Azide rearrangements in electron-deficient systems

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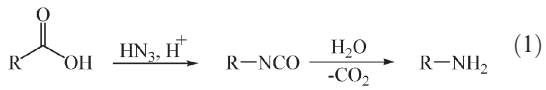
The azide group has a diverse and extensive role in organic chemistry, reflected in the power of azide anion as a strong nucleophile, the role of organic azides as excellent substrates for cycloaddition reactions, the uses of azides as precursors of amines and nitrenes, and azide rearrangements known as the Curtius and Schmidt reactions. In recent years the scope of the Schmidt reaction has begun to be explored in depth, so that it now represents an important reaction in synthetic chemistry. This *tutorial review* analyses and summarises key recent developments in the field of Schmidt reactions.

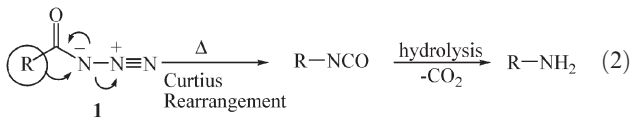
The Schmidt reaction with carboxylic acids

The Schmidt reaction[1,2] was originally a generic term for a class of reactions that involved the addition of hydrazoic acid to a carbonyl or other compound to cause insertion of a nitrogen atom into a chain or ring. The most common form was the reaction with a carboxylic acid (eqn (1)).



(1)

The mechanism of the reaction is thought to be similar to that of the Curtius rearrangement (eqn (2)), which involves an acyl azide, except that in this case it is the protonated azide that undergoes the rearrangement (eqn (3)).



(2)

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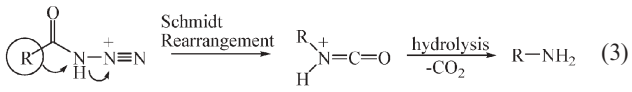

(3)

2

The Schmidt reaction of carboxylic acids proceeds well with hindered acids. Hence Newman and Gildenhorn[3] proposed a mechanism for the addition of HN_3, formed *in situ* from acidification of NaN_3, to 2,6-dimethylterephthalic acid **3** in the presence of H_2SO_4 (Scheme 1). The protonation of **3** results in the formation of dihydroxycarbocation **4**, which is in equilibrium with acylium ion **5**. The necessary formation of **5** would explain why hindered carboxylic acids are favourable substrates. The addition of HN_3 followed by loss of N_2 and H^+ gives isocyanate **6**, which can undergo hydrolysis to give **7** and then undergoes decarboxylation to produce 4-amino-3,5-dimethylbenzoic acid **8** in 87% yield.

The Schmidt reaction with ketones

It is clear that compound **2** above features a very reactive diazonium leaving group that triggers the reaction. A similar diazonium leaving group would also be revealed following attack of azide anion on any electrophile, and so it is not

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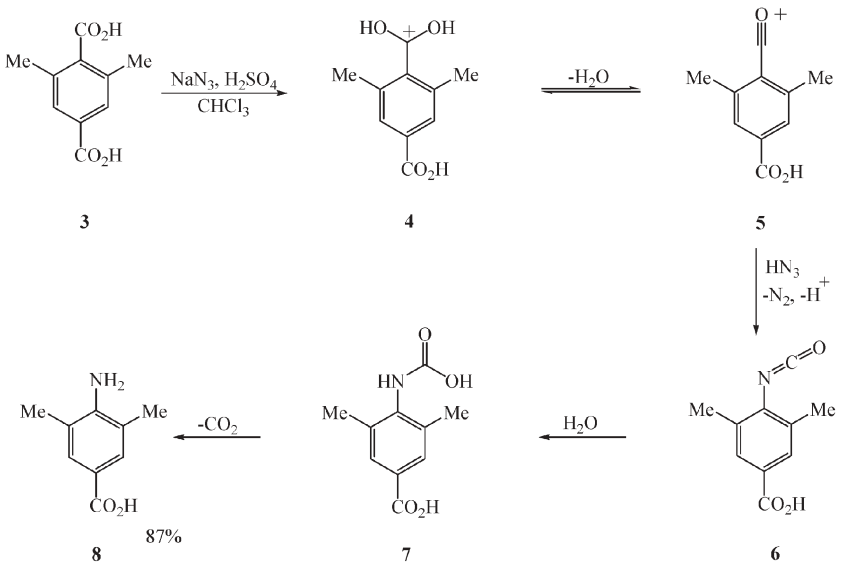


Scheme 1

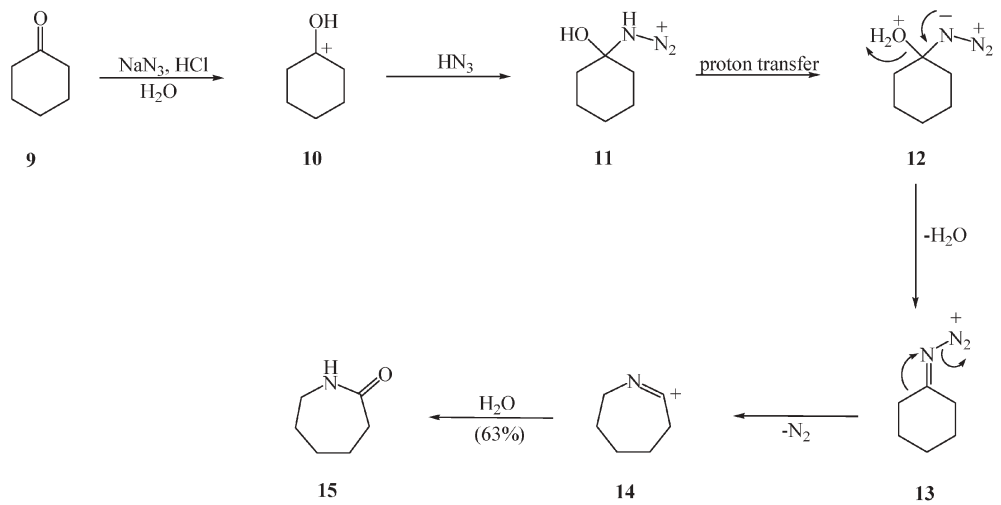
surprising that the family of Schmidt reactions is not confined to carboxylic acids. Simultaneously with Newman and Gildenhorn, Smith[4] independently published results following his observations on the reaction of hydrazoic acid with ketones in the presence of mineral acid (Scheme 2). He showed that when ketone **9** was treated with acid it formed carbocation **10**. Intermediate **10** was then attacked by azide to give **11**. Proton-transfer would result in formation of **12**. The loss of water gave **13**, which rearranges, again losing N_2, to give **14**. Cation **14** is then trapped by water present in the mixture to give lactam **15**.

