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Reactions of Alkyl Azides and Ketones as Mediated by Lewis Acids: Schmidt and Mannich Reactions Using Azide Precursors

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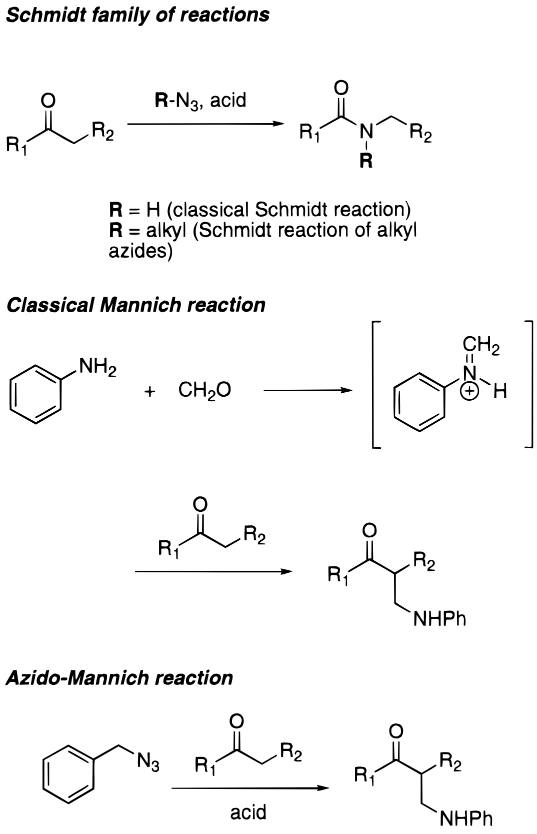
Abstract: The Lewis acid-promoted reactions of alkyl azides with ketones can afford several products. Chief among these result from a Schmidt-like insertion of the azide into the carbon−carbon bond adjacent to the carbonyl group. Alternatively, an acid-promoted rearrangement of the azide to an iminium species can occur, mostly with benzylic azides; the iminium species can then be trapped by the enol of the carbonyl compound in a variation of the Mannich reaction. The scope of each of these reactions, the dependence of the observed products upon azide and ketone structure, and the nature of acid promotion are discussed. In broad strokes, cyclohexanones and other cyclic ketones react in the presence of $TiCl_4$ to afford insertion products, whereas the Mannich route predominates when benzyl azide and triflic acid are used. The features that lead to each reaction type and possible mechanistic implications are discussed.

The insertion of an alkyl azide into a carbonyl compound to afford an amide is analogous to the Schmidt reaction of hydrazoic acid and ketones (Scheme 1).[1] Mostly based on experiments carried out by Briggs[2] and Smith[3] in the 1940s, conventional wisdom had long dictated that a Schmidt reaction using alkyl azides was not possible. However, work in this decade clearly demonstrated *intramolecular* reactions of alkyl azides with ketones,[4] oxonium ions[5,6] and carbocations[7] to be efficient and synthetically useful processes.

Scheme 1



The Mannich reaction and variations thereof have also loomed large in the synthesis of nitrogenous compounds.[8] The traditional formulation of this process as applied to aniline is shown in Scheme 1. It involves the condensation of an amine with an aldehyde to afford a reactive iminium salt (formaldehyde, shown in the Scheme, is a common partner). Condensation with an enolizable ketone then affords the product, which is often called a Mannich base.

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[1] For relevant reviews, see: (a) Wolff, H. *Org. React.* **1946**, *3*, 307−336. (b) Smith, P. A. S. In *Molecular Rearrangements*; de Mayo, P., Ed.; John Wiley & Sons: New York, 1963; Vol. 1, pp 457−591. (c) Abramovich, R. A.; Kyba, E. P. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley & Sons: London, 1971; pp 221−329. (d) Kyba, E. P. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: Orlando, 1984; pp 2−34. (e) Krow, G. R. *Tetrahedron* **1981**, *37*, 1283−1307.

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[6] (a) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 8047−8048. (b) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aubé, J. *Tetrahedron* **1997**, *53*, 16241−16252.

[7] (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. (d) Pearson, W. H.; Fang, W.-k. *J. Org. Chem.* **1995**, *60*, 4960−4961. (e) Pearson, W. H. *J. Het. Chem.* **1996**, *33*, 1489−1496. (f) Pearson, W. H.; Gallagher, B. M. *Tetrahedron* **1996**, *52*, 12039−12048.

