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Introduction.

Placement of a strong electron-withdrawing group on a nitrogen atom is a popular way to promote carbon-to-nitrogen rearrangement reactions; *e.g.* the Beckman, Curtius, Hoffman, Lossen, Schmidt, and Stieglitz rearrangements [1]. We are interested in the particular 1,2-rearrangment shown in Figure 1. The rearrangement results in the formation of a new C-N bond and the formation of a potentially useful α-amino carbocation (or iminium ion) (**2**). There are two basic strategies for carrying out such a rearrangement. In the Stieglitz rearrangement [2], an *N*-chloro- or *N*-arenesulfonoxyamine (**1**) (X = Cl or OSO_2Ar) is first prepared from a secondary amine. The rearrangement is then promoted thermally or by the presence of a Lewis acid. In a version of the Schmidt rearrangement [2], an aminodiazonium ion (**1**) (X = N_2^+) is generated *in situ* by the capture of an azide with a carbocation [e.g., (**3**) → (**4**)]. The Schmidt method has the potential advantage of brevity; a secondary amine need not be prepared prior to rearrangement. We envisioned the synthesis of bicyclic tertiary amines by an overall process such as that shown in the example, where the azido carbocation (**3**) would produce the bicyclic iminium ion (**5**) through the intermediacy of the aminodiazonium ion (**4**). Two of the three C-N bonds in (**5**) would thus be formed in one operation.

The reaction of hydrazoic acid (HN_3) with carbocations is known to produce primary aminodiazonium ions (**6**), which undergo rearrangement (Figure 2). Alternatively, the primary aminodiazonium ion may be generated by protonation of an azide. This variant of the Schmidt rearrangement has not seen widespread use. The Schmidt reactions of HN_3 with ketones and carboxylic acids, however, are well known. For the process shown in Figure 1, we require the reaction of an aliphatic azide with a carbocation to produce a *secondary* aminodiazonium ion. However, the use of aliphatic (or aromatic) azides in any type of Schmidt rearrangement has long been thought to be unfavorable due to their poor nucleophilicity [2]. Recently, Aubé [3] and Pearson [4] have independently reported that this limitation may be overcome. Aubé has shown that aliphatic azides are useful in intra- and intermolecular Schmidt reactions with ketones [*e.g.*, (**7**) → (**8**)] [3]. Our group has shown that aliphatic azides may undergo intra- and intermolecular Schmidt reactions with carbocations [4], the subject of this article.

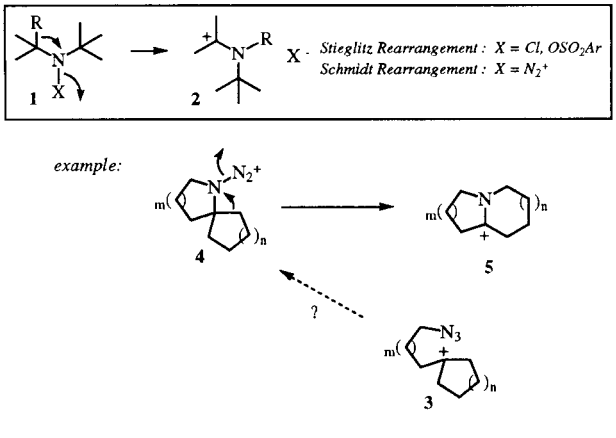


Figure 1

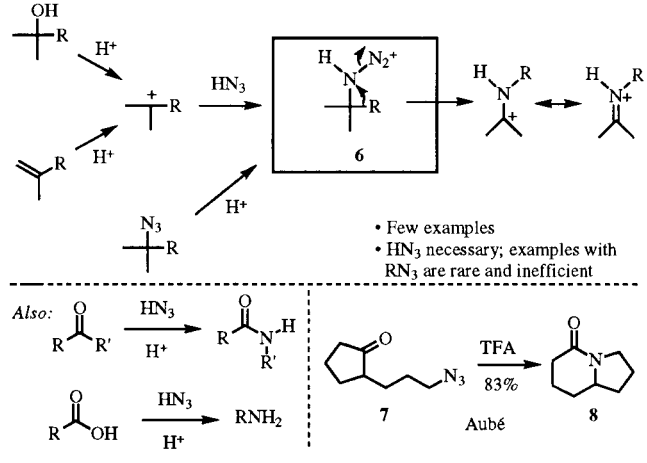
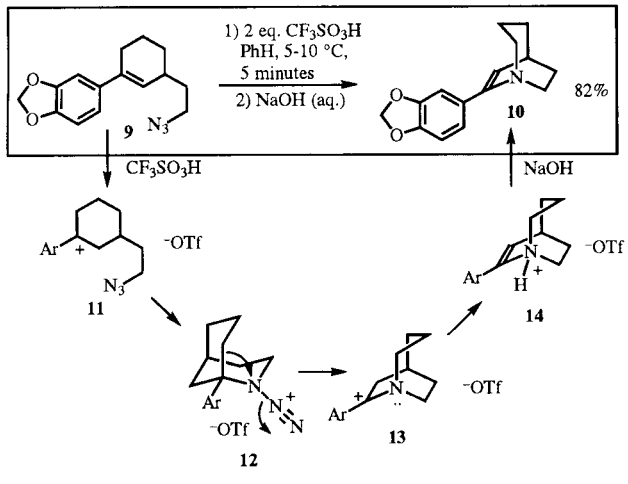