Krow and co-workers[5] have studied the regiochemistry of the Schmidt reaction of 7-substituted norcamphors **16** and related compounds (Scheme 3). When **16** was exposed to conc. H_2SO_4 and NaN_3 in $CHCl_3$ the reactions proceed predominantly by a methylene migration to form lactam **17**, except when one of the substituents at the 7-position (R^1, R^2) is OTs. In that case, the regioselectivity of migration is reversed and **18** forms as the major product.

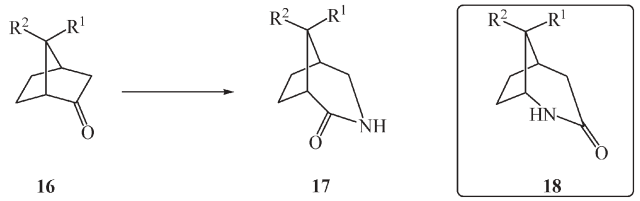
In many cases, Schmidt reactions were carried out in halogenated solvents; this is potentially dangerous as poly-halogenated alkanes can give rise to explosive polyazides. Moreno-Mañas *et al.*[6] proposed the use of DME as a safer solvent than chloroform and dichloromethane for performing reactions involving azides. Using their reaction conditions, NaN_3 and methanesulfonic acid in DME, ketones were converted to amides in high yield, *e.g.* cyclohexanone **9** was converted into lactam **15** in an excellent yield of 96%.

The Schmidt reaction with ketals and related derivatives

Electrophiles can also be generated from activation of ketals and related functional groups. In this context, Trost *et al.*[7] performed a Schmidt type process using thionium ions as a carbonyl substitute (Scheme 4). Thioketal **19**, dissolved in CH_2Cl_2, was exposed to IN_3 to prepare azide **20**. Azide **20** was



Scheme 2



Scheme 3

subsequently treated with TFA in $CHCl_3$ at 25 °C forming lactam **15** in 79% yield, probably *via* **13** after loss of methanethiol. Additionally when **20** was reacted with $SnCl_4$ in MeCN it formed imino thioether **21** in 80% yield. It was also shown that **21** could be prepared directly from **19** by treating it with NaN_3 and $SnCl_4$ in CH_2Cl_2 at −78 °C. This produced **21** in 46% yield.

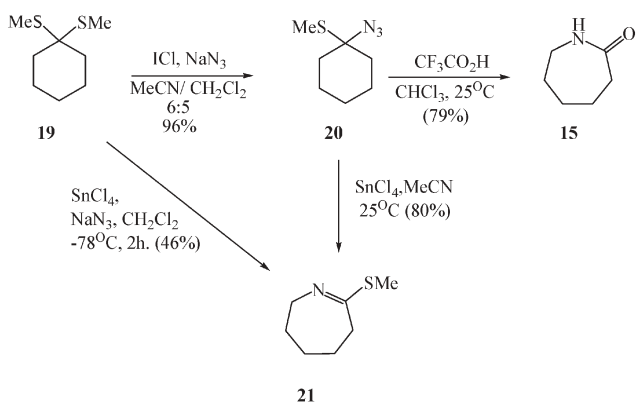
2 Organoazides in Schmidt type reactions

With ketones and ketal derivatives

The reactions described so far originated from attack of inorganic azide ion on electrophiles. The azide group in organic azides, RN_3, should be much less nucleophilic than azide ion, but nevertheless retains the important dipolar character of the azide group. Hence, in the presence of an electrophile, and particularly an intramolecular electrophile, we might also observe rearrangements. This underpins many important recent discoveries that have transformed these Schmidt reactions into the exciting reactions of excellent potential in synthesis.

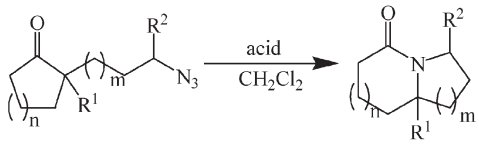
Aubé *et al.*[8,9,12,14–21] have been at the forefront of recent applications showing the versatility of the Schmidt reaction of azidocarbonyl compounds and their protected analogues, azidoketals. Aubé *et al.*[8] performed intramolecular Schmidt reactions with efficient conversion to bicyclic lactams (Table 1). Using either protic or Lewis acid conditions in CH_2Cl_2, keto azides **22** underwent Schmidt reactions.

Mossman and Aubé[9] also showed that bicyclic lactam **23c** could be prepared from dimethyl ketal **24** (Scheme 5). The treatment of **24** in CH_2Cl_2 with TFA resulted in initial formation of an oxonium ion **26**, which is then set-up to undergo the Schmidt reaction (similar to that shown in



Scheme 4

Table 1



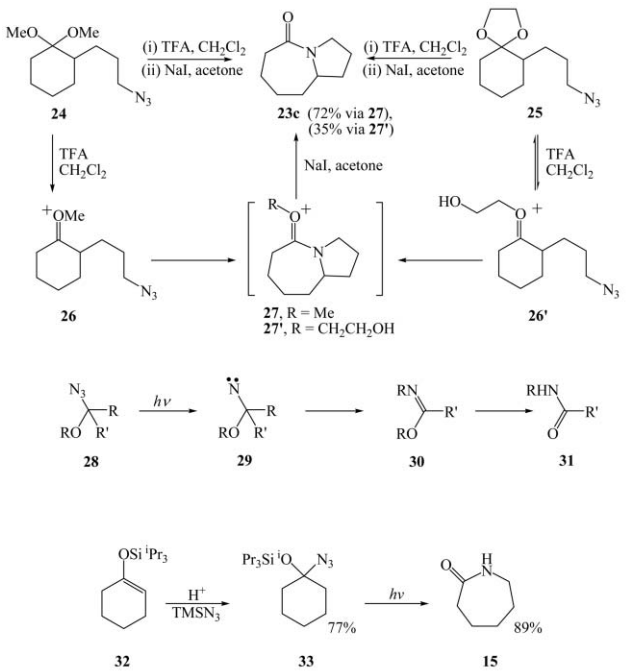
22 **23**

Compound	*n*	*m*	R^1	R^2	Acid	Time/min.	Yield/%
a	1	1	H	H	TFA	45	83
b	1	1	CO_2Me	H	$TiCl_4$	20	70
c	2	1	H	H	TFA	10	90
d	2	1	CO_2Et	H	TFA	1	93
e	2	1	H	Me	TFA	20	74
f	2	2	H	H	$TiCl_4$	16	91