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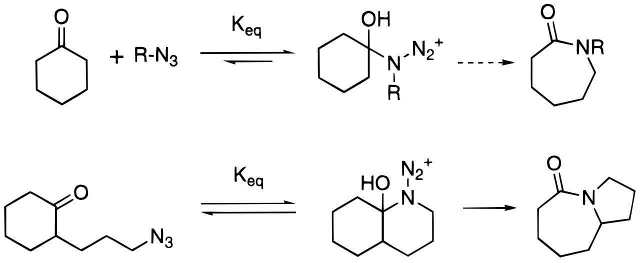
Our continuing studies of the Schmidt reaction of alkyl azides led us to consider whether simple azides (i.e., those lacking additional functionality) could react with appropriately activated ketones after all. In particular, the use of Lewis acid activation instead of the protic conditions almost exclusively used in the era of Briggs's and Smith's work was thought worthy of examination. The initial results of this study, which showed that $TiCl_4$-promoted Schmidt reactions did occur with a limited range of cyclic ketones, have been published in preliminary form.[9] When the same reaction conditions were attempted with *acyclic* ketones, however, no insertion chemistry was observed. Instead, a rearrangement/addition product reminiscent of the Mannich reaction was the only tractable substance obtained (the "azido-Mannich" process shown at the bottom of Scheme 1). The substitution of triflic acid for $TiCl_4$ resulted in a significant improvement in the efficiency, cleanliness, and scope of the reaction.[10]

In addition to providing the details of new variations of two venerable synthetic methods, this full account will examine the factors that determine whether the Schmidt or Mannich manifold will predominate. The emergence of several interesting side reactions and the relationship of these methods to other techniques will also be discussed.

Results and Discussion

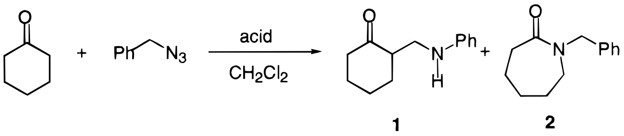
Survey of Reaction Conditions. The success of the intramolecular Schmidt reaction had clearly established alkyl azides as useful nucleophilic partners with ketones. In addition, this work unambiguously showed for the first time that the azidohydrin intermediate initially formed in the Schmidt reaction of either hydrazoic acid or an alkyl azide could undergo nitrogen elimination and directly afford lactam (Scheme 2). In contrast, the Schmidt reaction of hydrazoic acid with ketones probably undergoes initial dehydration followed by rearrangement of an iminodiazonium species, reminiscent of the Beckmann rearrangement.[11] The failure of simple alkyl azides to react with ketones under classical protic conditions, therefore, seemed most likely to result from the unfavorable formation of the initial azidohydrin adduct (i.e., K_{eq} in Scheme 2 is too small). In the intramolecular case, this equilibrium might be more favorable due to entropy. It was reasoned that more aggressive Lewis acid activation of the carbonyl should also facilitate azidohydrin formation in intermolecular cases, and thus a range of acids was surveyed with benzyl azide and cyclohexanone as representative reactants (Table 1).

Scheme 2



In accord with our previously published account,[9] trifluoroacetic acid did not effectively promote the reaction. Lewis acid activation led to variable results, but far and away the most effective promoter of the insertion reaction was $TiCl_4$ (generally used in methylene chloride solution). Although decent conversions to lactam could be obtained using approximately equimolar ratios of reactants and promoter, best results were obtained when the azide was used in excess (cf. entries 3 and 4). Under no circumstances was less than a full equivalent of Lewis acid sufficient, presumably because the product amide is a better Lewis base than the reactant ketone and therefore holds onto the promoter until workup.

Table 1. Effect of Lewis Acids on the Reaction of Benzyl Azide with Cyclohexanone

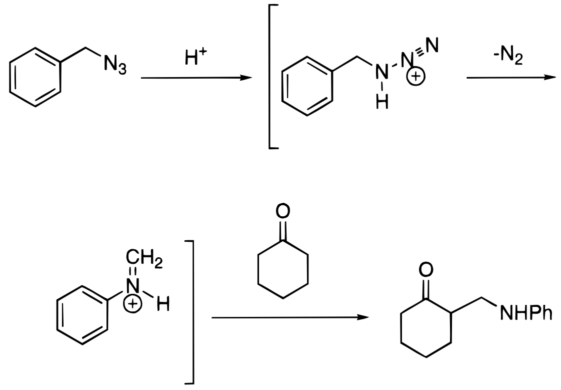


entry	acid	equiv	product ratios[a] 1	2	recovered azide
1	TFA	excess			100
2	TfOH	1.1	79[b]		
3	$TiCl_4$	1.1	39	45	16
4	$TiCl_4$	2.5	15	85	
5	$SnCl_4$	1.1	11		89
6	$SnCl_4$	2.5	?		90
7	$BF_3{\cdot}OEt_2$	1.1	11		89
8	$BF_3{\cdot}OEt_2$	2.5	8		92
9	$AlCl_3$	1.1			100
10	$AlCl_3$	2.5			100

[a] Ratios are normalized to 100 and calculated on the basis of proton NMR integrations of crude reaction mixtures after workup (except where noted). [b] Isolated yield.

When benzyl azide, cyclohexanone, and triflic acid were combined, no Schmidt reaction product was obtained. Instead, a structure strongly suggestive of a Mannich process was obtained in this experiment (entry 2). However, ~30% yields of insertion product had been elsewhere noted when triflic acid was used with nonbenzylic substrates.[12] The (phenylamino)-ketone was also formed in significant amounts when a single equivalent of $TiCl_4$ was added to the two reactants (entry 3). This reaction is thought to proceed as indicated in Scheme 3.

