Intramolecular Schmidt Reactions of Alkyl Azides with Ketones: Scope and Stereochemical Studies

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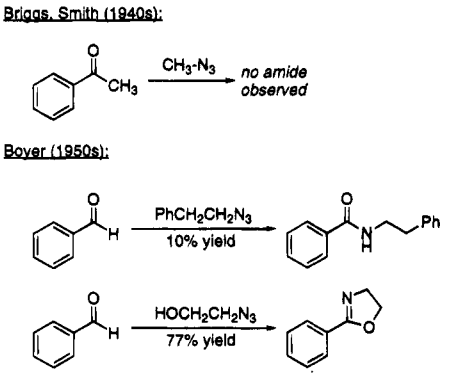
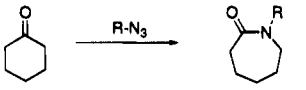
Received May 25, 1995[⊗]

Abstract: The intramolecular Schmidt reaction of alkyl azides and ketones has been demonstrated. The reaction is proposed to occur via initial attack of an azide on a ketone activated by a variety of protic or Lewis acids, including trifluoroacetic acid, titanium tetrachloride, and others. The resulting azidohydrin undergoes a direct rearrangement to afford the product amide and molecular nitrogen. When cyclic ketones are used, fused bicyclic lactams of types encountered in a wide variety of natural products are obtained. Although the distance allowed between the carbonyl group and the alkyl azide is quite restricted, the reaction is general with respect to the ketone component, including acyclic ketones and cyclic substrates ranging from standard to large ring sizes. The reaction also succeeds with aldehydes, although elimination or hydride migration products compete. In several cases examined, the reaction was found to proceed with retention of configuration at the migrating carbon. Competing reactions with β-diketones and α,β-unsaturated ketones were found to predominate over ring expansion.

Along with the Beckmann rearrangement, the Schmidt reaction is the most commonly used method for the conversion of an aldehyde or ketone to an amide (as illustrated for cyclohexanone in eq 1, R = H).[1] The power of this reaction would be greatly enhanced were it feasible to replace hydrazoic acid with an alkyl azide, which would extend its scope to directly provide N-substituted amides. Such a method would find its greatest utility in lactam synthesis (i.e., ring expansion chemistry), particularly when the lactam substituent R in eq 1 contains a stereogenic center directly bound to the amide nitrogen or is part of another ring system. A number of methods to effect the formal insertion of *N*-alkyl moieties into carbonyl compounds have been introduced. These include direct reactions of ketones with *N*-arylsulfonyloxy amines[2] and chloramines with cyclopropanones.[3] In addition, multistep methods involving oxaziridine[4] or nitrone[5] intermediates have been reported, including photochemical rearrangement reactions of tricyclic oxaziridines to give bicyclic lactams.[6] Still, a one-step process using readily available alkyl azides (R = alkyl, eq 1) would add a degree of simplicity and convenience to these methods.

Scheme 1





(1)

The potential of alkyl azides in insertion reactions was recognized during the heyday of Schmidt reaction development. In 1942, Briggs and co-workers attempted the reaction of methyl azide and sulfuric acid with one or more unspecified ketones and reported azide decomposition but no amide formation (Scheme 1).[7] A few years later, these results were confirmed by Smith, using acetophenone as the carbonyl component.[8,9] Smith also tried $AlCl_3$ as a Lewis acid. More assiduous attempts to utilize alkyl azides in Schmidt-type chemistry were made by Boyer and co-workers in the 1950s. Low yields of amide products could be obtained in the reactions of aromatic

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1995.

(1) Reviews of the Schmidt reaction: (a) Wolff, H. *Org. React.* **1946**, *3*, 307−336. (b) Uyeo, S. *Pure Appl. Chem.* **1963**, *7*, 269−283. (c) Smith, P. A. S. In *Molecular Rearrangements*; de Mayo, P., Ed.; John Wiley & Sons: New York, 1963; Vol. 1, pp 457−591. (d) Banthorpe, D. V. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley & Sons: London, 1971; pp 397−440. (e) Abramovich, R. A.; Kyba, E. P. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley & Sons: London, 1971; pp 221−329. (f) Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279−1300. (g) Krow, G. R. *Tetrahedron* **1981**, *37*, 1283−1307. (h) Kyba, E. P. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: Orlando, 1984; pp 2−34.

(2) (a) Hoffman, R. V.; Salvador, J. M. *Tetrahedron Lett.* **1989**, *30*, 4207−4210. (b) Hoffman, R. V.; Salvador, J. M. *Tetrahedron Lett.* **1991**, *32*, 2429−2432. (c) Hoffman, R. V. *Tetrahedron* **1991**, *47*, 1109−1135.

(3) (a) Wasserman, H. H.; Adickes, H. W.; Espejo de Ochoa, O. *J. Am. Chem. Soc.* **1971**, *93*, 5586−5587. (b) Wasserman, H. H.; Glazer, E. A.; Hearn, M. J. *Tetrahedron Lett.* **1973**, 4855−4858.

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(5) (a) Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Chem. Commun.* **1971**, 945−946. (b) Jeffs, P. W.; Molina, G. *J. Chem. Soc., Chem. Commun.* **1973**, 3−4. (c) Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1764−1767. (d) Prager, R. H.; Raner, K. D.; Ward, A. D. *Aus. J. Chem.* **1984**, *37*, 381−387.

(6) Johnson, G. P.; Marples, B. A. *Tetrahedron Lett.* **1985**, *26*, 4115−4118.

(7) Briggs, L. H.; De Ath, G. C.; Ellis, S. R. *J. Chem. Soc.* **1942**, 61−63.

(8) Smith, P. A. S. *J. Am. Chem. Soc.* **1948**, *70*, 320−323.

(9) After treatment of the reaction mixture with aqueous Br_2, tiny amounts of *p*-bromoacetanilide (≤2.6%) were isolated. Since *N*-methyl acetanilide is likely stable under acidic conditions, this product probably resulted from adventitious HN_3.

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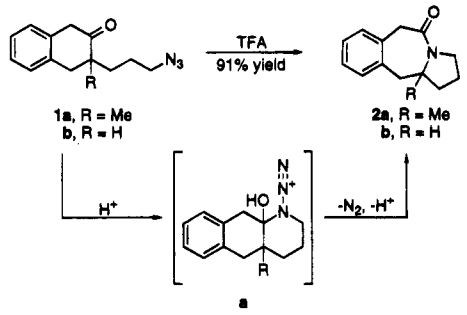
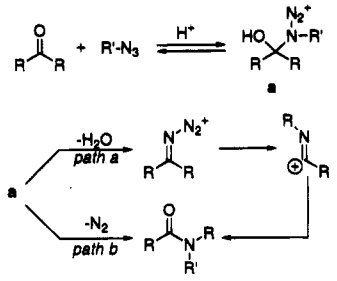
Scheme 2



Scheme 3



aldehydes with alkyl azides, but the reactions failed with a variety of ketones and aliphatic aldehydes.[10] Notably, the yields of these reactions were substantially improved when β- or γ-hydroxy azides were utilized, now yielding oxazolines or dihydrooxazines, respectively (Scheme 1). But again, the reactions failed when attempted with ketones. Some mechanistic implications of these experiments will be discussed in a later section of this paper.

In 1991, one of us (G.L.M.) attempted a previously unknown intramolecular variant of the Schmidt reaction, in which an alkyl azide was separated by four carbons from an aliphatic ketone. The results of this first experiment are given in Scheme 2.[11] Thus, dissolution of keto azide **1a** in trifluoroacetic acid (TFA) resulted in immediate gas evolution, which ceased after 10−15 min. A standard basic workup followed by flash chromatography resulted in a 91% yield of tricyclic lactam **2a**. Later, the analogous experiment lacking a methyl group (**1b** → **2b**) was carried out in the same yield. These experiments established without question the ability of alkyl azides and ketones to participate in Schmidt-type chemistry under appropriate conditions.

In analogy with all accepted mechanisms for the Schmidt reaction itself, the formation of an azidohydrin **a** in Scheme 2 was proposed. Although the Schmidt reaction of hydrazoic acid is often thought to involve the dehydration of similar azidohydrins (path a in Scheme 3), such a route is highly unlikely where $R' \neq H$. Therefore, the conversions of keto azides **1** to lactams **2** proved the viability of both alkyl azide addition to activated carbonyl compounds and the direct rearrangement of azidohydrins to afford amides (path b in Scheme 3).

This paper describes the results of our work on the intramolecular Schmidt reactions of alkyl azides with ketones and aldehydes. Specifically, we address the following questions: (1) What are the effects of ring size and tether length on the process? (2) Which reaction conditions effectively promote it? (3) What regiochemical rules can be formulated to predict the product of a given intramolecular Schmidt reaction? (4) Does the reaction proceed with retention of stereochemistry at the migrating carbon? And we will briefly consider (5): why did it take so long to discover such a facile reaction involving two garden-variety functional groups, especially considering the superficial resemblance of the process to the classical Schmidt reaction of hydrazoic acid and ketones?

It is important to recognize some work contemporaneous with our own. Most germane are the ongoing investigations by Pearson and co-workers on the closely related intramolecular reactions of alkyl azides with carbocations derived from alkenes.[12] Some conceptually related reactions involving the use of alkyl azides as nucleophiles in other processes have also been reported; the electrophilic partners include boranes,[13] carbocationic species,[14] carbenes,[15] and activated esters.[16] Ring expansions have been triggered by azide photolysis,[1d,e,h,17] alkyl azides can be reacted with ketones to give ring-expansion/fragmentation products,[18] and a formal nitrogen insertion product from an azide and C_{60} has been reported.[19]

Results

The Effects of Ring Size and Tether Length on the Reaction. Preparation of Substrates. An initial goal was to determine which bicyclic ring systems could be synthesized using the intramolecular variant of the Schmidt reaction. Relevant parameters are the ring size of the reacting ketone and the number of atoms between the reacting carbonyl group and the azido group. These issues were systematically examined as listed in Table 1.

The azidoalkyl side chains were appended to simple cycloalkanones by conversion of the starting ketone to the corresponding dimethylhydrazone, deprotonation with lithium diisopropylamide, and alkylation with 1-chloro-3-iodopropane, 1-chloro-4-iodobutane, or 1-iodo-3-bromobutane as appropriate (Scheme 4). In each case the iodide was cleanly displaced. The alkylated hydrazones were then hydrolyzed in acid, and the resulting ketones were treated with NaN_3 in DMF. All but four of the ketones in Table 1 were made in this way. Cyclobutanone **3a**

(10) (a) Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951−954. (b) Boyer, J. H.; Canter, F. C.; Hamer, J.; Putney, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 325−327. For the extension of this chemistry to ketones, including some examples that proceed with enantiotopic group selectivity, see: (c) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 8047−8048.

(11) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966.

(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*, 10183−10194. (c) Pearson, W. H.; Fang, W.-k.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682−2684.

(13) (a) Brown, H. C.; Midland, M. M.; Suzuki, A.; Sono, S.; Itoh, M. *J. Am. Chem. Soc.* **1971**, *93*, 4329−4330. (b) Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Am. Chem. Soc.* **1972**, *94*, 2114−2115. (c) Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Am. Chem. Soc.* **1973**, *95*, 2394−2396. (d) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151−7157. (e) Brown, H. C.; Salunkhe, A. M.; Singaram, B. *J. Org. Chem.* **1991**, *56*, 1170−1175. (f) Jego, J. M.; Carboni, B.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1992**, *129*, 554−565. (g) Noiret, N.; Youssofi, A.; Carboni, B.; Vaultier, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1105−1107. (h) Carboni, B.; Benalil, A.; Vaultier, M. *J. Org. Chem.* **1993**, *58*, 3736−3741. (i) Brown, H. C.; Salunkhe, A. M. *Tetrahedron Lett.* **1993**, *34*, 1265−1268.