Scheme 2); after a subsequent work-up with NaI in acetone (used to dealkylate oxonium ion **27**), formation of the desired lactam **23c** resulted in a yield of 72%.

It was also shown that treatment of 1,3-dioxolane **25** under the same conditions only resulted in a 35% conversion to lactam **23c**. The reason for the lower yield in the case of the cyclic ketal could be to do with likely reversible nature of the conversion of **25** to **26′** due to the cyclic structure of the starting ketal **25** (Scheme 5).

Because of the photoreactivity of azides, it is not surprising that a photochemically driven Schmidt reaction is known. Hassner and co-workers[10] showed that α-azidoalkyl ethers **28** are photolysed to afford imino ethers **30** that can then be hydrolysed to amides **31**. The initial reaction probably involves formation of a reactive nitrene **29**, followed by alkyl group migration. More recently, this has been developed[11] into a convenient conversion of silyl enol ethers **32** to amides *via*



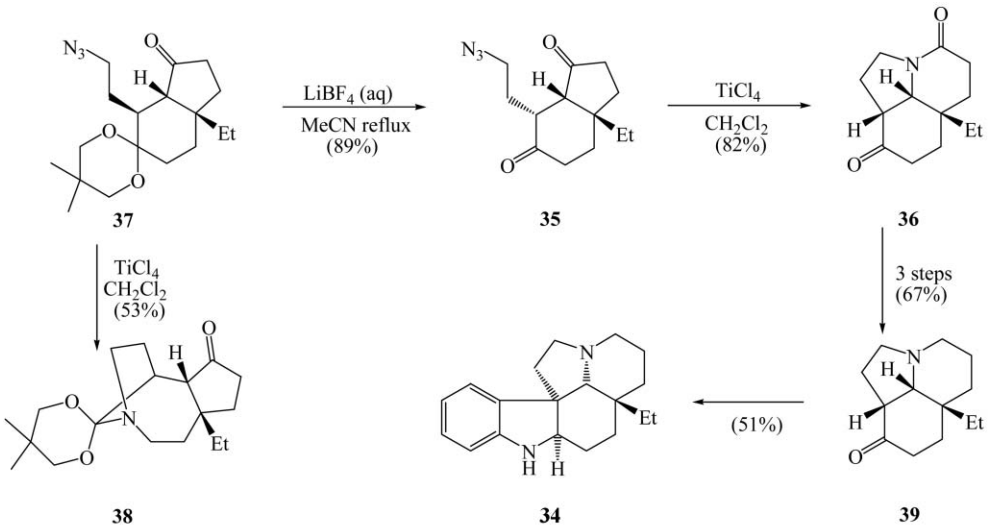
Scheme 5

easily formed triisopropylsilyl-azidohydrins **33**. In the photochemical reactions, the migration step shows very little selectivity, so that this reaction works best for symmetrical compounds like **33** (Scheme 5).

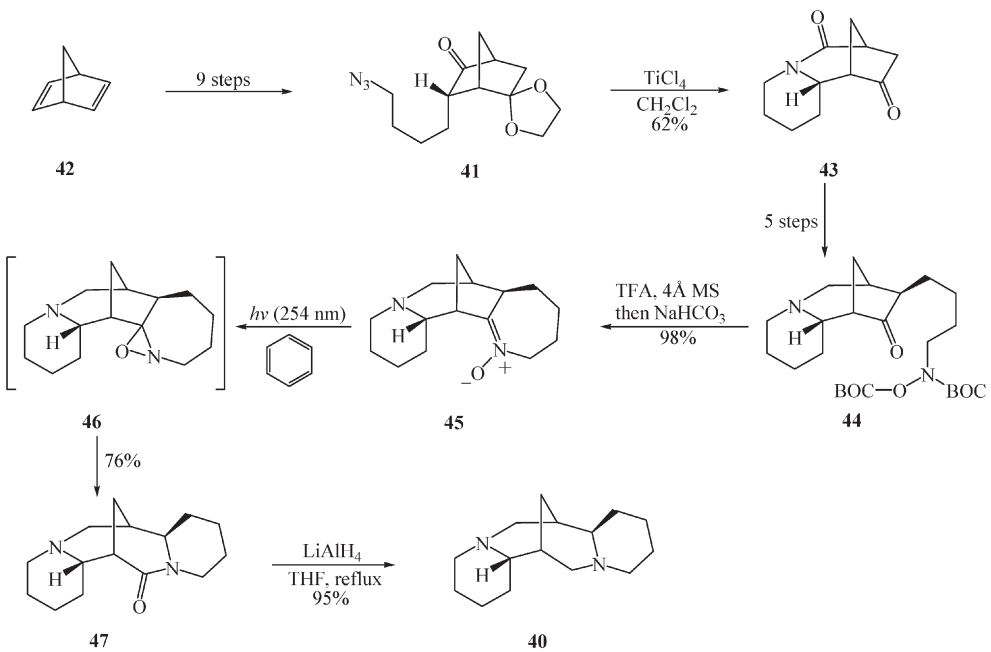
One of the key tests of any reaction is whether it can be applied to synthesis of polyfunctional complex molecules; in this regard, the Schmidt reaction is now proving of value. Aubé *et al.*[12] utilised this intramolecular Schmidt reaction in their total synthesis of (+)-aspidospermidine **34**. Their strategy was based on a regioselective intramolecular Schmidt reaction of diketoazide **35**. Previous studies had shown them that the intramolecular Schmidt reactions proceed faster when there is a four-carbon spacer between ketone and azide, as opposed to a three-carbon spacer.