Scheme 3



Initial activation of the azide functional group by protonation (or by Lewis acid coordination, not shown) leads to a migration of the phenyl substituent with loss of nitrogen gas, which serves as a driving force. This leads to the Mannich intermediate shown

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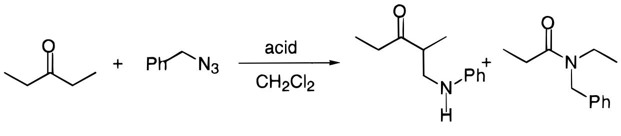
(9) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635−1637.

(10) Schildknegt, K.; Agrios, K. A.; Aubé, J. *Tetrahedron Lett.* **1998**, *39*, 7687−7690.

(11) Richard, J. P.; Amyes, T. L.; Lee, Y.-G.; Jagannadham, V. *J. Am. Chem. Soc.* **1994**, *116*, 10833−10834.

(12) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aubé, J. *Tetrahedron* **1997**, *53*, 16241−16252.

Table 2. Effect of Lewis Acids on the Reaction of Benzyl Azide with 3-Pentanone



3 **4**

entry	acid	equiv	product ratios[a] **3**	**4**	recovered azide
1	TfOH	1.1	84[b]		
2	$TiCl_4$	1.1	62		38
3	$TiCl_4$	2.5	62		38
4	$SnCl_4$	1.1			100
5	$SnCl_4$	2.5			100
6	$BF_3 \cdot OEt_2$	1.1	30		70
7	$BF_3 \cdot OEt_2$	2.5	10		90

[a] Ratios are normalized to 100 and calculated on the basis of proton NMR integrations of crude reaction mixtures after workup (except where noted). [b] Isolated yield.

which is then captured by the enol of the ketone component of the reaction.[13]

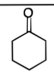
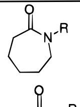
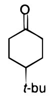
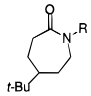
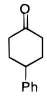
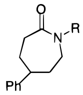
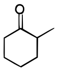
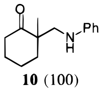
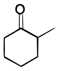
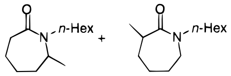
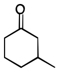
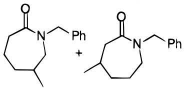
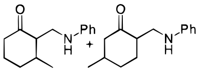
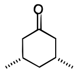
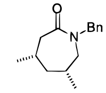
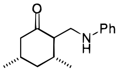
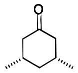
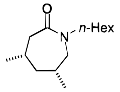
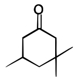
A few experiments explored the effects of changing the order of reagent addition. Little difference was observed when $TiCl_4$ was added to either a mixture of ketone and azide or when added to benzyl azide followed immediately by addition of ketone (4–5:1 ratio of Schmidt to Mannich product being observed in each case). However, when benzyl azide was allowed to react with $TiCl_4$ overnight (to room temperature), a powdery precipitate formed. Removal of solvent by cannula was followed by adding fresh methylene chloride; when the resulting suspension was cooled to 0 °C and cyclohexanone added, only Mannich product was observed by NMR. Standard workup resulted in the isolation of 18% of 2-(phenylamino)methylcyclohexanone. These results are consistent with the powder—which was often observed in the reactions of benzyl azide but absent in those of hexyl azide (see below)—being the proposed iminium ion intermediate.

An analogous study carried out with 3-pentanone as the carbonyl component revealed contrasting results in the sense that no insertion product whatsoever was observed in these cases (Table 2). Instead, both triflic acid and $TiCl_4$ resulted in the formation of Mannich-type product, although the former was the superior reagent for preparative use. As in the case of cyclohexanone, other Lewis acids were relatively inert. We have yet to observe an acyclic ketone that undergoes a Schmidt-type insertion reaction with an alkyl azide (besides 2-pentanone, we have tried acetone, 2-butanone, 2-hexanone, and several β-keto esters and β-diketones).

With boundary conditions thus laid out, we set about the task of determining the scope of these two divergent processes. The goals were (1) to establish the level of synthetic utility that could be expected from each reaction, (2) to further delineate when each reaction pathway was likely to predominate, and (3) to learn what we could about the mechanisms underlying this chemistry.

$TiCl_4$-Promoted Reactions of Substituted Cyclohexanones. Having established that only cyclic ketones apparently undergo Schmidt reaction and that $TiCl_4$/CH_2Cl_2 offers the best reaction conditions for effecting the process, a variety of cyclohexanones were reacted with benzyl azide and *n*-hexyl azide, the latter serving as a prototypical aliphatic alkyl azide (Table 3).

Table 3. $TiCl_4$-Promoted Reactions of Substituted Cyclohexanones

entry	ketone	azide	product(s) (yield, %)
1		BnN_3	 **2**, R = Bn (88)
2		*n*-$HexN_3$	**5**, R = *n*-Hex (80)
3		BnN_3	 **6**, R = Bn (65)
4		*n*-$HexN_3$	**7**, R = *n*-Hex (63)
5		BnN_3	 **8**, R = Bn (70)
6		*n*-$HexN_3$	**9**, R = *n*-Hex (48)
7		BnN_3	 **10** (100)
8		*n*-$HexN_3$	 **11** (12) + **12** (7)
9		BnN_3	 **13** + **14** (44)[a]  **15** + **16** (11)[a]
10		BnN_3	 **17** (52)  **18** (35)
11		*n*-$HexN_3$	 **19** (62)
12		*n*-$HexN_3$	*no reaction*

[a] Isolated as an inseparable mixture of regiosiomers.