Figure 2

The first example of an efficient Schmidt reaction of an aliphatic azide with a carbocation was discovered while attempting to promote the intramolecular 1,3-dipolar cycloaddition reaction of azide (**9**) by treatment with Lewis and protic acids (Scheme 1) [4a,5]. Upon treatment of (**9**) with triflic acid in cool benzene, rapid nitrogen evolution was observed. After workup with base, the bridged-bicyclic amine (**10**) was isolated in good yield rather than products derived from cycloaddition. The proposed mechanism of this reaction is shown. Intramolecular capture of the carbocation (**11**) with the azide produces the secondary aminodiazonium ion (**12**), which undergoes a regioselective 1,2-rearrangement to

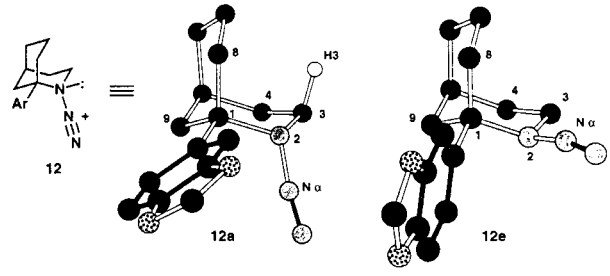
produce the α-amino carbocation (**13**). This cation cannot enter into effective resonance with the amino group, since the lone pair and the empty p-orbital are nearly orthogonal. Hence, elimination of a proton followed by reprotonation on nitrogen gives the enammonium ion (**14**). The efficiency of this process prompted us to begin a program aimed at investigating the scope and applications of this new version of the venerable Schmidt reaction. Two issues were of immediate interest. First, why is the rearrangement of (**12**) to (**13**) so regioselective? In principle, any one of the six groups attached to the α-carbons of the aminodiazonium ion could have migrated. Second, is the reaction limited to intramolecular examples using stabilized carbocations such as the tertiary benzylic cation encountered here? These issues are addressed below.



Scheme 1

Regioselectivity of the Intermolecular Schmidt Reaction of Aliphatic Azides with Carbocations.

In order to develop an explanation for the regioselective rearrangement of (**12**) to (**13**), we first examined the stability of (**13**) relative to all of the other possible rearrangement products and found it to be 25 kcal/mol higher in energy than the lowest energy product using the AM1 semi-empirical MO method [4b]. Hence, the regioselectivity must be a result of a kinetic rather than thermodynamic process. When considering 1,2-rearrangements to electron deficient centers, three factors should be taken into account. First, if the process in a concerted one involving departure of the leaving group in the rate-determining step, an anti-periplanar orientation of the migrating group and the leaving group is preferred (*i.e.*, stereoelectronics). Second, the atom at the origin of migration should be able to stabilize a positive charge. Third, the migrating group should be able to bear a positive charge in the transition state. Assuming the rearrangement of (**12**) to (**13**) is concerted [4b], we examined the structure of (**12**) with semi-empirical molecular orbital calculations (AM1 method). The two lowest-energy structures, (**12a**) and (**12e**), differing mainly in the axial or equatorial disposition of the N_2^+ group, are shown in Figure 3. In accord with existing experimental and theoretical data, the aminodiazonium ion is pyramidal at the internal nitrogen atom [6]. In (**12a**), methylene group 8 is well-suited for migration, since it is nearly anti-periplanar to the departing dinitrogen. Migration of this group would also leave a benzylic cation at the origin of migration. Methylene 9 would also leave a benzylic cation, but the dihedral angle 9-1-2-Nα is 84.4°, nearly orthogonal. Methylene 4 has a similar problem. Stereoelectronically, H3 is well-suited for migration, but is less-able to carry a positive charge in the transition state than a methylene group. Hence, it is reasonable to postulate that methylene 8 is likely to lead to rearrangement, which is the experimental result. In (**12e**), methylene 9 is best suited for migration. However, this aminodiazonium ion is 2.14 kcal/mol higher in energy than (**12a**). The experimental result is rationalized by assuming that a concerted rearrangement of the most abundant aminodiazonium ion occurs with stereoelectronic control.