Exposure of **35** to $TiCl_4$ in CH_2Cl_2 constructed lactam **36** in 82% yield. Previously they had attempted this selectivity using monoketal **37** thus presenting only one carbonyl group. Treatment of **37** with $TiCl_4$ in CH_2Cl_2 only resulted in formation of **38** in a yield of 53%, probably *via* Lewis acid activation of the ketal. Conversion of **36** to **39** was effected in 67% over three steps, with the synthesis of **34** being completed using a Fischer indole synthesis according to the procedure described by Stork[13] (Scheme 6).

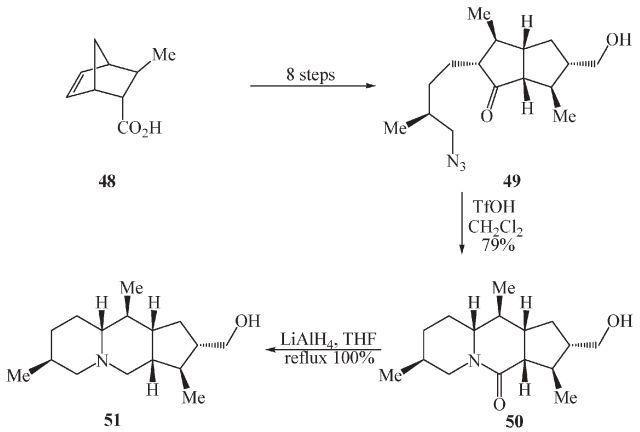
Aubé and co-workers[14] have also used this methodology in their total synthesis of (+)-sparteine **40** (Scheme 7). They found that when keto-azide **41**, which can be prepared in nine steps from norbornadiene **42** using standard chemical transformations, was treated with $TiCl_4$, lactam **43** resulted in 62% yield.



Scheme 6



Scheme 7



Scheme 8

This lactam **43** was then converted to BOC-protected hydroxylamine **44** in five steps. Treatment of **44** with TFA and 4Å molecular sieves followed by $NaHCO_3$ gave nitrone **45**, which, when subjected to ultra-violet irradiation in benzene, underwent a photo-Beckmann rearrangement to give lactam **47** in 76% yield. Compound **47** was then reduced with $LiAlH_4$ to give (+)-sparteine **40** in 95% yield. It is worth pointing out that attempts to form this second lactam system using Schmidt type conditions on an azide analogue of **44** were unsuccessful. It was reasoned that this was due to the Lewis acid or protic acid coordinating to the basic piperidine nitrogen thus hindering the reaction.

Aubé *et al.*[15] also used this reaction as a crucial step in their total synthesis of the dendrobatid alkaloid indolizidine 251 F **51**. Treatment of azide **49**, which can be prepared in eight steps from literature Diels–Alder adduct **48**, with TfOH gave lactam **50** in 79% yield (Scheme 8). This lactam was then reduced to amine **51** using $LiAlH_4$ in quantitative yield.

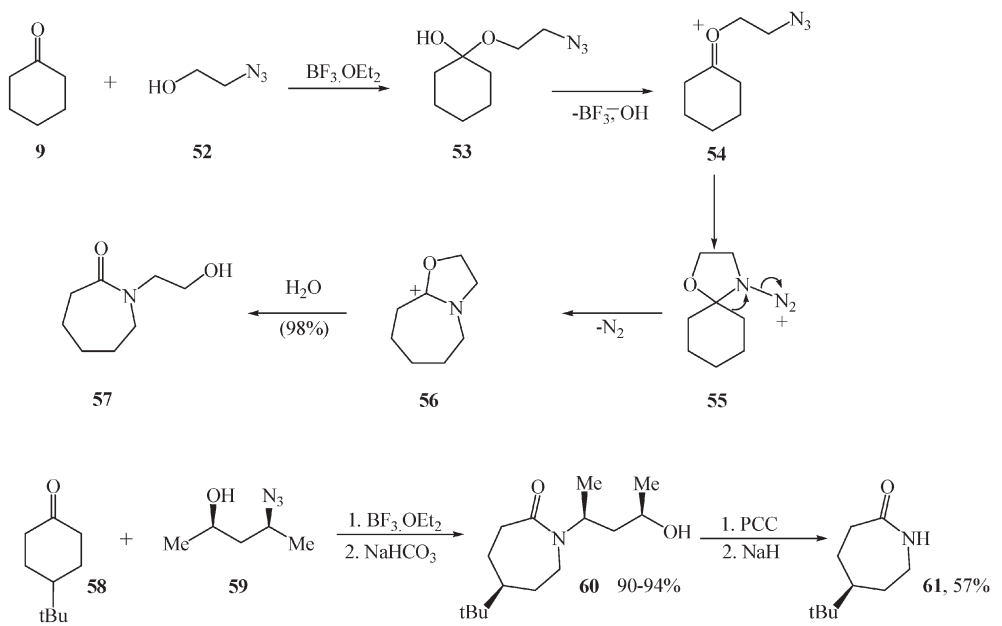
Intermolecular examples using organoazides

Plainly, the above reactions feature both the azide and the ketone in the same molecule. The scope of the Schmidt reaction could be extended if it were possible to accomplish such reactions in an intermolecular fashion, starting from two different molecules, one an azide and the other a ketone, a much more difficult task. A clever way of achieving this end was developed by Aubé *et al.*[16,17] who performed these reactions using azido alcohols, as the azide-containing moiety. (See later for intermolecular attack of alkyl azides on substrates other than ketones.)