The results of these experiments led to several useful generalizations. Unhindered cyclohexanones and their derivatives generally worked well in these reactions. However, dramatically lowered yields and sluggish reactions resulted when even modest α-substitution was added to the carbonyl substrate. (Of less practical importance, due to the poor chemical yields, is the observation that the reactions are also poorly regioselective.)

The effect of more distant substitution can be seen in a series of progressively methylated cyclohexanones (entries 9–12). Although it was possible to optimize the yields of Schmidt reactions of 3,5-dimethylcyclohexanone to the 50–60% range, we never saw any analogous product arise from 3,3,5-trimethylcyclohexanone. It is evident that 1,3-axial methylation suffices to lower the yields of insertion product dramatically. These results are probably due to steric crowding in the transition structures as it is unlikely that such conservative substitution can sufficiently perturb the electronic nature of the system to have this effect. It is instructive that, in some cases, products arising from Mannich processes resulted even when benzyl azide and $TiCl_4$ were used (entries 9 and 10).

Reactions of Other Cyclic Ketones with Alkyl Azides and $TiCl_4$. A selection of other representative ketones yielded further information (Table 4). Again, the generalization that sterically unhindered ketones underwent the most efficient insertion reactions seemed to hold. In these experiments, we did not assiduously search out Mannich products for all cases. Rigidified or "tied-back" examples such as adamantanone or the steroid derivative shown gave the best results. However, simple cyclopentanones gave very poor yields (although the five-membered ring ketone embedded in norbornanone did prove a

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[13] Pearson, W. H.; Fang, W.-k. *Isr. J. Chem.* **1997**, *37*, 39–46.

Table 4. $TiCl_4$-Promoted Reactions of Ketones with Alkyl Azides

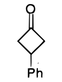
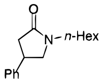
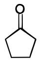
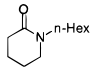
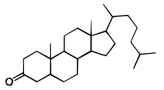
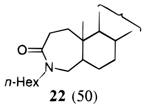
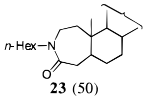
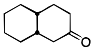
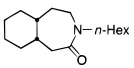
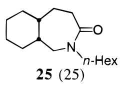
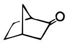
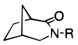
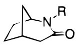
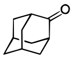
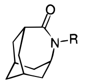
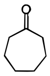
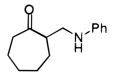
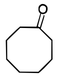
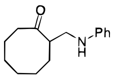
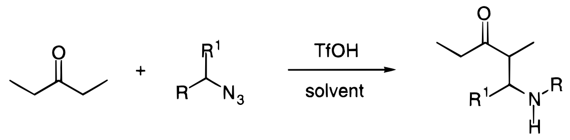
entry	ketone	azide	product(s) (yield, %)	
1		*n*-HexN$_3$	 **20** (51)	
2		*n*-HexN$_3$	 **21** (<5)	
3		*n*-HexN$_3$	 **22** (50)	 **23** (50)
4		*n*-HexN$_3$	 **24** (25)	 **25** (25)
5		*n*-HexN$_3$	 **26**, R = *n*-HexN$_3$ (32)	 **27**, R = *n*-HexN$_3$ (8)
6		BnN$_3$	**28**, R = BnN$_3$ (30)	**29**, R = BnN$_3$ (15)
7		*n*-HexN$_3$		**30**, R = *n*-HexN$_3$ (100)
8		BnN$_3$		**31**, R = BnN$_3$ (98)
9		BnN$_3$	 **32** (93)	
10		BnN$_3$	 **33** (33)	

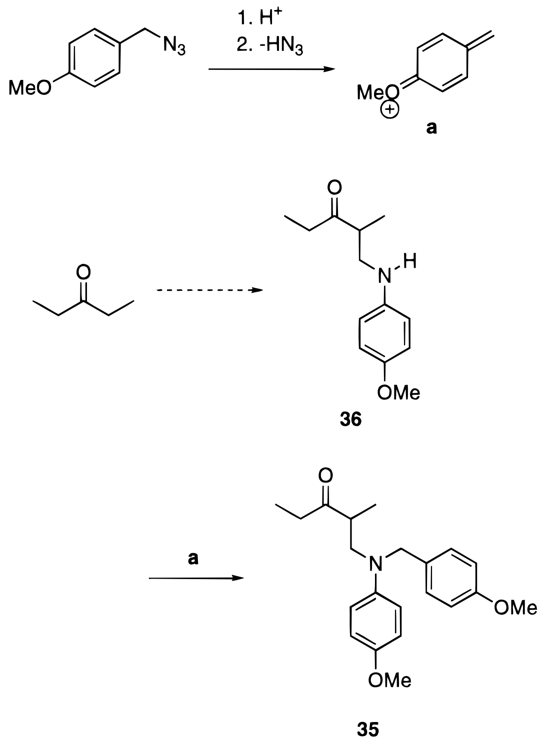
Table 5. Reaction of 3-Pentanone with Alkyl Azides Using Triflic Acid