(14) (a) Pritzkow, W.; Pohl, G. *J. Prakt. Chem.* **1963**, *20*, 132. (b) Wiberg, N.; Schmid, K. H. *Angew. Chem.* **1964**, *76*, 381.

(15) (a) Baldwin, J. E.; Patrick, J. E. *Chem. Commun.* **1968**, 968. (b) Szönyi, F.; Cambon, A. *Tetrahedron Lett.* **1992**, *33*, 2339−2342. (c) Moss, R. A.; Jang, E. G.; Krogh-Jespersen, K. *Tetrahedron Lett.* **1995**, *36*, 1409−1412.

(16) Bartra, M.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1992**, *33*, 3669−3672.

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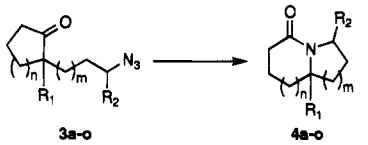
(19) Prato, M.; Li, C. Q.; Wudl, F.; Lucchini, V. *J. Am. Chem. Soc.* **1993**, *115*, 1148−1150.

Table 1. Reactions of Alicyclic Keto Azides

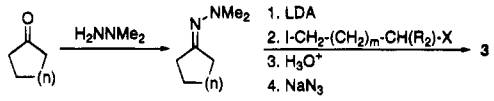


3a-o 4a-o

entry	compd[a]	*n*	*m*	R_1	R_2	conditions[b]	yield (%)[c]
1	**a**	0	1	Me	H	TFA, 0.25 h	66
2	**b**	1	1	H	H	TFA, 0.75 h	83
3	**b**					$TiCl_4$, 16 h	64
4	**c**	1	1	CO_2Me	H	TFA, 16 h	66
5	**c**					$TiCl_4$, 0.5 h	70
6	**d**	1	1	H	Me	$TiCl_4$, 16 h	68
7	**e**	1	2	H	H	$TiCl_4$, 16 h	56
8	**f**	2	0	H	H	TFA, 24 h	0[d]
9	**g**	2	1	H	H	TFA, 3.5 h	85
10	**h**	2	1	CO_2Et	H	TFA, 1 h	93
11	**i**	2	1	H	Me	TFA, 0.25 h	74
12	**j**	2	2	H	H	TFA, 16 h	0[d]
13	**j**					$BF_3{\cdot}OEt_2$, 16 h	29
14	**j**					$TiCl_4$, 16 h	91
15	**k**	2	3	H	H	$TiCl_4$, 16 h	0[d]
16	**l**	3	1	H	H	TFA, 3 h	80
17	**m**	3	2	H	H	$TiCl_4$, 16 h	0[d]
18	**n**	4	1	H	H	TFA, 16 h	96
19	**o**	8	1	H	H	TFA, 2 h	89

[a] All compounds were prepared in racemic form and, where applicable, as a mixture of diastereomers. [b] See text and Experimental Section for full descriptions of reaction conditions. [c] All yields are based on starting azide and refer to purified, chromatographically homogenous products. [d] Starting material recovered (≥50% yield).

Scheme 4



was prepared via application of the Trost spiroannulation procedure[20] to 6-azido-2-pentanone.[21] Keto esters **3c** and **3h** were prepared by direct alkylation of the stabilized enolate followed by azide displacement as described for the hydrazones, and **3f** was prepared from 3-allylcyclohexanone (see supporting information). The use of 1,ω-azidoiodoalkanes[22] as alkylating partners would be more convergent, but our preference has been to introduce the azide unit as late as possible for safety reasons.[23]

Intramolecular Schmidt reactions were attempted on 3-azidopropyl cyclic ketones containing 4−12 membered rings (Table 1). These reactions were generally successful and led to six different ring systems containing a nitrogen atom at a ring fusion, including the pyrrolizidine[24] and indolizidine[25] ring systems found in many natural products. The utility of this technique in the synthesis of medium (eight- and nine-membered) and large (13-membered) lactams is especially notable, given the need for general methods to provide these ring systems.[26]

In reactants lacking an electron-withdrawing substituent adjacent to the carbonyl group, immediate gas evolution was observed, and good results were obtained by merely dissolving the starting material in TFA at room temperature. The addition of a carbomethoxy substituent to the migrating carbon atom appeared to slow the reaction considerably in the case of compound **3c** (cf. entries 2 and 4), lengthing the reaction time from less than 1 h to more than 16. More than 90% of the starting azide was recovered when **3c** was allowed to react with TFA for only 1 h, which demonstrates the stability of the azide to acid in the absence of reaction with ketone. Although this effect appears to be attenuated in the cyclohexanone-containing substrate **3h**, this point was not vigorously pursued.[27] Still, these results provide some support for the mechanistic proposal in Scheme 2 (above), as they are inconsistent with an alternative mechanism whereby the azide undergoes acid-promoted conversion to a nitrene or nitrenium species which would then undertake C−C insertion.[1e,h,28] Given the high reactivity of nitrenes, one would expect that their formation would be rate-limiting and little affected by structural changes near the carbonyl group four atoms away.

The most readily accomplished ring-expansion reactions involved substrates containing four carbons between the carbonyl group and the azido subsitutuent. In these cases, the reaction proceeds through a presumably optimal six-membered cyclic azidohydrin intermediate, as shown in Scheme 2 above. Although formation of the analogous five-membered azidohydrin should also be facile, the reaction fails, presumably due to strain encountered en route to the expected azetidine product (entry 8, Table 1). In addition, lengthening the distance between carbonyl and alkyl azide to five carbons resulted in no reaction with TFA (entry 12). Significantly, the barriers associated with the longer tether could be substantially overcome by using a powerful Lewis acid to promote the reaction. Although $BF_3{\cdot}OEt_2$ was only moderately successful, $TiCl_4$ proved an excellent reagent for this purpose, affording a 91% yield of lactam **4j** (entry 14). A full equivalent of $TiCl_4$ is necessary, probably because the reagent remains bound to the lactam after nitrogen loss and rearrangement occur. $TiCl_4$ also turned out to be useful for accelerating at least one other recalcitrant example (cf. entries 4 and 5), but it is not a panacea: the synthesis of the [8.6.0]-azabicyclo system **4m** remains elusive.

Aromatic ketones are less reactive, as expected. Treatment of the 1-tetralone derivative **5** with TFA afforded only 15−21% of lactam, whereas the $TiCl_4$ conditions gave no product (with recovery of starting material). However, lactam **6** could be obtained in moderate yield using a triflic acid medium for the reaction (eq 2).

5 6

Regiochemistry. A key regiochemical concern is illustrated for the reaction of compound **3g** (Scheme 5). In the azidohydrin intermediate depicted, both bonds connected to the azidohydrin carbon might migrate to form lactam. Bond a, which is connected to the carbon bearing the azidopropyl side chain (i.e., the on-tether carbonyl substituent) would lead to fused lactam **4g**. Alternatively, migration of the off-tether carbonyl substituent connected to bond b would afford the bridged isomer shown. In contrast to the analogous intermediates formed by the

(20) Trost, B. M.; Scudder, P. H. *J. Am. Chem. Soc.* **1977**, *99*, 7601−7610.

(21) Wagner, P. J.; Scheve, B. J. *J. Am. Chem. Soc.* **1979**, *101*, 378−383.

(22) Khouki, M.; Vaultier, M.; Carrié, R. *Tetrahedron Lett.* **1986**, *27*, 1031−1034.

(23) **CAUTION**. Although we have not experienced any difficulties with the azides used in this paper, it is prudent to consider all alkyl azides as potential explosion hazards and to take appropriate precautions.

(24) Robins, D. J. *Adv. Heterocyclic Chem.* **1979**, *24*, 247−291.

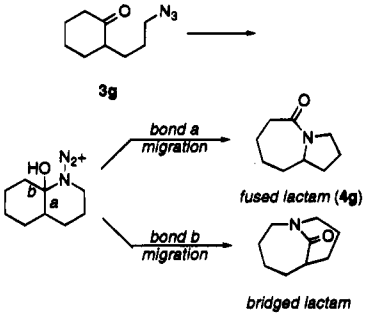
(25) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Daly, J. W., Spande, T. F., Eds.; John Wiley & Sons: New York, 1986; Vol. 4, pp 1−274.

(26) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131−9166.

(27) In another experiment, a yield comparable to that shown in entry 9 was obtained in less than 10 min of reaction time vs the 3.5 h shown in the table. In the latter case, given in the table, the experimentalist permitted the reaction to continue solely for the sake of convenience. This particular example is included here because the purity of the product obtained in it was of marginally better purity than that reported in our original disclosure.[11]

(28) Lwowski, W. *Nitrenes*; John Wiley & Sons: New York, 1970.

Scheme 5

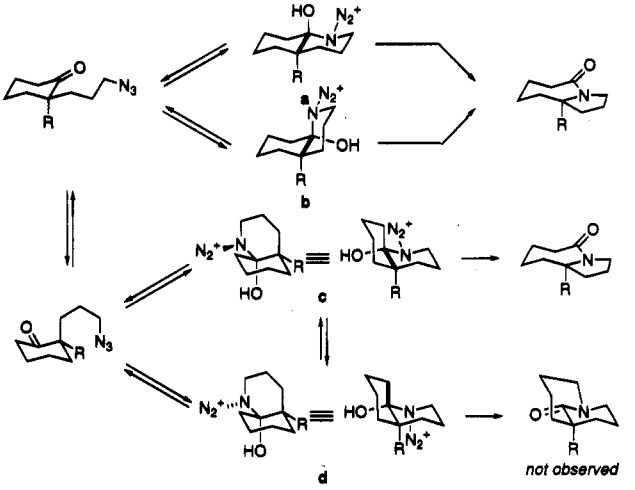


reactions of alkyl azides with cabocations,[12] migration of other substituents or skeletal rearrangements are unlikely due to the stability of the amide linkage formed in this step.