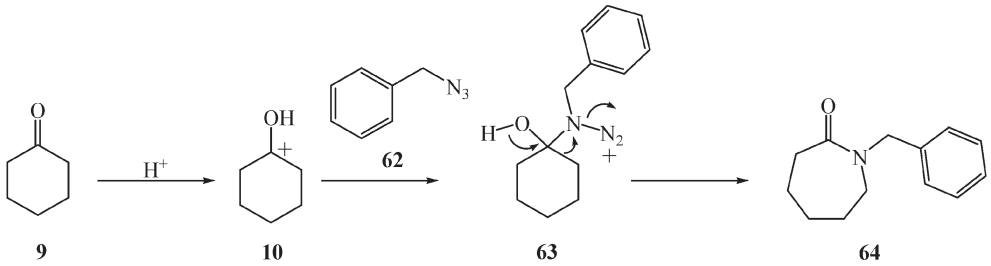
The alcohol unit of the azido-alcohol reacts *in situ* with the target ketone to form a hemiketal; this renders the subsequent attack on the activated hemiketal intramolecular, even though the ketone and azide originated in different molecules. For example, when cyclohexanone **9** is treated with azido alcohol **52** and $BF_3.OEt_2$ it initially forms hemiketal **53**, which dehydrates generating oxonium ion **54**. Cyclisation of the azide onto the oxonium ion constructs aminyl diazonium **55**. Migration of the alkyl group with loss of N_2 results in formation of cation **56**, which, after hydrolysis, furnishes amido alcohol **57** in 98% yield (Scheme 9).

One of the most exciting prospects for the future development of the reaction lies in the field of asymmetric Schmidt reactions,[18] based on this idea of hemiketal formation. Thus reaction of ketone **58** with hydroxy azide **59** afforded lactam **60** as a single diastereomer; deprotection afforded enantiomerically pure lactam **61** (Scheme 9. A computational study leading to a rationalisation of related reactions has recently been published.[19]

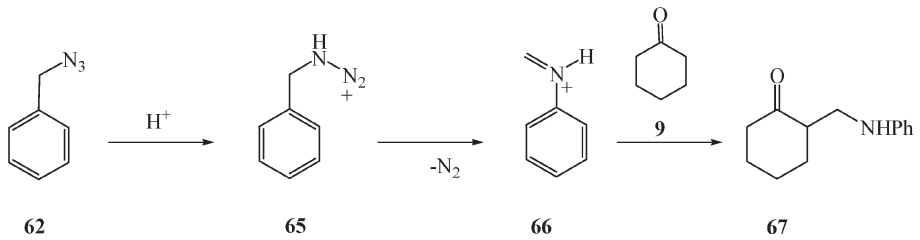
Aubé and co-workers[20,21] attempted to go a step further, and to find conditions for a strictly intermolecular Schmidt reaction of a ketone with an organic azide. They reported that treatment of a mixture of benzyl azide **62** and cyclohexanone **9** in CH_2Cl_2 with acid leads to two competing reactions.



Scheme 9



Scheme 10



Scheme 11

The first one is the desired Schmidt process where **9** is protonated forming **10** (equivalent pathways can of course be proposed for the Lewis acid induced reactions). Cation **10** is then attacked by **62** to form tetrahedral intermediate **63**, which is analogous to **11**. This time, however, the reaction does not follow a dehydration pathway, as was thought with the reactions involving HN_3, but instead undergoes a direct migration resulting in loss of N_2 to give amide **64** (Scheme 10). The second process is a competing Mannich type reaction (Scheme 11). This involves **62** being protonated to give **65**, which undergoes phenyl migration resulting in loss of N_2 to form **66**. Mannich intermediate **66** then reacts with the enol form of **9** resulting in construction of the Mannich base **67**.

This reaction was carried out using a number of different protic and Lewis acids with only limited success (Table 2). The only Lewis acid showing any insertion product was found to be $TiCl_4$ with every other acid screened either yielding Mannich product **67** or recovered starting ketone **9**. When the reaction was tested on acyclic ketone **68**, no Schmidt product **69** was formed, with only the Mannich product **70** along with starting material **68** being detected (Scheme 12).

With alkenes and alcohols

Pearson *et al.*[22] have studied how organoazides react after generation of a cation separated by an appropriate number of bonds. They were encouraged by finding that when azide **71** was treated with triflic acid followed by neutralisation with NaOH, enamine **72** was formed in 71% yield as the sole product (Scheme 13).

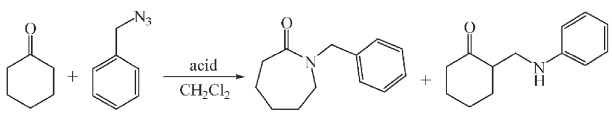
They reasoned that this reaction must proceed by protonation of **71** forming cation **73**, which underwent cyclisation giving bicyclic compound **74**. Migration of the axial alkyl group resulting in loss of N_2 gave cation **75**, which underwent proton transfer to leave **76**. Enammonium ion **76** was then neutralised furnishing **72**.

Since this original finding, Pearson *et al.*[23–27] have created cations similar to **73** by subjecting a range of both alcohols and alkenes to acid conditions (Table 3).

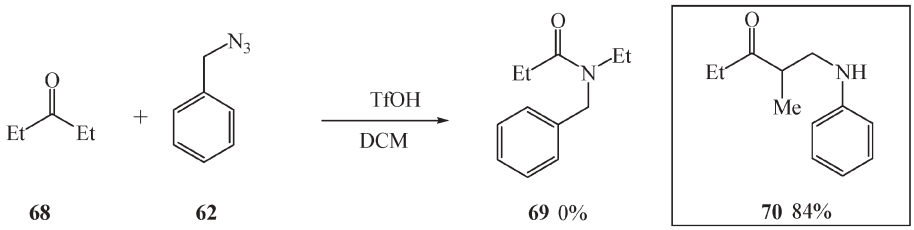
In addition to intramolecular Schmidt processes they have also published examples of alcohols undergoing *intermolecular* Schmidt reactions (Scheme 14).

