m, 4H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 29.5, 37.0, 43.2, 50.9, 58.0, 124.9, 126.5, 127.1, 127.5, 130.8, 131.8, 170.1; IR (CCl_4) 3440, 2920, 1640, 1070 cm^{-1}; MS (EI) *m/e* 206 (M^++1), 205 (M^+), 146, 104, 78; HRMS calcd for $C_{12}H_{16}NO_2$ (M^++1): 206.1181, found 206.1180.

1-(3'-Hydroxypropyl)-5-methylazepan-2-one (21). Synthesized by the general procedure except that 2.0 equiv. of both the azide and acid were used and the reaction time was increased to 48 h. Oil (343 mg, 83%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 3H), 1.10-1.32 (m, 2H), 1.61-1.77 (m, 3H), 1.78-1.90 (m, 2H), 2.48-2.62 (m, 2H), 3.20 (ddd, J = 1.5, 6.6, 15.3 Hz, 1H), 3.43-3.62 (m, 6H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 22.5, 30.1, 31.3, 35.6, 36.0, 36.3, 44.5, 48.7, 57.9, 176.9; IR (CCl_4) 3420, 2920, 1630 cm^{-1}; MS (EI) *m/e* 186 (M^++1), 185 (M^+), 167, 154, 140, 128, 83, 44; HRMS calcd for $C_{10}H_{20}NO_2$ (M^++1): 186.1494, found 186.1492.

1-(3'-Hydroxypropyl)-5-phenylazepan-2-one (22). Synthesized by the general procedure except that 2.0 equiv. of both the azide and acid were used and the reaction time was increased to 48 h. Oil (310 mg, 88%); ^1H NMR (500 MHz, $CDCl_3$) δ 1.65-1.76 (m, 4H), 2.03 (m, 2H), 2.66-2.78 (m, 3H), 3.28 (dd, J = 5.2, 14.5 Hz, 1H), 3.52-3.67 (m, 5H), 4.09 (br s, 1H), 7.15-7.39 (m, 5H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 30.1, 30.6, 35.9, 36.1, 44.6, 48.1, 48.9, 57.9, 126.52, 126.54, 128.5, 145.6, 177.1; IR (CCl_4) 3420, 2920,

1630, 1490, 910, 700 cm^{-1}; MS (EI) *m/e* 248 (M^++1), 247 (M^+), 229, 214, 145, 115, 104, 58, 44; HRMS calcd for $C_{15}H_{22}NO_2$ (M^++1): 248.1650, found 248.1645.

1-(3'-Hydroxypropyl)-5-*t*-butylazepan-2-one (23). Synthesized by the general procedure except that 2.0 equiv. of both the azide and acid were used and the reaction time was increased to 48 h. White solid (305 mg, 83%); mp 71-73 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 9H), 1.00-1.22 (m, 4H), 1.62 (m, 4H), 1.97 (m, 2H), 2.53 (m, 2H), 3.18 (dd, *J* = 6.3, 8.7 Hz, 1H), 3.47 (m, 2H), 4.07 (m, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.1, 27.5, 29.2, 30.2, 33.0, 36.0, 44.3, 49.2, 51.5, 57.9, 177.1; IR (CCl_4) 3400, 2940, 1620 cm^{-1}; MS (EI) *m/e* 228 (M^++1), 196, 182, 154, 44; HRMS calcd for $C_{13}H_{26}NO_2$ (M^++1): 228.1963, found 228.1953.

4-(3'-Hydroxypropyl)-1-methyl-[1,4]-diazepan-5-one (24). Synthesized by the general procedure except that 3.0 equiv. of acid was used and the reaction time was increased to 48 h. Pale yellow oil (120 mg, 73%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (pentet, *J* = 5.7 Hz, 2H), 2.32 (s, 3H), 2.51-2.55 (m, 5H), 2.67 (m, 2H), 3.41 (m, 2H), 3.48-3.53 (m, 4H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 30.0, 37.7, 44.7, 46.4, 49.5, 52.5, 57.7, 57.9, 175.5; IR (neat) 3380, 2930, 1630 cm^{-1}; MS (CI) *m/e* 187 (M^++1), 169, 71; HRMS calcd for $C_9H_{19}N_2O_2$ (M^++1): 187.1446, found 187.1443.