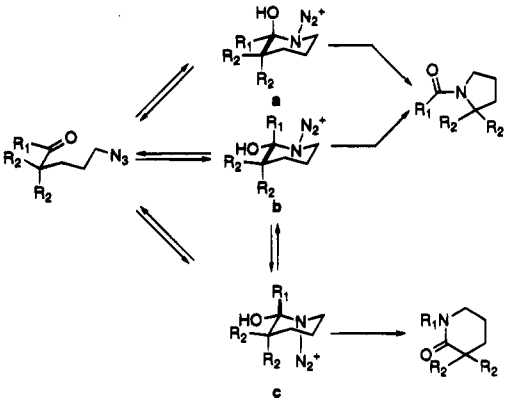
All evidence to date points to the exclusive formation of fused products. The assignment of fused products was generally evident from ^1H and ^{13}C NMR data. For example, the bridged isomers arising from ketones **3b** and **3c** would have symmetrical [3.3.1] ring systems that are ruled out by the ^{13}C NMR spectra of compounds **4b** and **4c**. In addition, NMR indicates three downfield protons adjacent to nitrogen, as opposed to four expected in the bridged isomers. The ^{13}C NMR carbonyl signals for the entire series of lactams appear between δ 167.8 and 175.2 (cf. values of 184−192 ppm reported for representative bridgehead lactams[29]). The 13-membered lactam **4o** exists as a mixture of cis/trans amide diastereomers,[30] with the methine proton adjacent to nitrogen appearing at δ 3.91 and 4.50 for the two isomers, respectively. These assignments were bolstered by infrared spectra. The $\nu_{C=O}$ in **4b**−**o** appears in the region of 1605−1636 cm^{-1}, as contrasted to the higher values ($\geq$1680 cm^{-1}) expected for the bridged amide isomers.[29] In one case (**2a**), an X-ray crystallographic study was carried out and confirmed the reported structure.[31]

The preference for regioselective migration of the on-tether substituent can be rationalized in several ways. Although calculations on these possible transition states have not been carried out, it is likely that the proximal nitrogen atom of the aminodiazonium ion intermediates has appreciable tetrahedral character in the transition state leading to product. The preponderance of the theoretical[32] and experimental[33] evidence available supports this supposition (see Pearson for an excellent discussion of this issue[12b]). If one assumes that chairlike azidohydrins are achieved when possible and that migration of an antiperiplanar substituent during nitrogen loss is preferred, transition states arising from four possible intermediates can be envisioned for the conversion of **3g** to **4g** (Scheme 6; cf. a related intermediate proposed for an intramolecular Baeyer−Villiger reaction[34]). The azidohydrins may be interconverted by reversion to keto azide or by nitrogen inversion. In this analysis, it is noteworthy that only transition state **d**, which has a pseudoaxial N_2^+ moiety, leads to bridged product. It may be

Scheme 6



Scheme 7



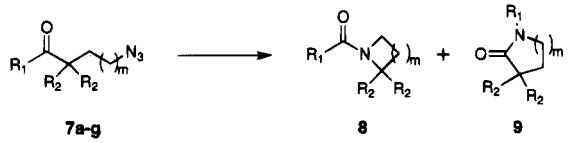
that this transition state is less favorable than alternatives **a**−**c**, so that products arising from it are not experimentally observed.[35]

Another explanation is that the bridged bicyclic amide is not accessible because of the instability of the amide linkage in that setting.[29] This would not be a factor in the rearrangements of acyclic carbonyl compounds, in which products resulting from migration of either carbon would have more nearly equal stability (Scheme 7). For keto azides separated by four carbons (the optimal arrangement in the cyclic series), migration of the tethered carbon could occur through either epimeric azidohydrin bearing an equatorial N_2^+ substituent (**a** and **b**). In contrast to the situation in Scheme 6 above, rearrangement of the off-tether substituent through intermediate **c** could provide six-membered lactam without encountering undue strain en route to product. Simplistically, the population of azidohydrin type **c** would be expected to increase with smaller R_1 substituents, like H. The results of a study addressing this issue are given in Table 2.

The behavior of aldehydes in these intramolecular Schmidt reactions differed markedly from that of ketones. For ketones in which the optimal four carbons intervened between the azide and carbonyl group, product arising from migration of the on-tether carbonyl substituent (i.e., **8**) always predominated. Although we cannot absolutely rule out small (<5%) amounts of products **9** from these reactions, their presence was not evident from examination of the crude reaction mixtures. However, increased amounts of product resulting from migration of R_1 could be observed when that substituent was a hydrogen,

(29) Greenberg, A. In *Structure and Reactivity*; Greenberg, A., Ed.; VCH: New York, 1988; pp 139−178.
(30) Lövy, J.; Dybal, J.; Puffr, R.; Doskocilová, D. *J. Mol. Struct.* **1980**, *66*, 301−308.
(31) Takusagawa, F. Unpublished results.
(32) (a) Cacase, F.; Attinà, A.; De Petris, G.; Grandinetti, F.; Speranza, M. *Gazz. Chim. Ital.* **1990**, *120*, 691−700. (b) Glaser, R.; Choy, G. S.-C. *J. Phys. Chem.* **1991**, *95*, 7682−7693. (c) Glaser, R.; Choy, G. S.-C. *J. Am. Chem. Soc.* **1993**, *115*, 2340−2347.
(33) (a) Mertens, A.; Lammertsma, K.; Arvanaghi, M.; Olah, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 5657−5660. (b) Christe, K. O.; Wilson, W. W.; Dixon, D. A.; Khan, S. I.; Bau, R.; Metzenthin, T.; Lu, R. *J. Am. Chem. Soc.* **1993**, *115*, 1836−1842.
(34) Chandreasekhar, S.; Deo Roy, C. *Tetrahedron Lett.* **1987**, *28*, 6371−6372.
(35) However, in one case, calculations carried out with MOPAC inidicated that an axially disposed aminodiazonium ion was more stable than its equatorial isomer.[12b]

Table 2. Reactions of Acyclic Keto Azides

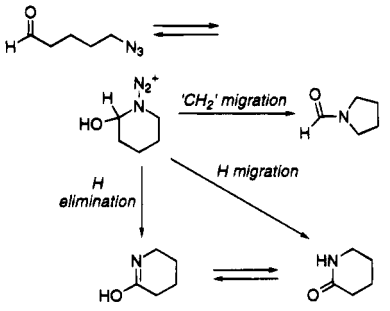


7a-g **8** **9**

entry	compd[a]	*m*	R_1	R_2	Lewis acid[b]	yd of **8** (%)	yd of **9** (%)
1	**a**	1	H	Ph	TFA		29
2	**b**	1	Me	H	TFA	0[c]	0[c]
3	**c**	1	$PhCH_2$	H	TFA *or* $TiCl_4$	0[d]	0[d]
4	**d**	2	H	Ph	TFA	81	8
5	**d**				$AlCl_3$	69	8
6	**d**				$SnCl_4$	59	15
7	**d**				$ZnCl_2$	48	17
8	**d**				TMSOTf	61	22
9	**e**	2	Me	H	TFA	75	
10	**f**	2	MeO_2CCH_2	H	TFA	69	
11	**g**	2	Ph	H	TFA	77	

[a] Details for the preparation of compounds **7a−g** are given in the supporting information [b] See Experimental Section for detailed conditions. [c] No nonvolatile products were isolated. [d] Starting material recovered (60−70% yield), with no evidence for formation of **8** or **9**.

Scheme 8



i.e., when aldehydes were subjected to the reaction conditions. Table 2 lists a number of Lewis acids that were used to promote this process; the ratios of **8/9** ranged from 8:1 to 3:1 depending upon conditions. As might be expected, the conversion **7a** → **9a** occurred in 29−30% yield without the formation of azetidine **8a** (although such a ring contraction has been observed in oxaziridine chemistry[36]). On one hand, it is conceivable that a hydrogen is the only substituent small enough to permit reaction through transition state **c** in Scheme 7. However, an azidohydrin formed from an activated aldehyde does have another mechanistic pathway available to it (Scheme 8). Thus, whereas direct migration of either the ring methylene group or a hydride could directly afford expected products, an elimination reaction would also give the product of hydride migration by way of the hydroxyimine tautomer depicted. A boda fide E2 elimination would also be facilitated by a conformation like **c** in Scheme 7. The Schmidt reactions of hydrazoic acid with aldehydes generally afford nitriles, which might arise from proton/N_2 elimination from an iminodiazonium ion, instead of amides. This, combined with the rare observation of H migration in closely related processes,[12b,37] leads us to favor the elimination/tautomerization pathway shown. Overall, the reluctance of the off-tether substituent to migrate in ketones **7a,e,f** may well reflect the operation of stereoelectronic preferences in these reactions, i.e., the migration of a C−C bond antiperiplanar to a favorably disposed N_2^+ moiety.

Stereochemistry of the Migrating Carbon. Migration reactions to electron-deficient heteroatomic species generally occur with retention of configuration at the migrating carbon.[1,38,39] We wanted to test the stereochemical outcome of the intramolecular Schmidt reaction; the first-generation experiment, in which the migration of a quaternary carbon was examined, is shown in Scheme 9. The known keto ester **10**, derived in enantiomerically enriched form from 2-methylcyclohexanone using a Pfau/d'Angelo "deracemization" sequence,[40] was converted to keto azide **12** using the sequence shown. (Note that it is possible to deprotect the carbonyl group without triggering the intramolecular Schmidt reaction using $LiBF_4$ in wet acetonitrile.[41]) The azide was thus obtained in 91% ee as determined by ^1H NMR using $Eu(hfc)_3$. Dissolution of **12** in TFA followed by the standard workup afforded lactam **13** in 87% yield ($[\alpha]_D = +10.7$ (*c* 1.35, EtOH)) and 89% ee (^1H NMR, (*R*)-2,2,2-trifluoro-1-(9′-anthryl)ethanol). That the reaction occurred with retention of configuration, as opposed to a highly unlikely inversion of same, was demonstrated by preparing **13** using the classical Schmidt reaction of **14**. The Schmidt reaction is well-known to proceed with retention of configuration.[42] Interestingly, the conversion of **14** → **15** affords the predicted product in only 42% yield, accompanied by its regioisomer and a tetrazole byproduct, which stands in sharp contrast to the highly efficient and selective transformation of **12** to **13**. Samples of **13** prepared via **14** had $[\alpha]_D = +10.4$ (*c* 1.38, EtOH). The preparation of (+)-**13** by either route confirmed that this intramolecular Schmidt reaction proceeded with retention of configuration.

Another stereochemical issue must be considered when the stereogenic carbon adjacent to the reacting ketone can enolize during the course of the reaction (Scheme 10). In such cases, it is possible that the strongly acidic reaction medium could cause epimerization to compete with rearrangement, rendering the point of retention or inversion a moot one. Two diastereomeric ketones, **16a** and **16b**, were prepared to address this issue. The diastereomers were identified on the basis of ^{13}C NMR. The C-4 methine carbon in the trans diastereomer **16b** appeared at 41.2 ppm, upfield of the corresponding carbon in **16a** (47.1 ppm), as expected for the isomer bearing an axial C-2 substituent. Should epimerization occur at an appreciable rate relative to ring expansion, crossover between the two possible reaction products would be observed. However, the conversions of **16a** → **17a** and **16b** → **17b** occurred cleanly and to the exclusion of one another under the conditions depicted. For a more direct comparison, treatment of **16b** with TFA gave 79% of **17b** contaminated with ca. 6% of **17a**. Therefore, at least in this system, enolization was not a serious problem. Incidentally, the high yield of lactam from **17b**, in which the tethering arm is axial, is circumstantial evidence for the accessibility of azidohydrin **c** in Scheme 6 (i.e., a *cis*-fused decalin-type intermediate).

Additional examples of stereoselective intramolecular Schmidt reactions have been reported by us (eq 3)[43] and the d'Angelo group (eq 4).[44] Although we suspect that Schmidt reactions that would scramble epimerizable centers could be found (particularly when less reactive azidoketones are used), the

(36) (a) Parello, J.; Rivière, M.; Desherces, E.; Lattes, A. *C. R. Hebd. Seances Acad. Sci., Ser. C.* **1971**, *275*, 1097−1100. (b) Black, D. S. C.; Watson, K. G. *Aus. J. Chem.* **1973**, *26*, 2505−2513.

(37) Abramovitch, R. A.; Jeyaraman, R. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: Orlando, FL, 1984; pp 297−357.