Pearson and Fang[28] found the intramolecular Schmidt reaction synthetically useful in the formal synthesis of the alkaloid gephyrotoxin **80** (Scheme 15). Gephyrotoxin **80** is known to be readily prepared from Ito's intermediate **81**. They demonstrated that treatment of azidobromide **82** with triflic acid afforded a mixture of iminium ions **83** and **84**. These salts

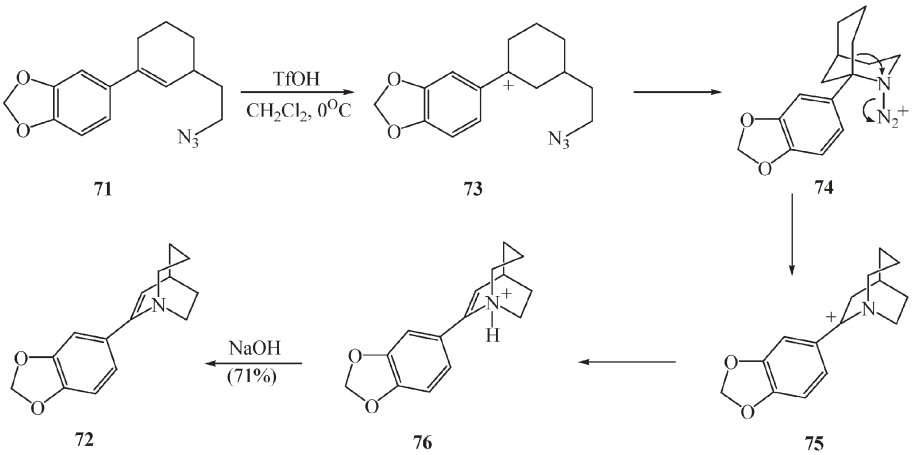
Table 2



		Yield/%		
Acid	Equiv.	**64**	**67**	**9**
TFA	XS	0	0	100
TfOH	1.1	0	79	0
$TiCl_4$	1.1	45	39	16
$TiCl_4$	2.5	85	15	0
$SnCl_4$	1.1	0	11	89
$SnCl_4$	2.5	0	0	90
$BF_3{\cdot}OEt_2$	1.1	0	11	89
$BF_3{\cdot}OEt_2$	2.5	0	8	92
$AlCl_3$	1.1	0	0	100
$AlCl_3$	2.5	0	0	100

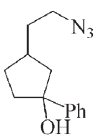
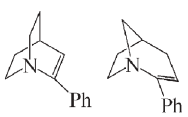
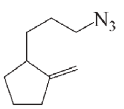
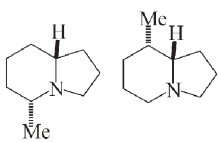
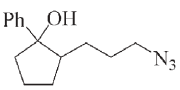
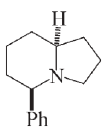
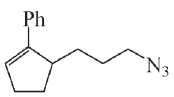
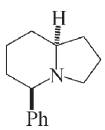


Scheme 12



Scheme 13

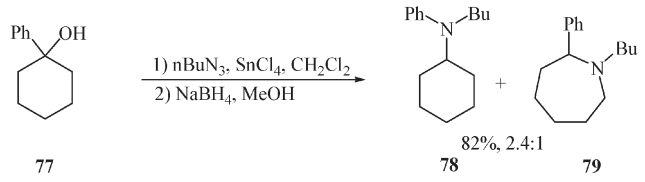
Table 3

Starting material	Conditions	Products	Yield (ratio)
	1) TfOH, PhH 2) $NaBH_4$, MeOH		76% (1.8 : 1)
	1) TfOH, PhH 2) $NaBH_4$, MeOH		71% (1 : 1)
	1) $SnCl_4$, CH_2Cl_2 2) $NaBH_4$,MeOH		63%
	1) TfOH, PhH 2) $NaBH_4$, MeOH		57%

were never isolated, but were instead exposed, in sequence, to L-Selectride, $^{n}Bu_4NOAc$ then $LiAlH_4$ to furnish benzo-fused 1-azabicyclo[4.3.0]alkane **81** in 45% yield along with 10% of isomer **85**.

With epoxides

Baskaran and co-workers[29] used acid-induced opening of an epoxide in order to activate an intramolecular Schmidt



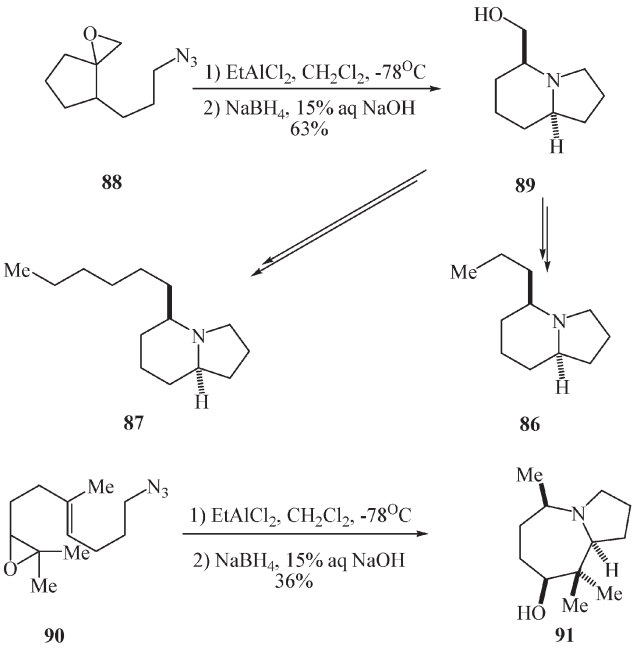
Scheme 14

reaction in their synthesis of indolizidine 168B and 209D, **86** and **87** respectively.

Treating easily prepared epoxy azide **88** with $EtAlCl_2$ in CH_2Cl_2 at −78 °C followed by *in situ* $NaBH_4$ reduction in 15% aq. NaOH furnished intermediate **89** in 63% yield, which could be converted to both **86** and **87** (Scheme 16).

Baskaran and co-workers[29] also showed that their epoxide-opening conditions could be used as part of a tandem cyclisation of acyclic **90** finishing with an intramolecular Schmidt reaction constructing bicyclic compound **91** in 36% yield (Scheme 16).

We have seen earlier in the case of aminodiazonium salt **65** that aryl rings can displace dinitrogen, and this has been used in a synthetically useful sense by Lang *et al.*[30] using styrene oxides. On activation of the epoxide **92**, they showed that facile migration of the arene to electron-deficient nitrogen occurred, leading to an unusual synthesis of complex aniline derivatives (Scheme 17).