8-(3'-Hydroxypropyl)-1,4-dioxa-8-azaspiro[4.6]undecan-9-one (25). Clear oil (174 mg, 79%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 2H), 1.70-1.90 (m, 4H), 2.58 (m, 2H), 3.33 (m, 2H), 3.40-3.60 (m, 4H), 3.94-4.00 (m, 5H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 30.2, 31.4, 33.2, 38.1, 44.5, 44.8, 58.0, 64.6, 108.6, 176.3; IR (neat) 3400, 2940, 1620 cm^{-1}; MS (CI) *m/e* 230 (M^++1), HRMS calcd for $C_{11}H_{20}NO_4$ (M^++1)): 230.1392, found 230.1392.

2-(3'-Hydroxypropyl)-hexahydro-[2]-pyrindine-3,6-dione (26). Reaction of *cis*-bicyclo[3.3.0]octane-3,7-dione with 3-azido-1-propanol under the standard conditions gave 82 mg of **26** (54%): ^1H NMR (500 MHz, $CDCl_3$) δ 1.66 (m, 2H), 2.00-2.13 (m, 2H), 2.26 (dd, *J* = 6.1, 17.0 Hz, 1H), 2.42-2.53 (m, 2H), 2.65 (dd, *J* = 7.1, 17.1 Hz, 1H), 2.70-2.81 (m, 2H), 3.16 (dd, *J* = 7.0, 13.3 Hz, 1H), 3.40-3.55 (m, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 29.5, 31.8, 33.0, 34.9, 41.7, 43.5, 43.9, 49.4, 57.9, 170.8, 216.0; IR (CH_2Cl_2) 3400, 2940, 1735, 1620 cm^{-1}; MS (EI) *m/e* 211 (M^+), 193, 178, 167, 154, 110, 42; HRMS calcd for $C_{11}H_{17}NO_3$ (M^+): 211.1208, found 211.1207.

Additionally, 60 mg of a ca. 1:1 mixture of compounds **27** and **28** was isolated (30% yield). This mixture was acetylated to aid in purification. The mass spectrometry data clearly indicated a second Boyer reaction had occurred. It was not possible to assign specific NMR signals to each component of the mixture. However, some diagnostic peaks are: (1) two acetate signals at δ 1.962 and 1.965 in the ^1H NMR, (2) two sets of doublets of doublets at δ 2.22 and 2.28 and at δ 3.16 and 3.33 in the ^1H NMR, (3) two signals at δ 61.62 and 61.69 in the ^{13}C NMR, and (4) two signals for the acetate carbonyls at δ 167.74 and 167.79 in the ^{13}C NMR. Full characterization of this mixture is as follows: ^1H NMR (500 MHz, $CDCl_3$) δ 1.83-2.06 (m, 4H), 1.962 (s, 3H), 1.965 (s, 3H), 2.22 (dd, *J* = 7.0, 18.0 Hz, 1H), 2.28 (dd, *J* = 6.0, 17.0 Hz, 1H), 2.43-2.54 (m, 4H), 3.16 (dd, *J* = 7.0, 15.0 Hz, 1H), 3.33 (dd, *J* = 5.0, 13.0 Hz, 1H), 3.44-3.38 (m, 6H), 4.04 (m, 4H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 20.7, 26.10, 26.12, 28.9, 29.9, 30.4, 33.0, 34.0, 43.9, 47.8, 49.5, 61.6, 61.7, 167.7, 167.8, 170.7; IR (CH_2Cl_2) 2910, 1735, 1640 cm^{-1}; MS (EI) *m/e* 368 (M^+), 265, 249, 150, 43; HRMS calcd for $C_{18}H_{28}N_2O_6$ (M^+): 368.1947, found 368.1937.