entry	R	R^1	product (yield, %)	notes[a]
1	phenyl	H	**3** (84)	
2	phenyl	H	**3** (14)	ether
3	phenyl	H	**3** (59)	hexane
4	*p*-methoxy phenyl	H	**34** (22)	compound **35**[b] also isolated (19%)
5	*m*-methoxy phenyl	H	**36** (44)	
6	*m*-methoxy phenyl	H	**36** (49)	2 equiv of azide used
7	*m*-methoxy phenyl	H	**36** (49)	2 equiv of TfOH used
8	*m*-methoxy phenyl	H	**36** (49)	2 equiv of ketone used
9	phenyl	Me	**37** (29)	
10	*p*-carbomethoxyphenyl	H	**38** (69)	
11	*p*-bromophenyl	H	**39** (77)	
12	*n*-hexyl	H		no product isolated

[a] Standard conditions (except where noted): equivalent amounts of all reagents, with reactions carried out in CH_2Cl_2. [b] See Scheme 4.

Scheme 4



fair substrate). On the other hand, the reaction of hexyl azide with 3-phenylcyclobutanone gave a somewhat better result. The observation that cyclopentanones are not good Schmidt reaction partners for alkyl azides is one of the most striking and unexpected outcomes of this study. Besides cyclopentanone itself (entry 2), we have examined 1- and 2-tetralones and several additional substituted cyclopentanones without success. For larger (seven- and eight-membered) ketones, only Mannich pathway was observed.

Scope of the Azido-Mannich Process. Additional studies pertaining to the rearrangement of alkyl azides prior to reaction with ketone are presented in Table 5. A series of aromatic azides gave various levels of the Mannich bases along with, in one instance, an interesting side product **35** (entry 4). The particularly low yields associated with *p*-methoxybenzyl azide and the byproduct obtained through this process could both be explained through the intermediacy of a stabilized benzylic cation resulting from loss of hydrazoic acid from the protonated substrate (Scheme 4). Alternatively, the low yields of the experiment in entry 4 might be due to competitive destruction of the reagent by α-hydride migration, which in this case would afford a benzylic cation stabilized by the *p*-methoxy group. In contrast, no Mannich product was observed when 3-pentanone was reacted with *n*-hexyl azide (entry 12).

Pragmatically, the most important data gleaned from this survey were that (1) approximately equimolar quantities of all reactants suffice for good results, (2) triflic acid in methylene chloride is a superior medium relative to ether or hexane, (3) when TfOH is used as the acid, the order of addition is relatively unimportant, and (4) a good migrating group like phenyl is apparently necessary for a successful reaction. Relevant and complementary results along these lines have been obtained by other workers. Kuwajima has reported an analogous aminomethylation procedure beginning with azido(trimethylsilyl)methane, in which the silyl group undergoes migration to generate an electrophilic Mannich species that reacts with ketones.[14] In addition, Pearson has reported that the iminium species from benzyl azide as shown in Scheme 3 can react as a partner in a Diels−Alder-style cycloadditions to afford 1,2,3,4-tetrahydroquinolines and 1,2-dihydroquinolines.[13] The effect of aromatic substitution in the Pearson chemistry mirrors that noted here.

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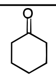
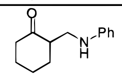
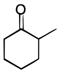
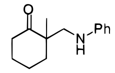
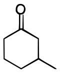
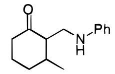
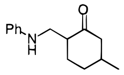
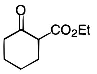
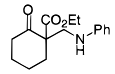
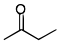
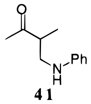
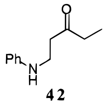
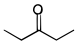
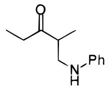
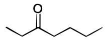
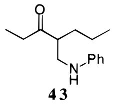
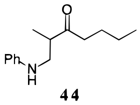
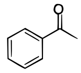
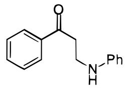
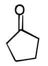
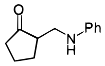
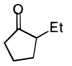
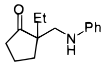
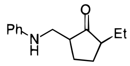
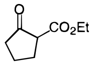
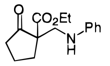
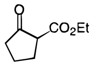
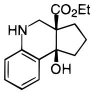
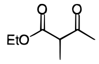
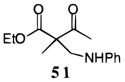
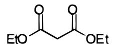
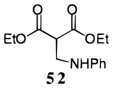
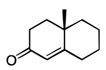
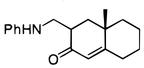
(14) Tanino, K.; Takahashi, M.; Murayama, K.; Kuwajima, I. *J. Org. Chem.* **1992**, *57*, 7009−7010.