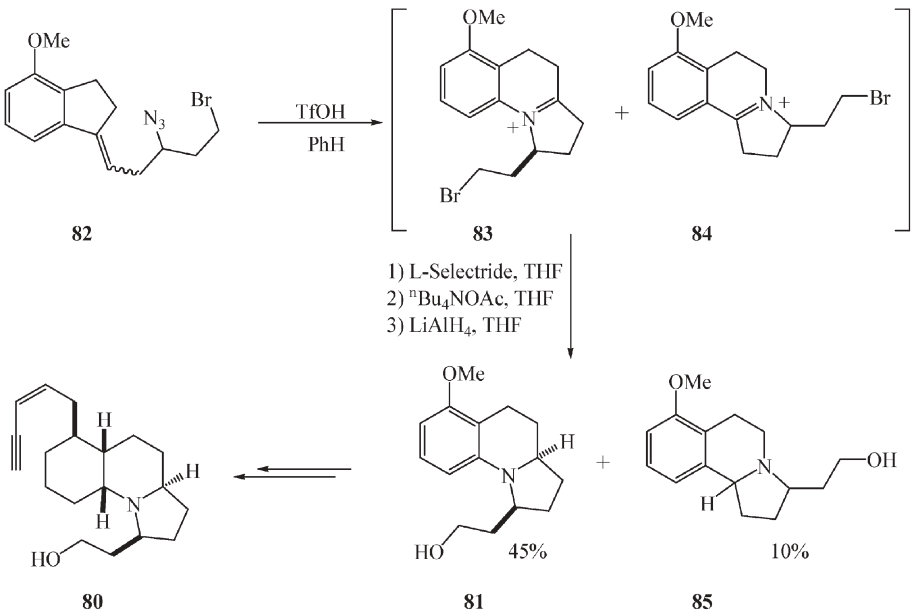


Scheme 16

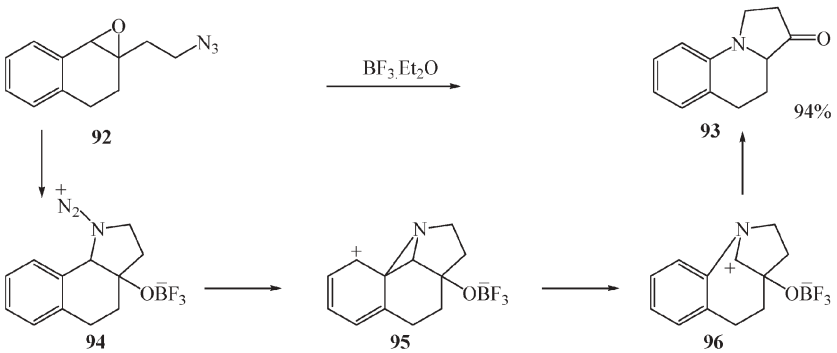
Via triazoline intermediates derived from α,β-unsaturated ketones and alcohols

Sha and co-workers[31] reported an intramolecular 1,3-dipolar cycloaddition of alkylazide-enones that is followed by the rearrangement of the triazoline intermediate (Scheme 18). They showed that if azide **97** is heated in refluxing toluene it undergoes a 1,3-dipolar cycloaddition to construct triazoline intermediate **98**, which decomposes giving **99**. Zwitterion **99** is then set-up for a 1,2-alkyl shift resulting in loss of dinitrogen and furnishing protonated imine **100** that loses a proton to give **101** in 64% yield.

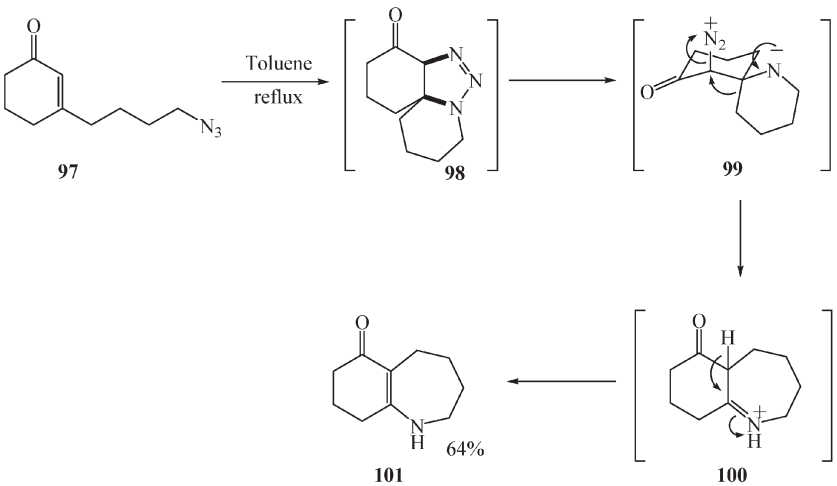
Molander and Bibeau[32] also studied how azidoalkenones rearrange when heated in different solvents. They found the optimum conditions for the reaction to be heating in refluxing xylenes for 15 h for both yield and ease of separation from the solvent. They then proceeded to test this reaction on a range of azidoalkylenones (Table 4).



Scheme 15



Scheme 17



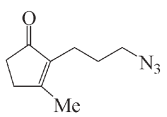
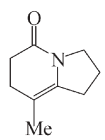
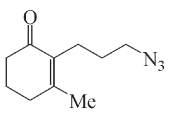
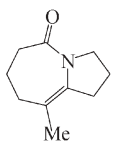
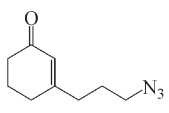
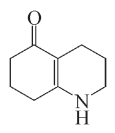
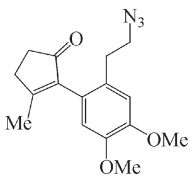
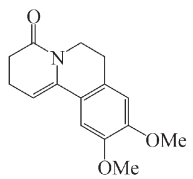
Scheme 18