E_{rel} = 0.00 kcal/mol

$\angle C_8,C_1,N_2,N\alpha = 156.5°$
$\angle C_9,C_1,N_2,N\alpha = 84.4°$
$\angle C_4,C_3,N_2,N\alpha = 92.35°$
$\angle H_3,C_3,N_2,N\alpha = 146.9°$

E_{rel} = 2.14 kcal/mol

$\angle C_8,C_1,N_2,N\alpha = 71.0°$
$\angle C_9,C_1,N_2,N\alpha = 170.8°$
$\angle C_4,C_3,N_2,N\alpha = 179.8°$

Figure 3

Scope and Applications of the Intramolecular Schmidt Reaction of Aliphatic Azides with Carbocations.

The Schmidt reaction of (**9**) proceeded through a tertiary benzylic carbocation. Are less stabilized carbocations viable partners in Schmidt reactions? In order to examine this question, we targeted simple 5-alkylindolizidine alkaloids such as indolizidine 209D (**15**) and indolizidine 167B (**16**) (Figure 4) [4b]. Before discussing the experimental observations, it is instructive to consider the retrosynthetic analysis of the target molecules. The indolizidines may be derived from the hydride reduction of the iminium ions (**17**), (**18**), or (**19**), each of which may result from two different aminodiazonium ions. For

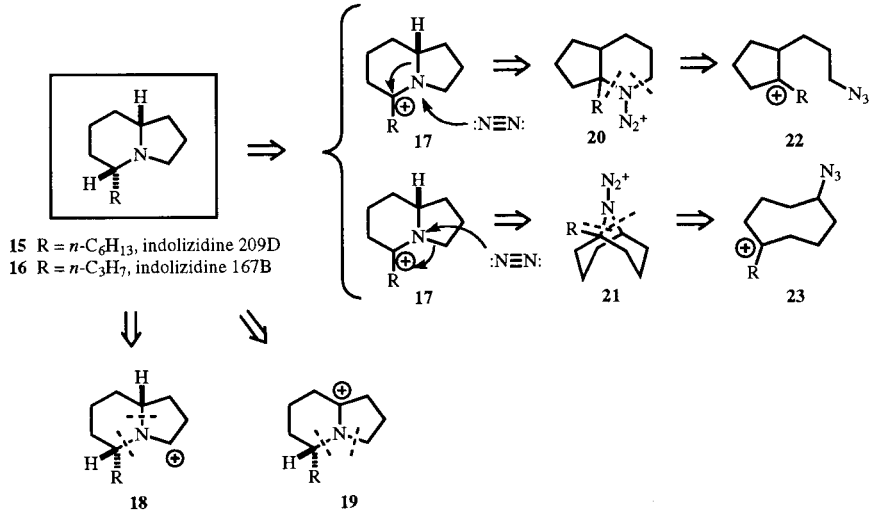
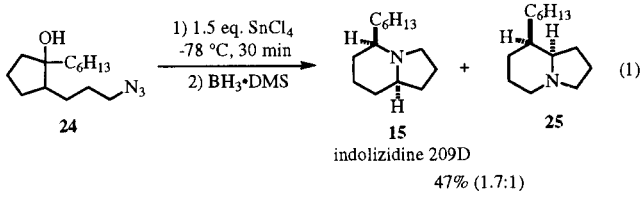