(38) Gawley, R. E. *Org. React.* **1988**, *35*, 1−420.

(39) Krow, G. R. *Org. React.* **1993**, *43*, 251−798.

(40) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273−274.

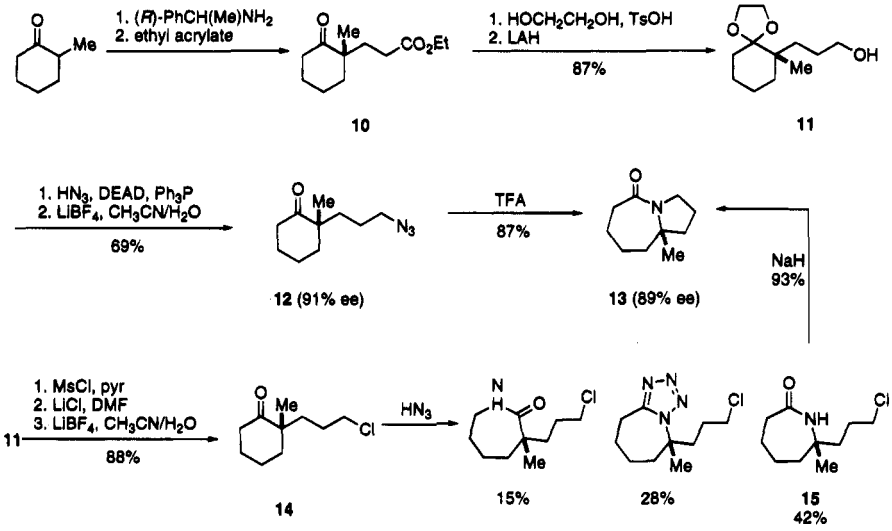
(41) Lipshutz, B. H.; Harvey, D. F. *Synth. Commun.* **1982**, *12*, 267−277.

(42) Georg, G. I.; Guan, X.; Kant, J. *Tetrahedron Lett.* **1988**, *29*, 403−406 and references contained therein.

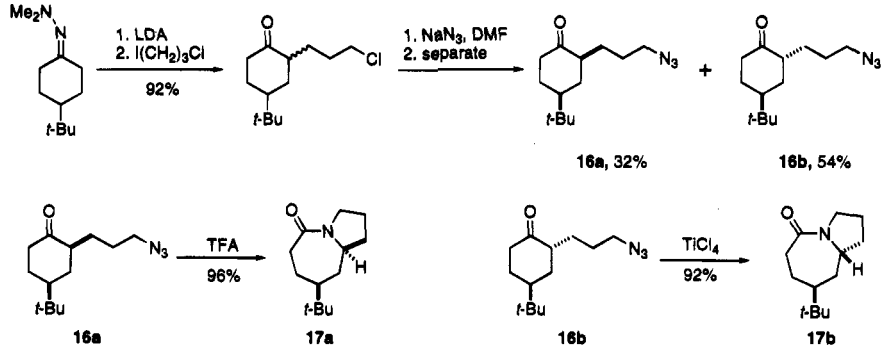
(43) Aubé, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141−1147.

(44) Le Dréau, M.-A.; Desmaële, D.; Dumas, F.; d'Angelo, J. *J. Org. Chem.* **1993**, *58*, 2933−2935.

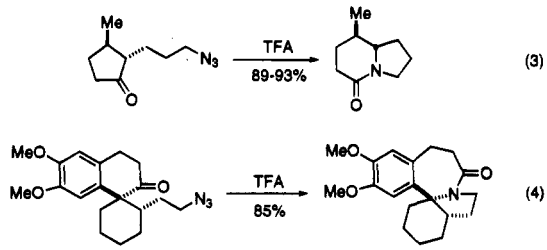
Scheme 9



Scheme 10



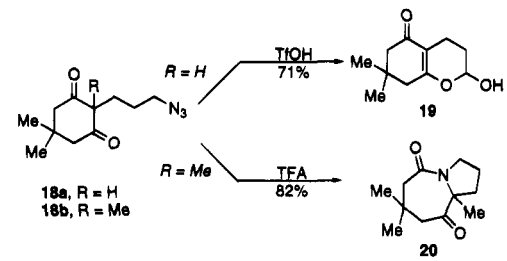
above results are encouraging vis à vis the use of this reaction in natural product synthesis.



Problematic Examples and Side Reactions. An honest inventory of the scope of this new reaction requires disclosure of substrate types that have, so far, been uncooperative. Several examples have already been presented: any substrate that requires the formation of an azetidine ring (entry 8, Table 1 and entries 1−3, Table 2), compounds with too long a tether (entry 15, Table 1), or certain combinations of medium-ring ketones and medium tethers (entry 17, Table 1). Aryl ketones are certainly less reactive, although moderate success has been achieved under more forcing conditions (see eq 2).

At this juncture, an important limitation involves reactions of substrates including some type of olefinic linkage. The first example involves a highly enolized β-diketone system **18a**[45] (Scheme 11). In this case, no ring-expansion product was observed under any conditions tried but only material derived from azide hydrolysis to aldehyde.[1e] That this was due to the presence of enol and not the reluctance of a carbonyl carbon to migrate was established by comparing this result to that of the corresponding dialkylated diketone **18b**,[45] which smoothly afforded lactam **20** when subjected to similar conditions (also cf. entry 10, Table 2).

Scheme 11



The specific issue of enone compatibility with the intramolecular Schmidt reaction was examined using keto azide **21**[45] (Scheme 12). Instead of attacking the protonated enone at the ketone carbonyl, the azide apparently adds to the unsaturated system in a conjugate fashion as shown (note the use of TMSOTf as the Lewis acid). Nitrogen loss followed by tautomerization would account for the observed product **22**, which was obtained in moderate yield. Attempted ring adjustment of **23** resulted in decomposition of starting material and was not pursued.[46] The Schultz[47] and Sha[48] groups have reported thermal conversions of azidoenones to formal Schmidt-type products. However, H_2SO_4 treatment of an azidoenone derived from isophorone epoxide resulted only in hydrolysis of the azide moiety to an aldehyde.[47a] These results are fully

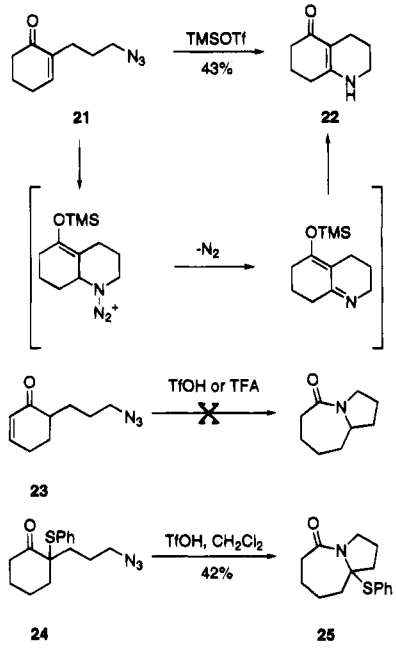
(45) The preparation of this compound is given in the supporting information.

(46) Mossman, C. J. Unpublished work from this laboratory.

(47) (a) Schultz, A. G.; Ravichandran, R. *J. Org. Chem.* **1980**, *45*, 5008−5009. (b) Schultz, A. G.; McMahon, W. G. *J. Org. Chem.* **1984**, *49*, 1676−1678.

(48) (a) Sha, C.-K.; Ouyang, S.-L.; Hsieh, D.-Y.; Hseu, T.-H. *J. Chem. Soc., Chem. Commun.* **1984**, 492−494. (b) Sha, C.-K.; Ouyang, S.-L.; Hsieh, D.-Y.; Chang, R.-C.; Chang, S.-C. *J. Org. Chem.* **1986**, *51*, 1490−1494.

Scheme 12



consistent with our own, and together the data support the contention[47a] that the thermal reactions occur by a different mechanism from that proposed for the acid-catalyzed process.

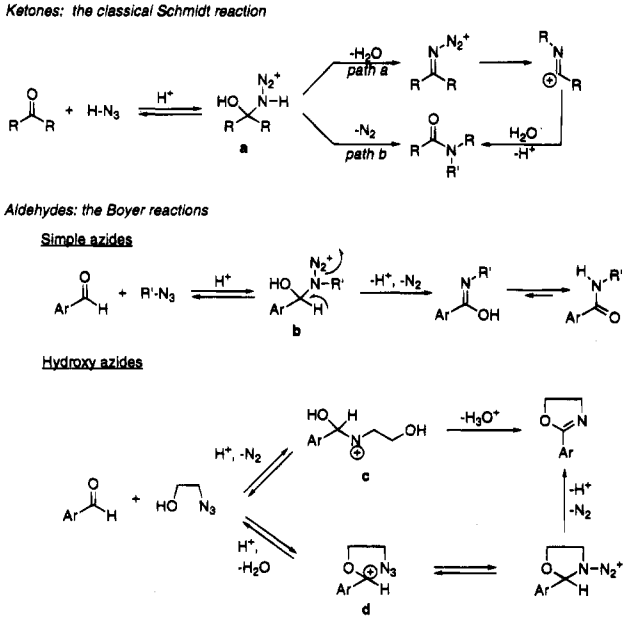
Scheme 12 depicts one possible approach to olefin-containing lactams. The 2-azidopropyl-2-thiophenyl compound **24** gave lactam **25** in 42% unoptimized yield using 1.5 equiv triflic acid in methylene chloride. The thiophenyl group could be oxidized and eliminated to afford olefin, but the regiochemistry of the reaction would presumably be substrate-dependent. We are continuing our efforts to find conditions to effect intramolecular Schmidt reactions of enones or to find useful synthetic equivalents of the process.

Discussion

Given the very high utilization of the Schmidt reaction in synthesis and the ubiquity of ketones and alkyl azides (often in the same molecule![49]), it is pertinent to briefly review the circumstances behind the seemingly late discovery of the intramolecular Schmidt reaction (and an effective intermolecular version; see below). Indeed, the recognition of the possibility of alkyl azides functioning in place of hydrazoic acid was clearly recognized and tested by Briggs and Smith in the 1940s (Scheme 1).[7,8] These results were echoed by the efforts of Boyer in the 1950s, whose sole success with a simple alkyl azide was the 10% yield of *N*-(2-phenylethyl)benzamide obtained from the reaction of phenylethylazide and benzaldehyde, but even benzaldehyde gave no insertion product when treated with *n*-butyl or benzyl azide.[10]

Mechanistically, the classical Schmidt reaction has been formulated along the lines summarized in Scheme 13.[1,8,50] Most commonly, the reaction has been thought to involve the elimination of water to afford the diazoimmonium species shown in path a, which then undergoes Beckmann-like rearrangement and rehydration to give amide, although some authors have expressed a preference for the alternative direct rearrangement

Scheme 13



(path b).[51] Although dehydration is unlikely with the initial adduct **b** from the reaction of an alkyl azide with an aldehyde (it would afford a dication), elimination of the aldehyde proton and nitrogen gas directly leads to the hydroximine tautomer of the amide. Although the reported yield of this process was low, such a mechanism would explain the regiochemistry of the reaction. The higher yields of oxazolines and dihydrooxazines when 1,2- and 1,3-hydroxy azides were used were rationalized by the greater stability of the azide reactants in H_2SO_4 by these authors, who proposed nitrenium ion **c** as an intermediate. Only in retrospect does it appear more likely that the hydroxy end attacks first to give a hemiketal (not shown) which undergoes elimination to afford **d**. Intramolecular attack of azide on the carbocation,[12] again followed by elimination and N_2 ejection, gives the product heterocycles.[10c]

This prior art strongly suggested that further attempts to replace hydrazoic acid with alkyl azides in a Schmidt-type process would be problematic at best. In addition, the dominance of the dehyration mechanism for the Schmidt reaction (path a, Scheme 13) might conceivably have further dissuaded chemists from attempting alkyl-Schmidt reactions, since such processes would necessarily involve a direct rearrangement pathway, which although possible, had not been unambiguously demonstrated. It turns out, however, that the intermolecular reaction of alkyl azides and ketones can be promoted by $TiCl_4$ in certain cases, but a number of other conditions, including TFA, fail.[52] In our opinion, there is no doubt that Briggs, Smith, or Boyer would have succeeded in discovering the Schmidt reaction of alkyl azides if either $TiCl_4$ or intramolecular reactions enjoyed the popularity in the 1940s and 1950s that they do today. In addition, it is worth noting that these authors almost always used aromatic ketones or aldehydes as their carbonyl components, which give some of the worst results even in intramolecular cases.