Table 6. Triflic Acid Promoted Reactions of Benzyl Azide with Carbonyl Substrates

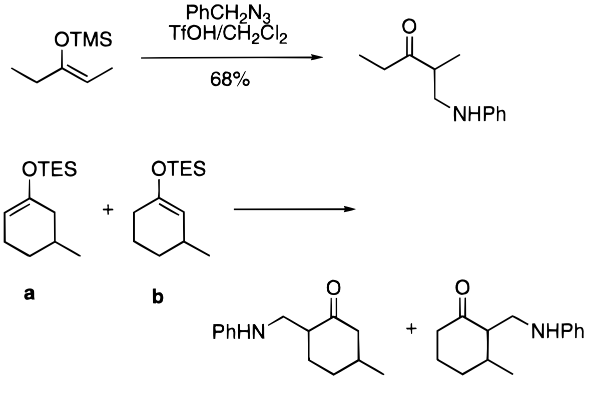
				yields (%)[a]	
entry	ketone	product(s)		TfOH	$TiCl_4$
1		 **1**		79	
2		 **10**		98	
3		 **15**	 **16**	54 (**15**:**16** = 5:1)	
4		 **40**		66	16
5		 **41**	 **42**	6 (**41**:**42** = 10:1)	
6		 **3**		84	46
7		 **43**	 **44**	75 (**43**:**44** = 2.4:1)	
8		 **45**		71	24
9		 **46**		50	23
10		 **47**	 **48**	82 (**47**:**48** = 4.6:1)	
11		 **49**		77	
12		 **50**			88
13		 **51**		77	
14		 **52**		59	59
15		 **53**			25

[a] Isolated yields of reactions promoted by the indicated acid.

The range of possible ketone partners was explored through the series of experiments compiled in Table 6. In some examples, both TfOH and $TiCl_4$ were assayed. Good yields could be obtained through most of the substrate types examined as long as reasonable amounts of enol could be generated in the reaction mixture. As was our experience with the intramolecular Schmidt reaction of alkyl azides, α,*β*-unsaturated ketones continue to pose a problem (entry 15).[4] On the other hand, *β*-keto esters generally gave good results, although we did not obtain tractable products from acetoacetone or dimedone.

As might be expected, the ratios of the regioisomeric α-phenylaminomethylated ketones roughly reflected the expected thermodynamic ratios of the intermediate enols. We briefly examined some silyl enol ethers as starting points for the reaction (Scheme 5). Although these compounds turned out to be acceptable substrates, the product ratios did not reflect the ratios of the starting enol ethers. This suggests that these reactions proceed through initial hydrolysis of the enol ethers and that the resulting ketones react with the aminomethylation reagent present in situ.

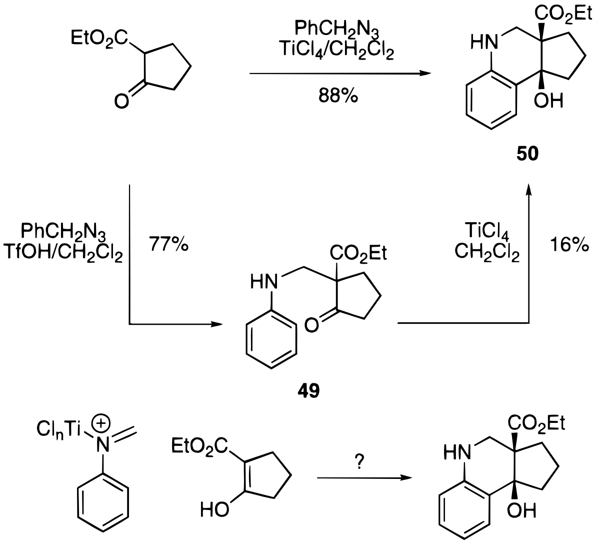
Scheme 5



ratio **a** : **b**	product ratio
2 : 1	4 : 1
b only	4: 1

An entirely different type of product was obtained from the reaction of 2-carboethoxycyclopentanone and benzyl azide in the presence of $TiCl_4$ (Table 6, entry 12 and Scheme 6). In this example, an 88% yield of the tricyclic compound **50** was obtained and its structure confirmed through X-ray crystallography. Although it is possible that the reaction occurs via a Mannich reaction followed by an intramolecular Friedel–Crafts process, this seems unlikely in view of the relatively poor yield obtained when bona fide Mannich product **49** was submitted to the reaction conditions that led to the tricyclic material. Another possibility is that the Lewis acid-activated iminium ion undergoes a hetero-Diels–Alder reaction with the enolized form of

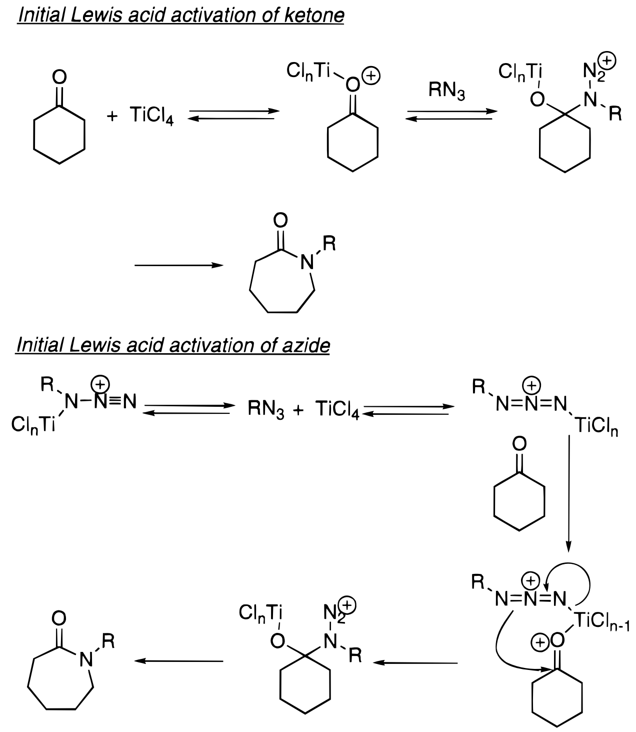
Scheme 6



the β-keto ester. Related Diels–Alder processes were independently observed by Pearson from rearrangement processes.[13] At any rate, this reaction remains a curiosity for the time being as it has not been observed in any other case, including the homologous 2-carbomethoxycyclohexanone.