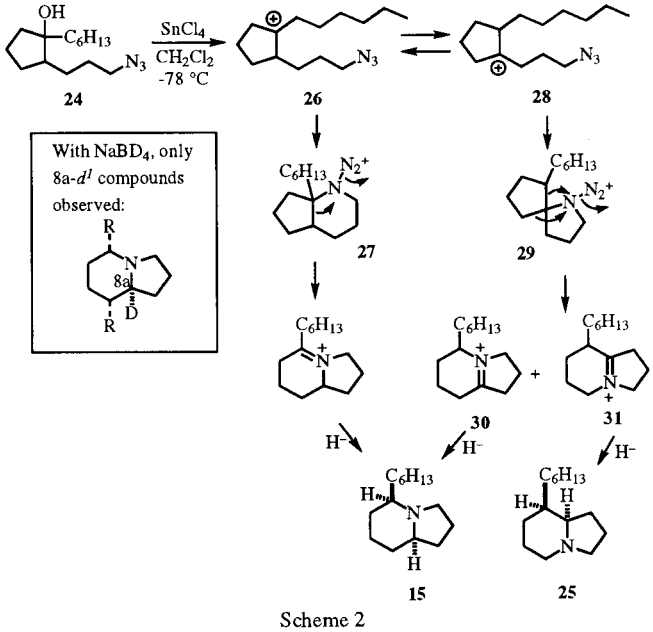
Figure 4

example, iminium ion (**17**) may be formed from either the aminodiazonium ion (**20**) or (**21**). Each aminodiazonium ion can, in principle, then be derived from two azido carbocations. For example, (**20**) could be derived from either (**22**) or an alternate structure involving a tertiary azide and a primary carbocation (not shown). *Hence, for any unsymmetrical tertiary amine, there are a maximum of twelve different azido carbocations that may be considered as starting points for synthetic design, a desirable feature in a synthetic method.* If one disconnection fails to produce the desired amine, others may succeed. This point will be illustrated below by a comparison of reactions involving (**22**) and (**23**).

The disconnection involving the azido carbocation (**22**) was studied first by examining the Schmidt reaction of the azido alcohol (**24**) (equation 1) [4b]. Ionization of the tertiary alcohol with tin tetrachloride caused nitrogen evolution. Reduction of the iminium ion intermediates led to the isolation of indolizidine 209D and the unexpected regioisomer (**25**).

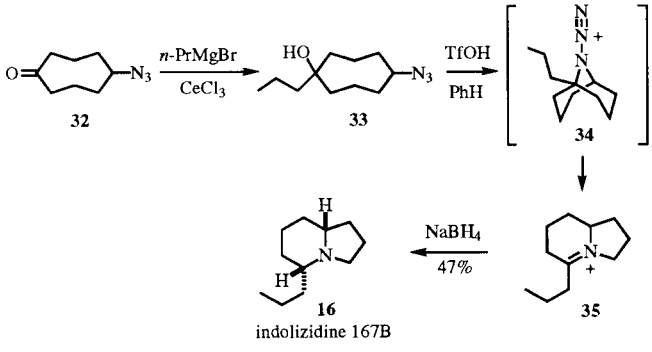


We were able to show that the undesired indolizidine (**25**) was the result of carbocation rearrangement, as shown in Scheme 2 [4b]. Ionization of (**24**) gave the cation (**26**). Rather than cyclizing to the aminodiazonium ion (**27**) as desired, a 1,2-hydride shift led to the cation (**28**) which cyclized to (**29**). Rearrangement of this spirocyclic aminodiazonium ion was unselective, producing the iminium ions (**30**) and (**31**), which upon reduction gave (**15**) and (**25**). Workup with sodium borodeuteride caused deuterium incorporation at C-8a only, proving that none of (**15**) was derived by the expected route involving (**27**). Hence, the rate determining step is the cyclization of the azido cations (**26**) and (**28**), which are probably rapidly interconverting. The rate of cyclization of (**28**) is higher than that of (**26**) due to five- versus six-membered ring formation. Hence, this disconnection was not satisfactory for the regioselective synthesis of 5-alkylindolizidines. Fortunately, an alternate disconnection involving an aminodiazonium ion such as (**23**) proved valuable, as shown below.



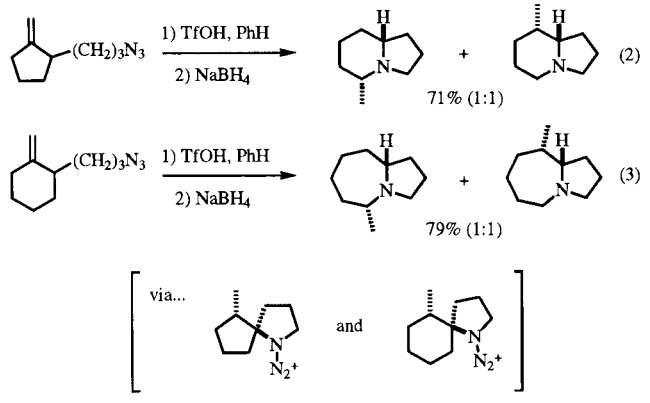
Scheme 2

The cerium-promoted addition [7] of *n*-propylmagnesium bromide to the azido ketone (**32**) gave the azido alcohol (**33**). Ionization of (**33**) with triflic acid presumably generated an azido carbocation such as (**23**) (see Figure 4), producing the aminodiazonium ion (**34**) without rearrangement. A regioselective rearrangement of the symmetrical ion (**34**) ensued, producing the iminium ion (**35**) and thus a single regioisomer of indolizidine 167B (**16**) [4b].