So why does the intramolecular Schmidt reaction proceed so spectacularly under conditions so unfavorable to its intermolecular counterpart? The success of the intramolecular

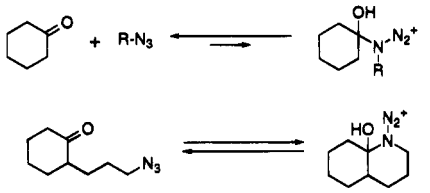
(49) For just a few examples of azidoketones prepared for other purposes, see: (a) Lambert, P. H.; Vaultier, M.; Carrié, R. *J. Chem. Soc., Chem. Commun.* **1982**, 1224–1225. (b) Vaultier, M.; Lambert, P. H.; Carrié, R. *Bull. Soc. Chim. Fr.* **1986**, 83–92. (c) Kajimoto, T.; Chen, L.; Liu, K. K.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6678–6680.

(50) For an excellent discussion of the mechanism of the classical Schmidt reaction, see: Sprecher, M.; Kost, D. *J. Am. Chem. Soc.* **1994**, *116*, 1016–1026.

(51) (a) Di Maio, G.; Permutti, V. *Tetrahedron* **1966**, *22*, 2059–2067. (b) Bhaleao, U. T.; Thyagarajan, G. *Can. J. Chem.* **1968**, *46*, 3367–3374. (c) Sasaski, T.; Eguchi, S.; Toru, T. *J. Org. Chem.* **1970**, *35*, 4109–4114. (d) Fikes, L. E.; Shechter, H. *Tetrahedron Lett.* **1976**, 2525–2528. (e) Fikes, L. E.; Shechter, H. *J. Org. Chem.* **1979**, *44*, 741.

(52) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635–1637.

Scheme 14



reaction does finally confirm the viability of direct rearrangement, so a distinct preference for the dehydration mechanism cannot be the reason.[53] The most likely explanation arises from the relative propensity of azidohydrin formation to occur in inter- vs intramolecular reactions (Scheme 14). In the former case, weakly nucleophilic alkyl azides are reluctant to add to ketones unless very strongly activated by a Lewis acid,[52] as opposed to protic acid solutions. This tendency is counteracted by rendering the reaction intramolecular, which diminishes the entropic cost of azidohydrin formation. The increased reactivity of hydrazoic acid vs alkyl azides in an intermolecular sense is not clear, although the latter reactions are extremely sensitive to even modest steric effects on the carbonyl group and the azide.[52] In addition, the relative facility of the intermolecular Schmidt reaction may in fact be due the availability of pathway a (Scheme 13) with hydrazoic acid but not for alkyl azides.[53b]

Summary

The intramolecular Schmidt reaction of alkyl azides and ketones has been demonstated. Although the distance allowed between the carbonyl group and the alkyl azide is quite restricted, the reaction is general with respect to the ketone component, including acyclic ketones and cyclic substrates ranging from standard to large ring sizes. The reaction also succeeds with aldehydes, although elimination or hydride migration products compete. In several cases examined, the reaction was found to proceed with retention of configration at the migrating carbon. Competing reactions with β-diketones and α,β-unsaturated ketones predominated over ring expansion. A mechanistic analysis suggests that these reactions proceed via an intermediate azidohydrin which rearranges directly to amide, possibly under stereoelectronic control. Work to extend the scope of this reaction and to apply it to problems in chemical synthesis continue.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-500 Aspect 3000 (500 and 125.5 MHz, respectively), QE 300, or a Varian XL 300 (300 and 75.6 MHz, respectively) instrument. Chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane with either TMS or residual solvent as an internal reference. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer. Low resolution mass spectra (EI, electron impact or CI, chemical ionization) were obtained using Ribermag R10-10 quadrupole instrument, and high resolution mass spectra (HRMS) were obtained using VG Analytical ZAB double focusing spectrometer. CD measurements were made on an Aviv 60DS spectrometer at ambient temperature. Optical rotations were taken on a Perkin-Elmer 241 polarimeter at ambient temperature; the concentrations are reported in g/dL. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were carried out in-house. Column chromatography was carried out with 230−400 mesh silica gel. THF and CH_2Cl_2 were distilled from sodium benzophenone ketyl and CaH_2 before use. Other reagents were purchased from Aldrich and used as received.

General experimental conditions are described in the context of individual experiments and are designated by bold type in titles of the appropriate procedures. Unless otherwise noted, all compounds were obtained as colorless or light yellow oils.

1-Carbomethoxy-3-(3′-azidopropyl)-3-methyl-2-tetralone (1a). Diisopropylamine (0.71 mL, 5.1 mmol) was dissolved in THF (5 mL), and the solution was chilled in an ice bath. *n*-Butyllithium (2.16 mL of a 2.28 M solution in hexane, 4.93 mmol) was added, and the solution was stirred for 10 min. A solution of 1-carbomethoxy-3-methyl-2-tetralone[54] (0.500 g, 2.29 mmol) in THF (2 mL) was added via cannula. The ice bath was removed. After 1 h, the ice bath was replaced, and 1-chloro-3-iodopropane (0.31 mL, 2.9 mmol) was added. After 45 min, ether (200 mL) was then added, and the solution was washed with 10% citric acid (1 × 25 mL) and concentrated to give an oil. The oil was combined with concentrated HCl (25 mL), and the heterogeneous mixture was allowed to reflux for 1 h, cooled, and diluted with water (25 mL). The mixture was extracted with ether (1 × 200 mL) and washed with saturated $NaHCO_3$ (1 × 25 mL), 20% $Na_2S_2O_3$ (1 × 10 mL), and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The oil was dissolved in DMF (5 mL), and NaN_3 (0.744 g, 11.45 mmol) was added. The heterogeneous mixture was stirred and heated at 80 °C for 2 h. The cooled mixture was taken up in ether (200 mL) and washed with water (2 × 25 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by flash chromatography (10% ethyl acetate/hexane) to give **1a** (0.424 g, 76% yield) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.45−1.60 (m, 4H), 2.83 (d, J = 15.5 Hz, 1H), 3.00 (d, J = 15.5 Hz, 1H), 3.16−3.24 (m, 2H), 3.55 (d, J = 17.1 Hz, 1H), 3.64 (d, J = 17.1 Hz, 1H), 7.08−7.14 (m, 1H), 7.15−7.25 (m, 3H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 22.5, 23.6, 34.3, 40.9, 44.1, 45.9, 51.6, 126.9, 127.0, 127.5, 128.0, 132.7, 135.1, 213.2; IR (neat) 2920, 2085, 1704 cm^{-1}. Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.10; H, 7.04; N, 17.27. Found: C, 69.04; H, 7.40; N, 17.16.

General Method for Keto Azide Preparation: 2-(3′-Azidopropyl)cyclohexanone (3g). Diisopropylamine (1.20 mL, 8.57 mmol) was dissolved in THF (10 mL), and the solution was cooled in ice. *n*-Butyllithium (4.17 mL of a 1.97 M solution in cyclohexane, 8.21 mmol) was added, and the solution was stirred for 10 min. Cyclohexanone dimethylhydrazone (1.13 mL, 7.14 mL) was added dropwise over 1 min, and the solution was stirred for 10 min. 1-Chloro-3-iodopropane (0.96 mL, 8.9 mmol) was then added. After 1 h, the reaction mixture was poured into a mixture of ether (150 mL) and 2 N H_2SO_4 (25 mL). The mixture was stirred vigorously. After 15 min, the organic layer was separated and washed with brine (1 × 50 mL), dried (Na_2SO_4), and concentrated to give an oil. The crude product was purified by flash chromatography (5% ethyl acetate/hexane) to give 2-(3′-chloropropyl)cyclohexanone (1.05 g, 85% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20−1.50 (m, 2H), 1.50−1.96 (m, 5H), 1.98−2.20 (m, 2H), 2.22−2.35 (m, 3H), 3.28 (dt, J = 2.7, 6.8 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.9, 26.8, 27.9, 30.2, 34.0, 41.9, 45.0, 49.9, 212.6; IR (neat) 2920, 1705 cm^{-1}. Anal. Calcd for $C_9H_{15}ClO$: C, 61.89; H, 8.66. Found: C, 61.58; H, 9.00.

2-(3′-Chloropropyl)cyclohexanone (0.800 g, 4.60 mmol) and NaN_3 (1.49 g, 23.0 mmol) were combined in DMF (8 mL), and the mixture was heated at 80 °C for 2.5 h. Ether (200 mL) was added, and the mixture was washed with water (2 × 25 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by flash chromatography (10% ethyl acetate/hexane) to give **3g** (0.821 g, 99% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20−1.48 (m, 2H), 1.50−1.73 (m, 4H), 1.73−1.93 (m, 2H), 1.97−2.18 (m, 2H), 2.22−2.45 (m, 3H), 3.28 (dt, J = 2.0, 7.1 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.9, 26.5, 26.6, 27.9, 33.9, 42.0,

(53) (a) However, one must not extend this realization too far with respect to the classical Schmidt reactions of hydrazoic acid. Although path b (Scheme 13) must now be considered a possibility in that case, the competency of iminodiazonium species in the Schmidt reaction has been recently demonstrated, and much evidence still strongly suggests that path a is favored in the HN_3 reactions: Richard, J. P.; Amyes, T. L.; Lee, Y.-G.; Jagannadham, V. *J. Am. Chem. Soc.* **1994**, *116*, 10833−10834. (b) We thank a referee for pointing out the possible role of path a in facilitating the intermolecular reactions of hydrazoic acid vs alkyl azides.

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50.2, 51.5, 212.6; IR (neat) 2925, 2080, 1704 cm^{-1}. Anal. Calcd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19. Found: C, 59.40; H, 8.71; N, 22.80.