Mechanistic Issues and Scope. It is apparent from these studies that the Schmidt reaction of alkyl azides with ketones is highly sensitive to steric effects. Furthermore, when an azide has an alternative pathway available to it, other processes begin to take over. It is also clear that powerful Lewis acid activation is needed for efficient addition of azide to the carbonyl group. There are a variety of mechanistic possibilities available to the reaction. Most similar to the classical Schmidt reaction mechanism[1] would be the simple Lewis acid activation of the carbonyl followed by the addition of alkyl azide (Scheme 7, top). As noted above, similarities to the Schmidt reaction of hydrazoic acid with ketones must stop with the formation of the initial azidohydrin adduct as dehydration to afford an iminodiazonium ion is not an option for this intermediate. Once formed, it can only undergo bond reorganization to yield the product lactam (as its $TiCl_4$ complex) or revert back to starting materials. (Note that the values of n for $TiCl_n$ are left open throughout this discussion.)

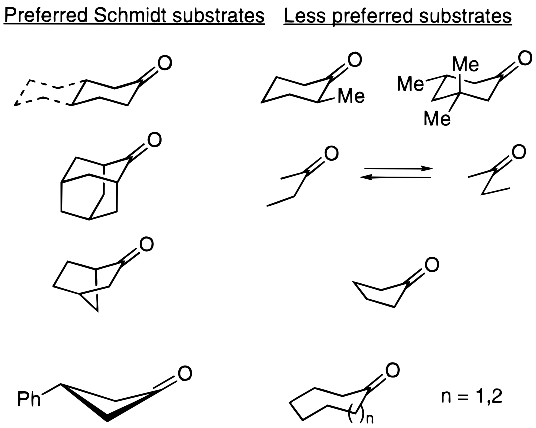
Scheme 7



An alternative would be for the azide to form an adduct with the Lewis acid (Scheme 7, bottom). The complexation of methyl azide with $SbCl_5$ has been reported; interestingly, the adduct leads to an imine upon treatment with HCl.[15] The titanium could coordinate azide at either the proximal (alkyl group-bearing) or distal nitrogen. In the present context, complexation of the $TiCl_4$ group with the ketone carbonyl might set up a six-membered ring transition structure allowing for transfer of the alkyl azide to the carbonyl group and establishing the azidohydrin intermediate. However, the addition of electrophiles to an alkyl azide is generally considered to occur at the proximal position based on observed chemistry. Such examples would include the azidohydrin intermediates proposed for both intermolecular and intramolecular Schmidt reactions, and protonation prior to imine formation in the Mannich process (Scheme 3). Olah and co-workers detected exclusively proximal protonation of methyl and ethyl azides in superacid medium; in addition, aminodiazonium ions are favored over the tautomeric iminodiazenium ions.[16] For these reasons and for the sake of simplicity, we prefer the former mechanism for rationalizing our results.

Significant steric crowding results from the addition of both Lewis acid and alkyl azide to the carbonyl component. Thus, unhindered cyclohexanones or multicyclic ring systems in which the ketone-bearing ring is immobilized without nearby substituents work best. However, the ketone's enthusiasm for ring-expansion diminishes with even moderate steric bulk or, it would seem, conformational flexibility. This would account for the lack of observed Schmidt reactivity with alkyl azides and acyclic ketones. As shown in Scheme 8, a terminal methyl group in the conformationally flexible butanone derivative shown can swing into the vicinity of the carbonyl, in a placement reminiscent of the 2-methyl group of 2-methylcyclohexanone, which is also a poor Schmidt substrate. In either case, the steric environment of the ketone is significantly crowded and apparently unable to accommodate both the Lewis acid and the poorly nucleophilic azide as is required for addition to the carbonyl.

Scheme 8



It seems unlikely that steric hindrance alone can account for the dependence of Schmidt reaction yields on ring size. In general terms, additions to cyclic ketones (such as cyanohydrin formation) are favorable for three-, four-, and six-membered rings but less facile for all other common ring systems.[17] These phenomena are usually attributed to the emergence of greater 1,2-torsional interactions encountered during additions to five- and seven-to-ten-membered ring systems or, alternatively, due to an increase in I-strain during the conversion of the carbonyl carbon from the sp^2 to the sp^3 hybridization state.[17] The present work indicates that the addition of an alkyl azide to a carbonyl, even when activated by a powerful Lewis acid, is a marginally acceptable process that only occurs when everything is right. These considerations can explain the failure of cyclopent-, cyclohept- and cyclooctanones to afford insertion product under the standard conditions described.