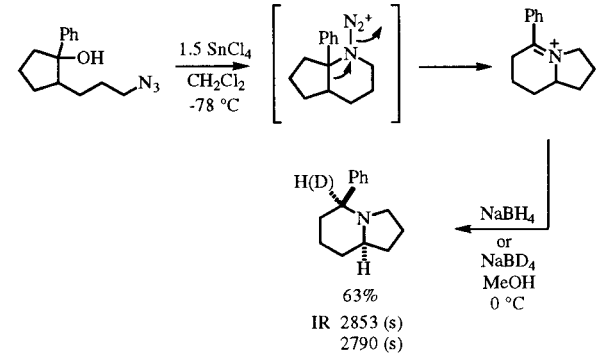


Scheme 3

The yields encountered in Schemes 2 and 3 were modest. An improvement was observed when the tertiary cations were derived from the protonation of alkenes rather than the ionization of alcohols (equations 2 and 3) [4b]. Again, regioisomeric indolizidines were formed in an unselective manner due to cation rearrangement followed by the formation of spirocyclic amino-diazonium ions.

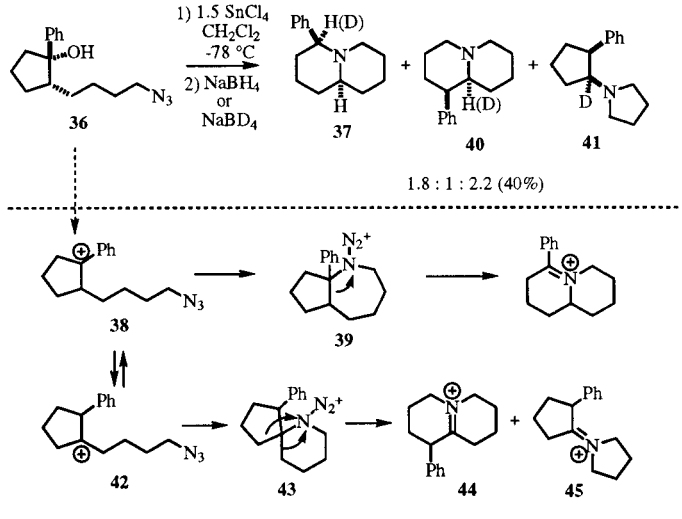


The carbocation rearrangements observed in Scheme 2 and equations 2 and 3 mar an otherwise simple approach to indolizidines. We sought to revive this approach by examining cation stabilizing groups that would prevent rearrangement prior to cyclization. Scheme 4 shows that a tertiary benzylic cation allows the synthesis of 5-phenylindolizidine without rearrangement, as proven by deuterium labeling [4b,8].



Scheme 4

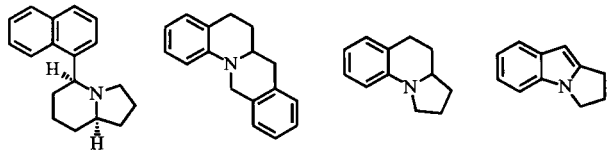
Surprisingly, benzylic stabilization was not sufficient to prevent carbocation rearrangement in an attempted synthesis of quinolizidines (Scheme 5) [8]. Ionization of (**36**) followed by reduction gave three compounds, one of which was the desired quinolizidine (**37**). This quinolizidine was shown by deuterium labeling to be the result of the expected cyclization of the cation (**38**) to the aminodiazonium ion (**39**). The regioisomeric quinolizidine (**40**) and the pyrrolidinyl cyclopentane (**41**) were shown by deuterium labeling to be the result of rearrangement of (**38**) to (**42**) followed by cyclization to (**43**). A surprisingly regioselective migration of the least substituted bond of the spirocyclic aminodiazonium ion gave (**44**) and hence (**40**). Competing ring contraction of (**43**) gave the iminium ion (**45**) and hence the cyclopentane (**41**). These events are interpreted as follows: A rapid pre-equilibrium of (**38**) and (**42**) precedes the rate determining step, namely the cyclization to (**39**) and (**43**). The equilibrium favors (**38**) due to benzylic stabilization. However, the majority of product is derived from the minor cation (**42**). It follows that the rate constant for cyclization of the minor cation (**42**) must be larger than the rate constant for cyclization of



Scheme 5

the major cation (**38**). This is reasonable, since the former process involves the formation of a six-membered ring, while the latter process leads to a seven-membered ring.

The successful preparation of fused-bicyclic amines using benzylic carbocations in the intramolecular Schmidt reaction of aliphatic azides has allowed us to study the application of this method to the synthesis of a variety of interesting compounds. In unpublished work, we have prepared the potential dopaminergic agent (**46**), the isoberberine (**47**), the gephyrotoxin skeleton (**48**), and the mitomycin skeleton (**49**) [9].