2-Carbomethoxy-2-(3′-azidopropyl)cyclopentanone (3c). 80% NaH/mineral oil (0.232 g, 7.75 mmol) was washed with hexane (2 × 5 mL) and suspended in dry dimethoxyethane (8 mL). Then 2-carbomethoxycyclopentanone (0.870 mL, 7.04 mmol) was added dropwise; gas evolution and formation of a precipitate was noted. 1-Chloro-3-iodopropane (0.945 mL, 8.80 mmol) was added, and the mixture was allowed to reflux. After 20 h, the solution was cooled, ether (200 mL) was added, and the solution was washed with 0.65 M $NaHCO_3$ (1 × 50 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The crude product was dissolved in DMF (8 mL) and NaN_3 (0.373 g) was added. The mixture was heated at 80 °C for 3 h. Ether (200 mL) was then added, and the mixture was washed with water (1 × 25 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by flash chromatography (25% ethyl acetate/hexane) to give **3c** (1.11 g, 70% yield): ^1H NMR (300 MHz, CDCl3) δ 1.43−1.61 (m, 1H), 1.61−1.78 (m, 2H), 1.82−2.12 (m, 4H), 2.21−2.37 (m, 1H), 2.37−2.49 (m, 1H), 2.49−2.61 (m, 1H), 3.29 (t, J = 6.2 Hz, 2H), 3.72 (s, 3H); ^{13}C NMR (75.6 MHz, CDCl3) δ 19.5, 24.3, 30.9, 33.0, 37.8, 51.3, 52.5, 59.8, 171.2, 214.3; IR (neat) 2950, 2090, 1746, 1720 cm^{-1}. Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 54.05; H, 6.71; N, 18.91. Found: C, 53.68; H, 6.90; N, 18.80.

2-(4′-Azidobutyl)cyclopentanone (3e). 80% NaH/mineral oil (0.362 g, 10.9 mmol) was washed with hexane (2 × 5 mL), suspended in dry dimethoxyethane (10 mL), and chilled in ice. Then 2-carbomethoxycyclopentanone (1.40 mL, 9.88 mmol) was added dropwise; gas evolution and formation of a precipitate was noted. After 40 min, 1-chloro-3-iodopropane (1.52 mL, 12.4 mmol) was added, and the mixture was allowed to reflux. After 20 h, the solution was cooled, ether (200 mL) was added, and the solution was washed with saturated Na_2CO_3 (1 × 25 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The crude product was suspended in concentrated HCl (25 mL) and refluxed overnight. Water (25 mL) was added, and the solution was extracted with CH_2Cl_2 (1 × 200 mL). The organic layer was washed with water (2 × 25 mL), 20% $Na_2S_2O_3$ (1 × 25 mL), dried (Na_2SO_4), and concentrated to give an oil. The oil was dissolved in DMF (10 mL), and NaN_3 (3.21 g, 49.4 mmol) was added. The mixture was heated at 80 °C for 2.5 h. Ether (200 mL) was then added, and the mixture was washed with water (1 × 50 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by flash chromatography (10% ethyl acetate/hexane) to give **3e** (0.997 g, 56% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 1.20−1.36 (m, 1H), 1.37−1.59 (m, 4H), 1.71−1.89 (m, 2H), 1.95−2.49 (m, 4H), 3.28 (t, J = 6.8 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 20.5, 24.5, 28.7, 29.0, 29.4, 37.9, 48.7, 51.0, 220.8; IR (neat) 2930, 2090, 1730 cm^{-1}. Anal. Calcd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19. Found: C, 59.45; H, 8.68; N, 23.36.

Lactam 2a. General Method for Intramolecular Schmidt Reaction with TFA. Keto azide **1a** (0.100 g, 0.412 mmol) was dissolved in TFA (5 mL) at room temperature, and the solution was stirred; gas evolution was observed. After 20 min, the solution was concentrated. Ether or ethyl acetate (100 mL) was added, and the solution was washed with $NaHCO_3$ (1 × 25 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by flash chromatography (ether, then ethyl acetate) to give **1a** (0.081 g, 91% yield) as a solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.73−2.30 (4), 3.10 (AB q, J = 14.6 Hz, $\Delta\nu$ = 34.2 Hz, 2H), 3.37−3.50 (m, 1H), 3.61−3.72 (m, 1H), 3.77 (AB q, J = 15.5 Hz, $\Delta\nu$ = 29.4 Hz, 2H), 7.05−7.13 (m, 1H), 7.13−7.25 (m, 3H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 19.1, 25.8, 25.8, 39.5, 42.9, 43.9, 46.3, 62.5, 127.0, 127.2, 128.8, 129.5, 135.6, 135.7, 167.8; IR (neat) 2960, 1625 cm^{-1}; MS (EI) *m/e* 215 (M^+), 200, 115, 84 (100); HRMS *m/e* calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1302.

5-Methyl-azabicyclo[3.3.0]octane-2-one (4a). 5-Azido-2-pentanone (0.150 g, 1.18 mmol), cyclopropyldiphenylsulfonium tetrafluoroborate (0.384 g, 1.22 mmol), and powdered KOH (0.144 g, 2.04 mmol) were combined in dimethyl sulfoxide (3 mL), and the mixture was stirred. After 1.5 h, water (25 mL) was added, and the solution was extracted with ether (3 × 100 mL). The combined organic layers were washed with brine (1 × 50 mL), dried (Na_2SO_4), and concentrated to give an oil. The oil was dissolved in TFA (1 mL); gas evolution and a strong exotherm ensued. After 10 min, the reaction mixture was concentrated, and the residue was dissolved in ether. The ether solution was allowed to stir over solid K_2CO_3 for 30 min. The solution was then decanted and concentrated to give an oil. The crude product was purified by flash chromatography (ethyl acetate) to give **4a** (0.109 g, 66% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.46−1.62 (m, 1H), 1.82 (ddd, J = 3.3, 7.0, 12.1 Hz, 1H), 1.90−2.20 (m, 4H), 2.42 (ddd, J = 2.4, 8.9, 16.7 Hz, 1H), 2.83 (dt, J = 9.8, 16.6 Hz, 1H), 3.05 (ddd, J = 4.9, 8.5, 12.1 Hz, 1H), 3.61 (dt, J = 8.2, 11.6 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.7, 25.7, 34.2, 34.5, 38.1, 40.1, 67.8, 174.5; IR (neat) 2950, 1675, 1400 cm^{-1}; MS (EI) *m/e* 139 (M^+), 124 (100), 111, 55; HRMS *m/e* calcd for $C_8H_{13}NO$ 139.0997, found 139.1004.

1-Carbomethoxyhexahydroindolizidin-5-one (4c). General Method for Intramolecular Schmidt Reaction with $TiCl_4$. Keto azide **3c** (0.100 g, 0.444 mmol) was dissolved in 1.0 M $TiCl_4/CH_2Cl_2$ (2 mL) at room temperature, and the solution was stirred; gas evolution was observed. After 30 min, ethyl acetate (200 mL) was added, and the solution was washed with $NaHCO_3$ (1 × 25 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by flash chromatography (ethyl acetate) to give **4c** (0.061 g, 70% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 1.50−1.61 (m, 2H), 1.61−1.84 (m, 2H), 1.84−1.98 (m, 2H), 2.23−3.38 (m, 1H), 2.41−2.58 (m, 3H), 3.56 (td, J = 2.7, 9.6 Hz, 1H), 3.65−3.73 (m, 1H), 3.75 (s, 3H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 18.8, 20.4, 30.3, 32.1, 38.1, 45.0, 52.7, 69.6, 169.0, 174.1; IR (neat) 3950, 1732, 1640, 1440, 1403 cm^{-1}; MS (EI) *m/e* 198 (M^+ + 1), 138 (100), 110, 84, 55; HRMS *m/e* calcd for $C_{10}H_{15}NO_3$ 197.1052, found 197.1045.

Lactam 4o: *Prepared Using TFA.* This lactam exists as a mixture of amide bond isomers (0.160 g, 89% yield). Isomer **1**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.13−1.59 (m, 14H), 1.59−1.75 (m, 2H), 1.75−2.09 (m, 4H), 2.10−2.52 (m, 3H), 3.37−3.50 (m, 2H), 3.90 (m, 1H), 4.46−4.54 (m, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 21.4−35.2 (complex, assigned to 12 Cs), 45.7, 56.0, 172.2. Isomer **2** (diagnostic peaks only): ^1H NMR (300 MHz, $CDCl_3$) δ 4.50 (m, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 47.7, 56.1, 172.9. IR (neat) 2923, 1635 cm^{-1}; MS (EI) *m/e* 237 (M^+), 222, 152, 140, 126, 124, 113, 70 (100), 69; HRMS *m/e* calcd for $C_{15}H_{27}NO$ 237.2093, found 237.2093.

1,2,10,11,11a-Hexahydrobenzo[*e*]pyrrolo[1,2a]azepin-5-one (6). Ring Expansion Using Triflic Acid. Azide **5**[45] (0.255 g, 1.11 mmol) was dissolved in 2 mL of CH_2Cl_2 and cooled in an ice bath. Trifluoromethanesulfonic acid (0.11 mL, 1.22 mmol) was added by syringe. The reaction was allowed to warm to room temperature and stirred for 48 h. After the addition of a few drops of a saturated $NaHCO_3$ solution, the reaction mixture was partitioned between ether and saturated $NaHCO_3$. The organic layers were washed with water and brine and dried over Na_2SO_4. Concentration afforded a residue that was chromatographed (1:1 ethyl acetate/hexane) to afford an oil (0.50 g, 45% yield). This compound could be further purified by column chromatography (ethyl acetate) to give a light green solid: mp 79−81 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69−2.25 (m, 3H), 2.18−2.31 (m, 1H), 2.95−3.14 (m, 2H), 3.47−3.66 (m, 3H), 4.08−4.22 (m, 2H), 7.14 (m, 1H), 7.32 (m, 2H), 7.72 (m, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 22.5, 33.3, 39.0, 43.7, 46.1, 56.6, 126.5, 126.9, 129.8, 130.5, 132.0, 136.0, 169.4; IR (neat) 2955, 1645 cm^{-1}; MS (EI) *m/e* 201 (M^+), 104, 70 (100); HRMS calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1150.

3,3-Diphenyl-2-pyrrolidone (9a). Reaction of 4-azido-2,2-diphenylbutanal **7a**[45] with TFA afforded the title compound as a white crystalline solid (0.031 g, 29%) after washing the crude residue with hexane: mp 212−214 °C (lit.[55] 220−221 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.84 (t, J = 6.4 Hz, 2H), 3.36 (t, J = 6.4 Hz, 2H), 6.71 (br s, 1H), 7.22−7.39 (m, 10H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 37.4, 39.2, 57.2, 126.9, 127.9, 128.4, 142.6, 178.9; IR ($CDCl_3$) 3420, 3150, 1685, 900 cm^{-1}.

***N*-Formyl-2,2-diphenylpyrrolidine (8d) and 3,3-Diphenylpyrrolidin-2-one (9d). From TFA, $AlCl_3$, $SnCl_4$, $ZnCl_2$, and TMSOTf.** Reaction of **7d**[45] with TFA afforded **8d** (R_f 0.50 (1:1 ethyl acetate/hexane), 0.078 g, 81%) and **9d** (R_f 0.35 (1:1 ethyl acetate/hexane), 0.0075 g, 8%) as solids: **8d**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (pentet, J = 6.8 Hz, 2H), 2.70 (t, J = 6.8 Hz, 2H), 3.73 (dt, J = 2.7, 6.8 Hz, 2H), 7.16−7.25 (m, 2H), 7.26−7.40 (m, 8H), 7.84 (s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 21.3, 43.3, 44.5, 72.5, 127.6, 127.7, 128.4,

142.7, 163.0; IR (neat) 2870, 1655, 1360 cm^{-1}; MS (EI) *m/e* 251 (M^+), 206, 179, 167 (100), 115, 91HRMS *m/e* calcd for $C_{17}H_{17}NO$: 251.1310, found 251.1308. **9d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72−1.82 (m, 2H), 2.59 (ddd, J = 3.2, 6.5, 6.5 Hz, 2H), 3.40 (dt, J = 3.3, 6.5 Hz, 2H), 6.09 (br s, 1H), 7.20−7.35 (m, 10H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 18.9, 34.7, 42.6, 56.8, 126.6, 128.0, 128.6, 143.9, 174.1; IR (neat) 3190, 2960, 1655, 1490 cm^{-1}; MS (EI) *m/e* 251 (M^+), 222, 194, 174, 146, 91 (100); HRMS *m/e* calcd for $C_{17}H_{17}NO$ 251.1310, found 251.1305.