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[15] Goubeau, J.; Allenstein, E.; Schmidt, A. *Chem. Ber.* **1964**, *97*, 884–890.

[16] Mertens, A.; Lammertsma, K.; Arvanaghi, M.; Olah, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 5657–5660.

[17] For a general discussion of these concepts and leading references, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 762 and 769–771.

Conversely, acyclic and larger-ring ketones appear to be perfectly good substrates for the Mannich process so long as benzyl azide is used (Table 4, entries 9 and 10, and Tables 5 and 6). The main requirement for reaction in this manifold seems to be simple enolizability, although additional functionality could prove problematic in more complex examples (Table 6, entry 15).

Summary. The Lewis acid-mediated reactions of simple ketones with alkyl azides have been explored. It has been shown that the Schmidt reaction of alkyl azides, a reaction proposed over 50 years ago, can occur but is only synthetically useful for a fairly restricted set of carbonyl-containing substrates. Fortunately, it is possible to overcome many of these limitations in the reactions of ketones with hydroxy azides,[6] which offer considerably greater synthetic flexibility (due to the presence of an ω-hydroxy or other[18] functional group in the product) as well as efficiency and scope. In the course of this work, the rearrangement of benzyl azides and subsequent Mannich reaction was discovered. The availability of this pathway imposes a limitation on the use of benzyl azide in the intermolecular Schmidt (and, to a lesser degree, on the intramolecular version as well[19]) but is significantly more forgiving with respect to ketone structure. Overall, these reactions further solidify the view of azides as viable nucleophilic species under favorable conditions.

Experimental Section

Spectral data for all new compounds are collected in the Supporting Information.

General Experimental Procedure for Schmidt Reactions Using $TiCl_4$. 4-Hexyl-4-azahomoadamantane (30). To a solution of 2-adamantanone (119 mg, 0.79 mmol) and 1-azidohexane (200 mg, 1.58 mmol) in 2.5 mL of methylene chloride, in an ice bath, was added dropwise $TiCl_4$ (380 mg, 2.0 mmol). The reaction was allowed to warm to room temperature with immediate gas evolution noted. A precipitate formed after 15 min, and the suspension was stirred for a total of 16 h at which time it was diluted with 20 mL of ethyl acetate and partitioned between 200 mL of ethyl acetate and 30 mL of saturated sodium bicarbonate. The organic layer was extracted with 30 mL of brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by flash chromatography (ethyl acetate−hexanes (1:4)) gave 197 mg of a clear oil (100%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (br t, $J = 4.78$ Hz, 3H), 1.31 (br s, 6H), 1.41−1.55 (m, 2H), 1.72 (br s, 2H), 1.72−1.85 (m, 4H), 1.85−2.00 (m, 5H), 2.06 (br s, 2H), 2.80−2.87 (m, 1H), 3.37 (br t, $J = 6.4$ Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 13.9, 22.4, 26.2, 26.5, 27.9, 31.0, 31.6, 34.4, 35.7, 42.4, 48.8, 52.7, 178.2; IR (neat) 2914, 1630 cm^{-1}; MS (EI) *m*/*e* 249 (M^+), 220, 206, 178. HRMS *m*/*e* calcd for $C_{16}H_{27}NO$: 249.2093, found 249.2092.

General Procedure for Mannich Reactions Using Triflic Acid. 2-Phenylaminomethyl Cyclohexanone (1). To a solution of benzyl azide (500 mg, 3.76 mmol) in 8 mL of CH_2Cl_2 at 0 °C was added cyclohexanone (0.39 mL, 3.76 mmol). The mixture was stirred for 10 min and TfOH (0.37 mL, 4.14 mmol) was added dropwise; gas evolution was observed. The reaction was allowed to warm to room temperature and stirred for 20 h at which time 0.2 g of solid $NaHCO_3$, 10 mL of CH_2Cl_2, and 20 mL of H_2O were added. The aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Concentration followed by chromatography (15% ether/hexanes) gave 480 mg of an off-white solid (63%): $R_f = 0.20$ (20% ether/hexanes); mp 86−87 °C; IR (CH_2Cl_2) 3360, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, $J = 8.5$, 7.4 Hz, 2H), 6.71 (t, $J = 7.3$ Hz, 1H), 6.61 (d, $J = 7.7$ Hz, 2H), 4.17 (br s, 1H), 3.45 (dd, $J = 13.6$, 7.7 Hz, 1H), 3.13 (dd, $J = 13.6$, 4.6 Hz, 1H), 2.66 (m, 1H), 2.44 (m, 2H), 2.33 (m, 1H), 2.22−2.07 (m, 2H), 1.94 (m, 1H), 1.78−1.63 (m, 2H), 1.51 (dq, $J = 12.7$, 3.8 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 213.5, 148.5, 129.7, 117.7, 113.3, 50.3, 44.3, 42.6, 32.5, 28.2, 25.3; CIMS *m*/*z* (relative intensity) 204 (MH^+, 30), 106 (95), 77 (15); HRMS calcd for $C_{15}H_{19}NO_3$: 261.1365, found: 261.1342.

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Supporting Information Available: Characterization data for all new compounds, details of the X-ray crystallographic determination of compound **50**, and copies of the NMR spectra of compounds **13**−**16** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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