46 **47** **48** **49**

We have experimented with a variety of other cation stabilizing groups which might prevent rearrangement, especially those which would leave behind a synthetically useful functional group. In unpublished work, the ionization of propargyl alcohols to propargyl cations appears to be a useful solution (not shown) [8].

Attempted Application to the Cinchona Alkaloids. Discovery of Some New Azide Chemistry.

Given the successful generation of the bridged-bicyclic amine (**10**) in Scheme 1, we embarked on a synthesis of the Cinchona alkaloid cinchonamine (**50**), which should be available by Schmidt reaction of the azido alcohol (**51**) (Figure 5) [4c]. These substrates were easily prepared by the addition of various 2-lithioindoles [10] to the keto ester (**52**) followed by reduction of the resultant lactone, tosylation of the primary alcohol, and azide displacement.

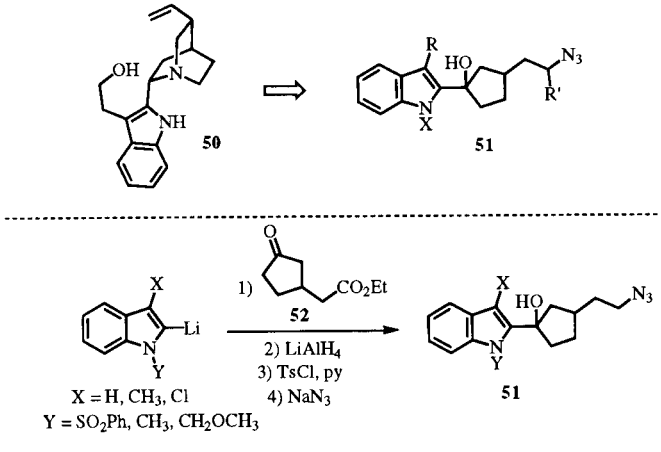
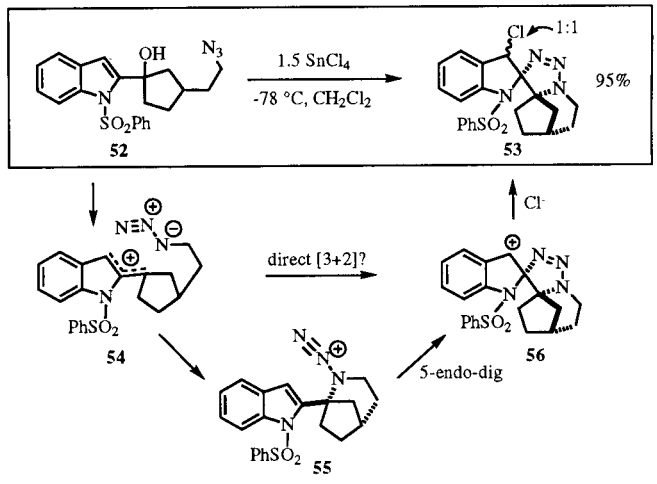