Compounds **8d** and **9d** were also obtained using other Lewis acids. In each case, the reactions were subjected to saturated $NaHCO_3$/ethyl acetate partitioning workups as described for **4c** above. **From $AlCl_3$**: Reaction of 0.200 g of **7d** (0.714 mmol) with a suspension of $AlCl_3$ (0.213 g, 1.60 mmol) in 2 mL of CH_2Cl_2 at −78 °C for 20 min gave **8d** (0.131 g, 69%) and **9d** (0.016 g, 8%). **From $SnCl_4$**: Reaction of 0.200 g of **7d** (0.714 mmol) with 2.0 mL of a 1.0 M solution of $SnCl_4$ in CH_2Cl_2 (2.0 mmol) at −78 °C for 20 min gave **8d** (0.113 g, 59%) and **9d** (0.029 g, 15%). **From $ZnCl_2$**: Reaction of 0.100 g of **7d** (0.357 mmol) with 1.0 mL of a 1.0 M solution of $ZnCl_2$ in Et_2O (1.0 mmol) at −78 °C for 3 days gave **8d** (0.043 g, 48%) and **9d** (0.016 g, 17%). **From TMSOTf**: Reaction of 0.100 g of **7d** (0.357 mmol) with 0.13 mL of TMSOTf (0.714 mmol) in 1 mL of CH_2Cl_2 at −78 → 25 °C for 2.5 h gave **8d** (0.055 g, 61%) and **9d** (0.020 g, 22%).

***N*-Acetylpyrrolidine (8e).** 6-Azido-2-hexanone **7e**[49b] was reacted with TFA to afford the title compound[56] as a brown oil (0.120 g, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86−2.0 (m, 4H), 2.06 (s, 3H), 3.45 (dd, J = 7.1, 16.0 Hz, 4H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 22.3, 24.4, 25.9, 45.4, 47.2, 169.0; MS (CI) *m/e* 114 (M^+ + 1), 70.

***N*-(Carbomethoxymethyl)pyrrolidine (8f).** Keto azide **7f**[45] was reacted with TFA to afford **8f** (0.059 g, 69% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89 (pentet, J = 6.8 Hz, 2H), 1.98 (pentet, J = 6.8 Hz, 2H), 3.41 (s, 2H), 3.46 (t, J = 6.8 Hz, 2H), 3.50 (t, J = 6.9 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.8, 26.4, 42.6, 46.3, 47.5, 52.8, 164.6, 168.4; IR (neat) 2940, 2864, 1740, 1640, 1436 cm^{-1}; MS (EI) *m/e* 171 (M^+), 112, 98, 83, 70 (100), 59, 43; HRMS *m/e* calcd for $C_8H_{13}NO_3$ 171.0895, found 171.0897.

***N*-Benzoylpyrrolidine (8g).** 5-Azido-1-phenyl-1-pentanone **7g**[49b] was reacted with TFA to afford the title compound[57] as a yellow oil (0.177 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81−1.99 (m, 4H), 3.41 (t, J = 6.6 Hz, 2H), 3.64 (t, J = 6.6 Hz, 2H), 7.31−7.41 (m, 3H), 7.48−7.53 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.2, 26.2, 46.0, 49.4, 126.8, 128.0, 129.5, 137.0, 169.4; IR (neat) 2950, 2860, 1640, 1440 cm^{-1}.

Ethylene Ketal of (*S*)-2-Methyl-2-(3-Hydroxypropyl)cyclohexanone (11). Keto ester **10**[40] (1.98 g, 9.35 mmol), ethylene glycol (5.23 mL, 93.5 mmol), and *p*-TsOH (0.050 g) were combined in benzene (50 mL) and refluxed under a Dean-Stark trap which had been packed with 3Å molecular sieves. After 16 h, the reaction was cooled and saturated aqueous $NaHCO_3$ (25 mL) was added. The mixture was then extracted with ether (1 × 200 mL). The organic layer was washed with water (1 × 50 mL) and brine (1 × 50 mL), then dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by flash chromatography (25% ethyl acetate/hexane) to give the ketal of 2-carbethoxyethyl-2-methylcyclohexanone (2.23 g, 93% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.43 (s, 4H), 1.70−1.88 (m, 2H), 2.27 (dd, J = 2.4, 6.6 Hz, 1H), 2.30 (dd, J = 3.1, 6.7 Hz, 1H), 3.88−3.97 (m, 4H), 4.12 (q, J = 7.1 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 14.2, 19.3, 20.7, 23.5, 29.4, 30.0, 30.5, 34.6, 40.7, 60.2, 64.6, 64.9, 112.7, 174.6; IR (neat) 2920, 1725 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.30; H, 9.40.

The ketal was dissolved in THF (15 mL), and the solution was chilled in an ice bath. LAH (0.495 g, 7.51 mmol) was added portionwise over 5 min. After 20 min, ethyl acetate (2 mL) was added carefully. After another 5 min, a 1:1 mixture of water/THF (1.0 mL) was added, then 15% KOH (0.5 mL), and then water (1.5 mL). After stirring for 20 min, the solution had deposited a white precipitate. The solution was filtered and concentrated to give an oil. The crude product was purified by flash chromatography (25 → 35% ethyl acetate/hexane) to give **11** (1.51 g, 94% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.35−1.70 (m, 13H), 3.62 (t, J = 6.5 Hz, 2H), 3.88−3.99 (m, 4H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 19.4, 20.8, 23.6, 26.9, 30.3, 30.4, 34.2, 40.9, 63.9, 64.7, 64.9, 112.9; IR (neat) 3380 (br), 2920, 1085 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_4$: C, 67.25; H, 10.35. Found: C, 66.86; H, 10.58.

(*S*)-2-Azidopropyl-2-methylcyclohexanone (12). Alcohol **11** (0.213 g, 0.995 mmol) was dissolved in a 1.42 M solution of HN_3/benzene (0.911 mL, 1.29 mmol), and the solution was chilled in an ice bath. Triphenylphosphine (0.313 g, 1.19 mmol) was added, followed by diethylazodicarboxylate (0.187 mL, 1.19 mmol). After 15 min, saturated aqueous $NaHCO_3$ (25 mL) was added, and the solution was extracted with ether (1 × 100 mL). The organic layer was washed with brine (1 × 25 mL), dried (Na_2SO_4), and concentrated to give an oil. The crude product was purified by flash chromatography (10% ethyl acetate/hexane) to give the ethylene ketal of **12** (0.186 g, 78% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.35−1.70 (m, 12H), 3.25 (t, J = 6.9 Hz, 2H), 3.77−3.98 (m, 4H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 19.4, 20.8, 23.3, 23.5, 30.4, 31.7, 34.3, 41.0, 52.5, 64.7, 64.9, 112.7; IR (neat) 2920, 2085, 1188 cm^{-1}. Anal. Calcd for $C_{12}H_{21}N_3O$: C, 60.25; H, 8.84; N, 17.57. Found: C, 60.00; H, 9.01; N, 17.18.

The above ketal (0.498 g, 2.08 mmol) and $LiBF_4$ (0.196 g, 2.08 mmol) were dissolved in 2% water/acetonitrile (4.2 mL) and stirred. After 16 h, ether (200 mL) was added, and the solution was washed with saturated aqueous $NaHCO_3$ (1 × 25 mL) and brine (1 × 25 mL). The organic layer was then dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by flash chromatography (5%, then10% ethyl acetate/hexane) to give **12** (0.357 g, 88% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.33−1.67 (m, 10H), 2.38 (t, J = 6.5 Hz, 2H), 3.28 (t, J = 6.2 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 20.9, 22.5, 23.4, 27.4, 34.6, 38.6, 39.1, 48.1, 51.8, 215.4; IR (neat) 2930, 2085, 1700 cm^{-1}. Anal. Calcd for $C_{10}H_{17}N_3O$: C, 21.52; H, 8.78; N, 12.52. Found: C, 21.18; H, 8.89; N, 21.18.

Racemic **12**, similarly prepared from 2-methylcyclohexanone and (±)-α-methylbenzylamine, was subjected to a chiral shift study (6.0 mg of **12** and 4.3 mg of Eu(Hfc)$_3$ in 0.66 mL $CDCl_3$) in which the C-2 methyl group was split into two well-resolved signals at δ 1.68 and 1.71 (500 MHz). Ketone (*S*)-**12** showed signals at 1.68 and 1.71 ppm in a ratio of 4.7:95.3 (90.6% ee).

Lactam (*S*)-13. Keto azide (*S*)-**12** (0.103 g, 0.528 mmol) was reacted with TFA to give (*S*)-**13** (0.077 g, 87% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.45−1.62 (m, 2H), 1.70−1.95 (m, 8H), 2.52−2.60 (m, 2H), 3.39−3.51 (m, 1H), 3.66−3.76 (m, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 21.0, 23.5, 23.9, 24.4, 37.5, 40.9, 44.3, 48.7, 61.4, 173.1; IR (neat) 2920, 1620, 1410 cm^{-1}; $[\alpha]_D$ = +10.7 (*c* 1.35, EtOH); MS (EI) *m/e* 167 (M^+), 152, 84 (100), 55; HRMS *m/e* calcd for $C_{10}H_{17}NO$ 167.1310, found 167.1314.

Racemic **13**, prepared from (±)-12, was subjected to a chiral solvation study (1.01 mg of **13** and 12.4 mg of (*R*)-2,2,2-trifluoro-1-(9′-anthryl)ethanol in 0.60 mL $CDCl_3$) in which the C-2 methyl group was split into two well-resolved signals at δ 1.21 and 1.22 (500 MHz). Ketone (*S*)-**13** showed analogous signals in a ratio of 5.4:94.6 (89.2% ee).

(*S*)-2-Methyl-2-(3′-chloropropyl)cyclohexanone (14). The hydroxy ketal **11** (1.14 g, 5.32 mmol) was dissolved in pyridine (5 mL), and the solution was chilled in an ice bath. Methanesulfonyl chloride (0.449 mL, 6.38 mmol) was added, and the ice bath was removed. After 1 h, the solution was diluted with ether (200 mL), and washed with 10% citric acid (1 × 50 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The oil was dissolved in DMF (5 mL), LiCl (2.25 g, 53.2 mmol) was added, and the solution was heated at 80 °C. After 1 h, the solution was cooled and diluted with ether (200 mL). The solution was washed with 10% aqueous citric acid (1 × 25 mL) and brine (1 × 25 mL), dried (Na_2SO_4), and concentrated to give an oil. The oil and $LiBF_4$ (0.997 g, 10.6 mmol) were dissolved in 2% water/acetonitrile (11 mL) and stirred. After 22 h, ether (200 mL) was added, and the solution was washed with saturated aqueous $NaHCO_3$ (1 × 25 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by flash chromatography (10% ethyl acetate/hexane) to give **14** (0.867 g, 87% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.50−1.68 (m, 3H), 1.69−1.95 (m, 7H), 2.45−2.52 (m, 2H), 3.53 (t, J = 5.6 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 20.9, 22.5, 27.1, 27.4, 34.8, 38.6, 39.2, 45.4, 48.1, 215.4; IR (neat) 2920, 1700 cm^{-1}. Anal. Calcd for $C_{10}H_{17}ClO$: C, 63.65; H, 9.08. Found: C, 63.34; H, 9.40.