6-Azido-5-hydroxyhexan-2-one (29a). A solution of 5-hexen-2-one (1.00 g, 10.2 mmol) in CH_2Cl_2 (120 mL) was cooled to -34 °C. Dimethyldioxirane (204 mL of a 0.1 M solution in acetone, 20.4 mmol) was added dropwise over 20 min. The reaction mixture was allowed to warm to room temperature over 5 h and was stirred at room temperature for an additional 17 h. The solution was concentrated to afford a clear oil (1.00 g, 8.77 mmol, 85%) which was used in the next step without further purification.

A solution of the crude epoxide (2.00 g, 17.5 mmol), sodium azide (1.47 g, 22.6 mmol) in H_2O (6 mL) and EtOH (25 mL) was refluxed for 1 h. The reaction mixture was cooled to room temperature, Et_2O (200 mL) was added, and the organic layer was separated, dried (anhydrous Na_2SO_4), filtered, and concentrated to afford a colorless oil. Flash chromatography (50% EtOAc/hexane) gave 1.42 g (51%) of **29a** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.60-1.80 (m, 2H), 2.15 (s, 3H), 2.58 (t, *J* = 7.4 Hz, 2H), 3.10-3.40 (m, 3H), 3.60 (br s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 27.7, 28.0, 39.9, 57.2, 71.2, 209.9; IR (neat) 3420, 2100, 1710 cm^{-1}.

5-Acetoxy-6-azidohexan-2-one (29b). A solution of alcohol **29a** (230 mg, 1.46 mmol), acetic anhydride (3.24 g, 31.7mmol), and pyridine (2.91 g, 36.7 mmol) was stirred at room temperature for 17 h. The reaction mixture was concentrated to afford a pale yellow oil. Flash chromatography (15% EtOAc/hexane) gave 214 mg (73%) of **29b** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.81-1.90 (m, 2H), 2.07 (s, 3H), 2.12 (s, 3H), 2.46 (t, *J* = 7.3 Hz, 2H), 3.34 (m, 2H), 4.97 (m, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 20.5, 25.2, 29.6, 38.6, 53.5, 71.6, 171.0, 207.0; IR (neat) 2100, 1710, 1740, 1230 cm^{-1}; MS (EI) *m/e* 200 (M^++1), 172, 140, 101, 84, 70; HRMS calcd for $C_8H_{14}N_3O_3$ (M^++1): 200.1047, found 200.1035.

1-Acetyl-3-acetoxypyrrolidine (30). A solution of the azide **29b** (0.11 g, 0.55 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C. TMSOTf (0.20 mL, 1.1 mmol) was added dropwise over 5 min. The ice bath was

removed and the reaction was allowed to warm to room temperature. Immediate gas evolution was noted. The reaction mixture was stirred at room temperature for an additional 16 h after which time it was diluted with additional CH_2Cl_2 (100 mL) and washed with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried (anhydrous Na_2SO_4), filtered, and concentrated to afford a clear oil. Flash chromatography (EtOAc) gave 74 mg (78%) of **30** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 & 2.02 (2 rotamers, s, 3H), 2.04 & 2.05 (2 rotamers, s, 3H), 2.08-2.18 (m, 2H), 3.40-3.72 (m, 4H), 5.30 (m, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 20.9, 22.1, 22.3, 30.0, 31.6, 43.3, 45.1, 51.2, 52.7, 72.2, 73.6, 170.0, 171.0; IR (neat) 1740, 1650, 1230 cm^{-1}; MS (EI) *m/e* 172 (M^++1), 111, 69; HRMS calcd for $C_8H_{14}NO_3$ (M^++1): 172.0947, found 172.0973.

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