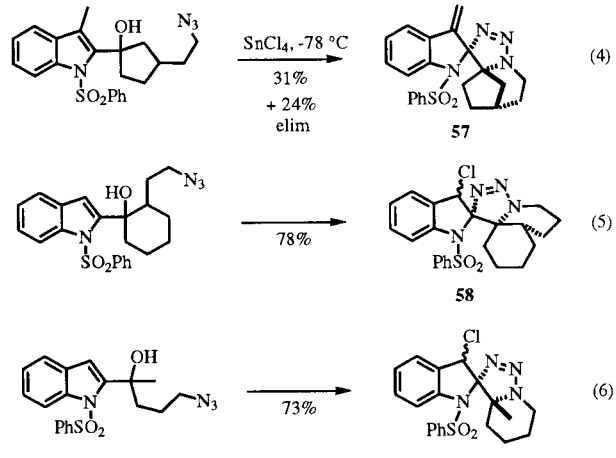
Figure 5

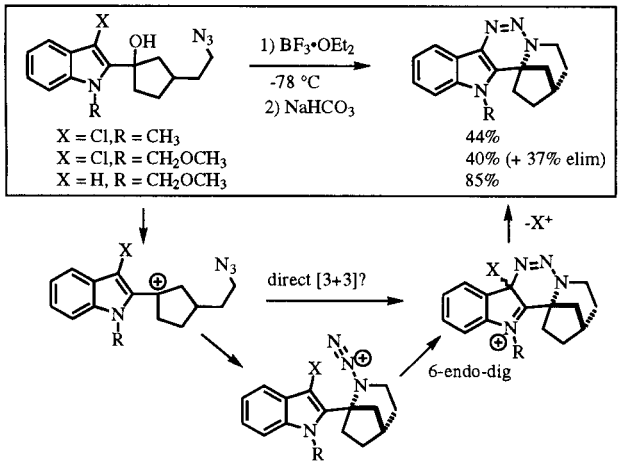
Treatment of the *N*-phenylsulfonylindole (**52**) with tin tetrachloride at -78 °C gave, instead of the desired quinuclidine ring system, the crystalline triazoline (**53**) as a mixture of two diastereomers (Scheme 6) [4c]. Ionization to the cation (**54**) followed by cyclization to the aminodiazonium ion (**55**) had occurred, but rather than 1,2-rearrangement, the π-electron rich indole was attacked at C-2 by the electrophilic diazonium ion to produce the highly stabilized benzylic cation (**56**), which was trapped by chloride ion to give (**53**). An interesting alternative mechanism is also shown, whereby a concerted 1,3-dipolar cycloaddition of the azide onto the allylic cation had occured, producing (**56**) directly. Azides are known to undergo dipolar cycloadditions with electron-poor alkenes. An allylic cation may be considered the ultimate electron-poor alkene, perhaps explaining the low temperature cycloaddition. The concerted mechanism also explains the lack of competition by Schmidt rearrangement.



Scheme 6

Other examples of the [3+2] cyclization of azides with indole cations are shown in equations (4)-(6). The structures of the triazolines (**57**) and (**58**) were verified by X-ray crystallography.



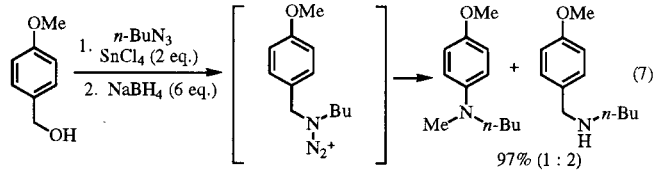


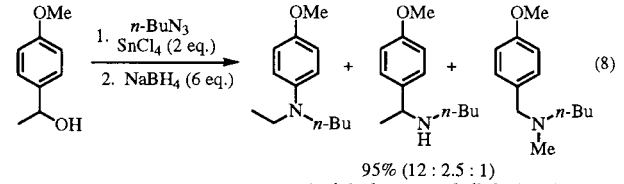
Scheme 7

We then examined the effect of changing the nitrogen substituent on the indole ring. Three indoles bearing an *N*-methyl or *N*-methoxymethyl group were cyclized using boron trifluoride as the promotor (Scheme 7). Rather than Schmidt reaction products or [3+2] cyclization products, a [3+3] cyclization ensued, producing 1,6-dihydrotriazines. In these cases, the aminodiazonium ion intermediate had cyclized at C-3 of the indole rather than C-2. Alternatively, a symmetry-allowed [π4s+π2s] cycloaddition may be responsible. The [3+3] cyclization of an azide with an allylic cation is unprecedented, although Schultz reported a related [3+3] cycloaddition of an azide with a photochemically generated oxallyl zwitterion intermediate [11]. A close analogy for the concerted mechanism is the cycloaddition of allylic cations with 1,3-dienes [12]. An explanation of the difference between the examples in Scheme 7 and those in Scheme 6 and equations (4)-(6) may lie in the greater stabilization of the cation resulting from [3+3] cyclization when a more electron-releasing substituent is present at the center carbon of the allylic cation (i.e., *N*-alkyl *vs* *N*-sulfonyl).

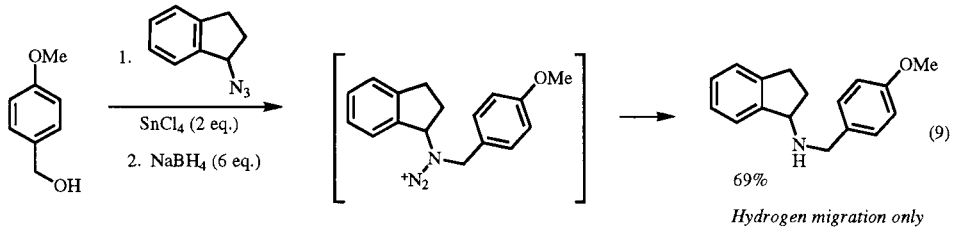
Intermolecular Schmidt Reactions of Aliphatic Azides with Carbocations.