2-(3′-Chloropropyl)-2-methyl-azacyclohept-7-one (15) and Cyclization to Lactam 13. Chloride **14** (0.491 g, 2.61 mmol) was dissolved in 1:1 TFA/water (10 mL), and the solution was chilled in an ice bath. NaN_3 (0.509 g, 7.83 mmol) was added portionwise over 5 min. The mixture was allowed to warm to room temperature over 16 h, and then the solvent was concentrated to give an oil. The oil was dissolved in ethyl acetate (200 mL) and washed with saturated aqueous $NaHCO_3$ (1 × 25 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by flash chromatography (50%, then 75%, then 100% ethyl acetate/ hexane) to give **15** (0.223 g, 42% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.51−1.86 (m, 10H), 2.46 (t, J = 6.4 Hz, 2H), 3.50 (t, J = 6.5 Hz, 2H), 6.05 (s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 23.5, 24.3, 26.9, 27.9, 37.3, 37.7, 39.7, 45.1, 53.9, 177.8; IR (neat) 2920, 1640 cm^{-1}; MS (EI) *m/e* 204 (M^+ + 1), 188, 126 (100), 83, 55; HRMS *m/e* calcd for $C_{10}H_{18}NOCl$: 203.1077, found 203.1068. A regioisomer and the tetrazole of **15** were also isolated.

Lactam **15** (0.101 g, 0.498 mmol) was dissolved in 2.7 mL of THF, and 0.030 g of an 80% suspension of NaH in mineral oil was added at room temperature. After stirring for 2 h, the reaction was poured into 200 mL of ethyl acetate and extracted with H_2O (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, concentrated, and chromatographed in 3:1 ethyl acetate/hexane followed by pure ethyl acetate. Compound **13** obtained in this way had $[\alpha]_D$ = +10.4 (*c* 1.38, EtOH) and identical spectral properties to those above.

***cis*- and *trans*-2-(3′-Azidopropyl)-4-*tert*-butylcyclohexanone (16a and 16b).** 2-(3′-Chloropropyl)-4-tert-butylcyclohexanone was prepared as described for compound **3g** (1.06 g, 91% yield); isolated as a mixture of isomers. The mixture could be separated by chromatography (5% ethyl acetate/hexane) for analytical purposes. Isomer **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 9H), 1.39−1.95 (m, 8H), 1.95−2.08 (m, 1H), 2.25−2.49 (m, 3H), 3.55 (t, J = 6.2 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 26.7, 27.3, 28.6, 30.2, 31.6, 32.3, 38.3, 41.3, 44.6, 48.2, 215.1; IR (neat) 2955, 1705 cm^{-1}. Anal. Calcd for $C_{13}H_{23}ClO$: C, 67.66; H, 10.05. Found: C, 67.80; H, 10.40. Isomer **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.10−1.24 (m, 1H), 1.25−1.52 (m, 2H), 1.60 (tt, J = 3.5, 12.2 Hz, 1H), 1.68−1.94 (m, 3H), 2.04−2.19 (m, 2H), 2.23−2.45 (m, 3H), 3.53 (dt, J = 2.5, 6.7 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 27.0, 27.6, 28.7, 30.4, 32.4, 35.3, 41.6, 45.2, 47.1, 49.1, 212.7.

The mixture of above chlorides was converted to **16a** (0.336 g, 32% yield) and **16b** (0.570 g, 54% yield) as described for **3g**. **16a** (cis): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.07−1.32 (m, 2H), 1.34−1.72 (m, 4H), 1.73−1.90 (m, 1H), 2.03−2.19 (m, 2H), 2.21−2.45 (m, 3H), 3.28 (dt, J = 2.9, 6.5 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 26.7, 26.8, 27.6, 28.7, 32.4, 35.3, 41.6, 47.1, 49.3, 51.6, 212.8; IR (neat) 2940, 2080, 1702 cm^{-1}. Anal. Calcd for $C_{13}H_{20}ClO$: C, 65.79; H, 9.77; N, 17.71. Found: C, 66.00; H, 10.00; N, 17.65. **16b** (trans): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 9H), 1.40−1.76 (m, 6H), 1.76−1.88 (m, 2H), 1.95−2.07 (m, 1H), 2.25−2.49 (m, 3H), 3.30 (t, J = 6.5 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 26.5, 26.6, 27.3, 28.4, 31.5, 32.3, 38.3, 41.2, 48.4, 51.0, 215.1; IR (neat) 2950, 2085, 1707 cm^{-1}. Anal. Calcd for $C_{13}H_{20}ClO$: C, 65.79; H, 9.77; N, 17.71. Found: C, 65.89; H, 9.75; N, 17.50.

Lactam 17a. The keto azide **16a** was reacted with $TiCl_4$ to give **17a** (0.081 g, 92% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 9H), 1.12−1.80 (m, 9H), 2.01 (sextet, J = 6.2 Hz, 1H), 2.36 (dt, J = 8.2, 15.6 Hz, 1H), 2.58 (dt, J = 7.0, 14.5 Hz, 1H), 3.50 (dt, J = 3.3, 6.5, Hz, 2H), 3.84 (pentet, J = 6.5 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 22.2, 22.4, 27.13, 32.9, 33.0, 34.0, 34.8, 42.8, 46.6, 55.1, 171.2; IR (neat) 2945, 1625 cm^{-1}; MS (EI) *m/e* 209, 168, 152, 70 (100); HRMS *m/e* calcd for $C_{13}H_{23}NO$ 209.1780, found 209.1776.

Lactam 17b. The keto azide **16b** was reacted with TFA to give **17b** (0.050 g, 96% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 9H), 1.06−1.45 (m, 3H), 1.60−1.77 (m, 2H), 1.70−2.01 (m, 3H), 2.18−2.30 (m, 1H), 2.37 (dd, J = 10.4, 13 Hz, 1H), 2.58 (dd, J = 7.2, 13.7 Hz, 1H), 3.30−3.42 (m, 1H), 3.61−3.75 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 23.4, 24.0, 27.5, 33.1, 35.3, 36.9, 37.2, 46.6, 51.4, 58.1, 173.9; IR (neat) 2950, 1620 cm^{-1}; MS (EI) *m/e* 209 (M^+), 152, 124, 83, 70 (100); HRMS *m/e* calcd for $C_{13}H_{23}NO$ 209.1780, found 209.1778.

7,7-Dimethyl-2,3,4,6,7,8-hexahydro-2-hydroxychromen-5-one (19). Azide **18a**[45] was reacted with triflic acid as described for **6** to afford **19** (0.76 g, 71% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 6H), 1.83 (m, 2H), 2.18−2.30 (m, 6H), 5.43 (br s, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 14.1, 26.9, 28.5, 29.5, 32.1, 42.3, 50.3, 93.9, 110.0, 168.4, 198.7; IR (neat) 3310, 2950, 1610 cm^{-1}; MS (EI) *m/e* 196 (M^+, 75%), 168 (100); HRMS calcd for $C_{11}H_{17}O_3$ 197.1178, found 197.1178.

Octahydro-7,7,9a-trimethylpyrrolo[1,2-*a*]-5-azepinone (20). Dione **18b**[45] was reacted with TFA to afford **20** as a white solid (0.102 g, 82%); mp 87−89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.17 (s, 3H), 1.43 (s, 3H), 1.82−2.09 (m, 5H), 2.21 (AB q, J = 12.8 Hz, $\Delta\upsilon$ = 30.6 Hz, 2H), 2.82 (d, J = 10.8 Hz, 1H), 3.59−3.78 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 20.6, 21.3, 28.9, 29.4, 35.7, 38.4, 46.5, 46.9, 48.6, 70.3, 169.0, 210.4; IR (neat) 2950, 1700, 1675 cm^{-1}; MS (EI) *m/e* 209 (M^+), 181, 166. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.94; H, 9.40; N, 6.68.

2,3,4,5,6,7-Hexahydro-1*H*-quinolin-8-one (22). To 2-(3′-azidopropyl)-cyclohex-2-en-1-one **21**[45] (0.110 g, 0.61 mmol) in CH_2Cl_2 (1 mL), cooled to 5 °C, was added trimethylsilyl triflate (0.164 g, 0.74 mmol), dropwise, resulting in steady gas evolution. The solution was stirred at ambient temperature for 1 h. Workup (EtOAc/H_2O) followed by chromatography (EtOAc) afforded the title compound[48] as an orange solid (0.040 g, 43%) mp 108−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (pentet, 7.7, 2H), 2.00 (pentet, J = 7.4 Hz, 2H), 2.28 (t, J = 7.7 Hz, 2H), 2.47 (t, J = 7.1 Hz, 2H), 2.52 (t, J = 7.7 Hz, 2H), 3.55 (t, J = 7.1 Hz, 2H), 9.15 (br s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 21.2, 21.3, 27.1, 31.1, 38.5, 47.4, 98.7, 161.9, 202.5; IR ($CDCl_3$) 3300, 2950, 1635, 1550 cm^{-1}; MS (EI) *m/e* 151 (M^+, 100%), 122; HRMS *m/e* calcd for $C_9H_{14}NO$ 152.1075, found 152.1077.

Hexahydro-4-(phenylthio)pyrrolo[1,2-a]azepine-9-one (25). Azide **24**[45] was reacted with TfOH to afford the title compound (0.060 g, 43%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25−2.05 (m, 9H), 2.36 (m, 1H), 2.76 (dt, J = 13.6, 6.0 Hz, 1H), 3.20−3.38 (m, 2H), 3.92 (dt, J = 13.6, 6.3 Hz, 1H), 7.26−7.41 (m, 3H), 7.57−7.64 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 22.5, 23.5, 25.6, 36.2, 41.3, 49.7, 50.0, 61.5, 128.3, 128.7, 133, 135.9, 181.8; IR (neat) 2920, 1680 cm^{-1}; HRMS calcd for $C_{15}H_{20}NOS$ 262.1266, found 262.1271.

Acknowledgment. This work was supported by the National Institutes of Health. We additionally thank John Wendt and Mendi Morton for their kind experimental assistance and Fusao Takusagawa for performing an X-ray crystallographic study on compound **2a**. J.A. acknowledges the receipt of an Eli Lilly Granteeship (1989−1991), an Alfred P. Sloan Fellowship (1993−1995), and an American Cyanamide Faculty Award (1994) during the tenure of this project.

Supporting Information Available: Synthetic procedures and characterization data for compounds **1b**, **2b**, **3b**, **3d**, **3f**, **3h−3l**, **3n**, **3o**, **4b**, **4e**, **4g−4j**, **4l**, **4n**, **5**, **7a**, **7c**, **7d**, **7f**, **18a**, **18b**, **21**, and **24** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA951711D