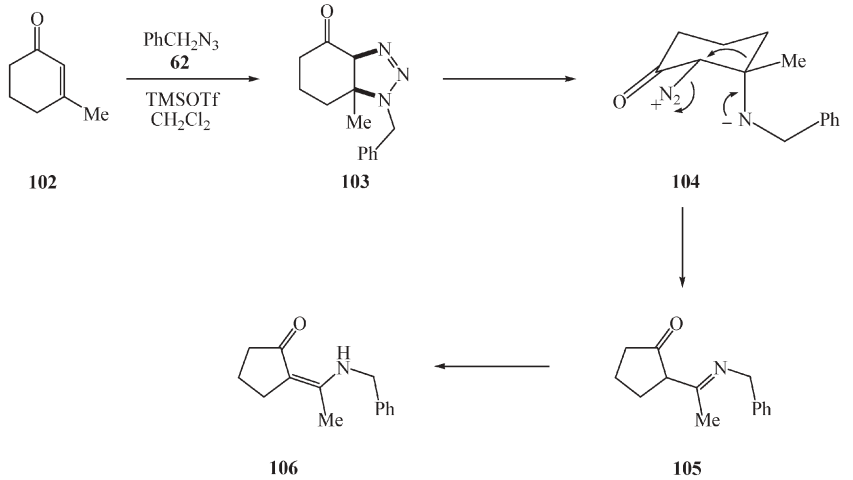
Aubé *et al.*[33] showed that α,β-unsaturated ketone **102** can, when activated with TMSOTf, react in a [3 + 2]-cycloaddition with azide **62** to give triazoline **103**, which then gives **104** (Scheme 19). Intermediate **104** can then undergo a migration reaction causing a ring contraction resulting in the formation of imine **105**, which after tautomerism gives enaminoketone **106** in 78% yield.†

Pearson *et al.*[25,35] also experienced triazoline formation in their attempt at an acid-mediated intramolecular Schmidt reaction on a 2-(α-hydroxyalkyl)indolesulfonamide. They reported that treatment of hydroxyazide **107** initially forms allylic carbocation **108** (Scheme 20). This then undergoes a cycloaddition, although the mechanism for this process is unclear. It has been proposed that the cycloaddition either proceeds stepwise *via* aminodiazonium **109** to give benzylic cation **110** or through a concerted π4s+ π2s cycloaddition forming **110** directly. Triazoline **110** then picks up a chloride ion to furnish **111** in 75–95% yield. Although the mechanism of the cycloaddition is not known it is noteworthy that there was none of Schmidt product **112**, which would arise from **109**.

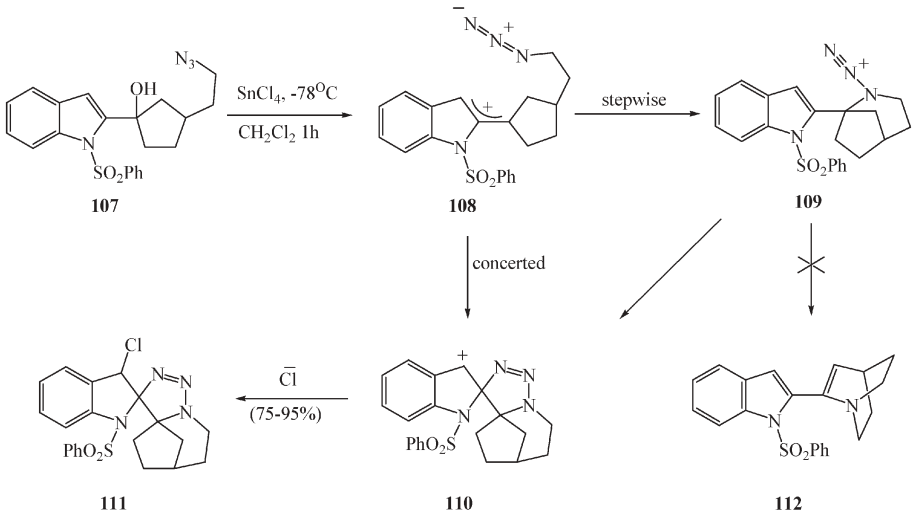
† A recent paper[34] suggests that formation of triazoline intermediates in intermolecular reactions of azides with α,β-unsaturated carbonyl groups may not be the unique reaction path.

Table 4

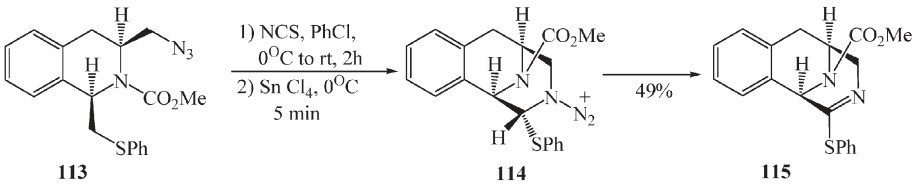
Subtrate	Product	Isolated yield/%
		80
		83
		71
		65



Scheme 19



Scheme 20



Scheme 21

Via Pummerer reactions

Magnus *et al.*[36] used methodology involving organic azides in their strategy for constructing tetrahydroisoquinoline alkaloids. They found that if azido sulfide **113** is treated with NCS followed by $SnCl_4$, amino diazo intermediate **114** is formed (Scheme 21). However instead of this molecule undergoing a migration pathway as was seen in work of Aubé and co-workers, transformation to the thioimidate **115** occurs in 49% yield.

Summary of azide rearrangements

Organoazides have been shown to be extremely versatile and effective substrates for performing different types of migration rearrangements with various activation methods available. Work in this area, particularly by the groups of Aubé and Pearson has really expanded the scope of these reactions pushing the boundaries beyond that of just being able to use hydrazoic acid as the azide source. The driving force for these

reactions is undoubtedly the production of nitrogen as a by-product, which is subsequently lost from the system, thus forcing the reaction to completion.

Due to the highly unstable nature of the amino diazo intermediate that is routinely generated, efficient decomposition pathways have to be carefully built into any substrate that is to be tested under these Schmidt conditions. If one rearrangement pathway is not dominant the reaction could then lead to total decomposition and the formation of a complex mixture of compounds. Current studies are focused towards deriving a greater understanding of selectivity in this reaction, and in extending the range of substrates that can be used in Schmidt reactions.

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