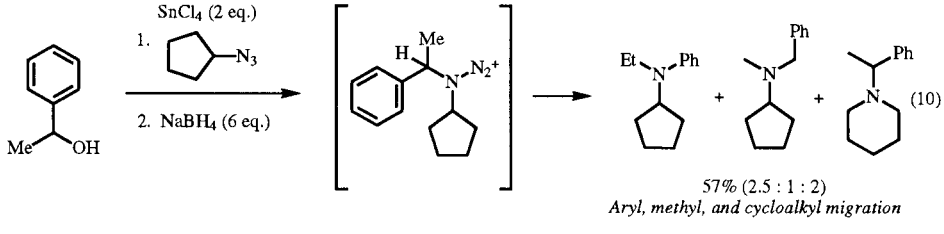
The literature of the Schmidt reaction of HN_3 with carbocations made it clear that aliphatic azides were not useful reaction partners. While we have shown that aliphatic azides are indeed useful, we originally felt that our success must be due to the intramolecular nature of our examples. Nonetheless, we felt it necessary to explore intermolecular reactions. To our surprise, we found that these reactions are not only possible, but can be extremely efficient [4d].





Our first attempts involved the use of benzylic cations with *n*-butyl azide, as shown in equations (7) and (8) [4d]. Nearly quantitative reactions ensued, producing products resulting from aryl, hydrogen, and alkyl migration. Primary benzylic alcohols were found to produce benzylic secondary amines, resulting from hydrogen migration, as the major products. Secondary benzylic alcohols generally gave anilines, the result of aryl migration. These results are com-

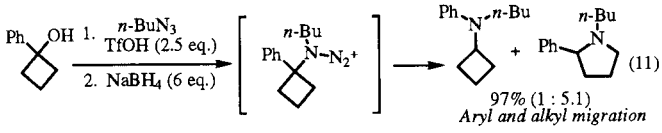


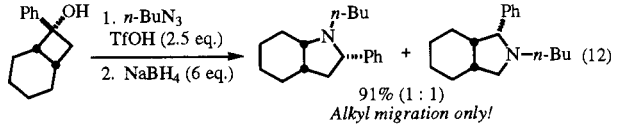


parable to the Stieglitz-type 1,2-rearrangement of *N*-(arenesulfonoxy)benzylic amines, studied by Hoffman [13].

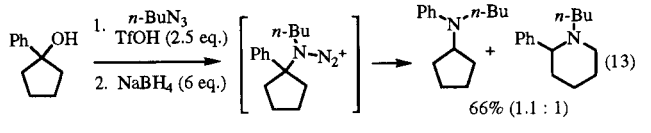
Cyclic azides were then examined, since it is possible that ring expansion of the cycloalkyl group originally attached to the azide may become competitive. In equation (9), the primary benzylic alcohol again leads to hydrogen migration [*c.f.* equation (7)]. The use of a secondary benzylic alcohol, however, allowed some ring expansion to compete, although phenyl migration was the major product [*c.f.* equation (8)].

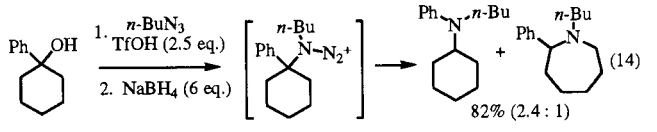
We examined the use of 1-phenylcyclobutyl cations, since relief of ring strain might favor ring-expansion over aryl migration [equations (11) and (12)]. This indeed proved to be a useful strategy, producing pyrrolidines in excellent yield. In equation (12), ring expansion was the only process observed.



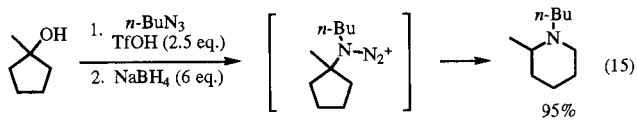


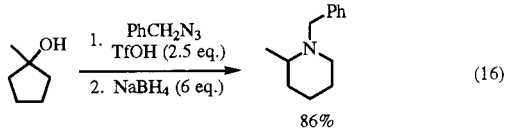
When moving from 1-phenylcyclobutyl cation to the five- and six-membered ring counterparts, a smooth transition from ring expansion to phenyl migration was observed [compare equation (11) with equations (13) and (14)].





All of the intermolecular Schmidt reactions covered so far involve benzylic carbocations. Will the reaction work with simple tertiary carbocations? To our surprise, such cations enter into very efficient Schmidt reactions. Equations (15) and (16) show that tertiary cyclopentyl cations produce piperidines as the sole products in excellent yield. Ring-expansion is now the dominant process; no methyl migration was observed.





Conclusion.

The Schmidt reaction of carbocations is no longer limited to the use of HN_3. Aliphatic azides have been shown to participate successfully in both intra- and intermolecular versions of this process, providing a new and often efficient route to both cyclic and acylic tertiary amines. In addition, the discovery that azides may enter into efficient, low-temperature [3+2] and [3+3] cyclizations with allylic cations may extend the utility of azides for the synthesis of heterocyclic compounds.

Acknowledgement.

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