The 2-(2-Azidoethyl)cycloalkanone Strategy for Bridged Amides and Medium-Sized Cyclic Amine Derivatives in the Aubé–Schmidt Reaction

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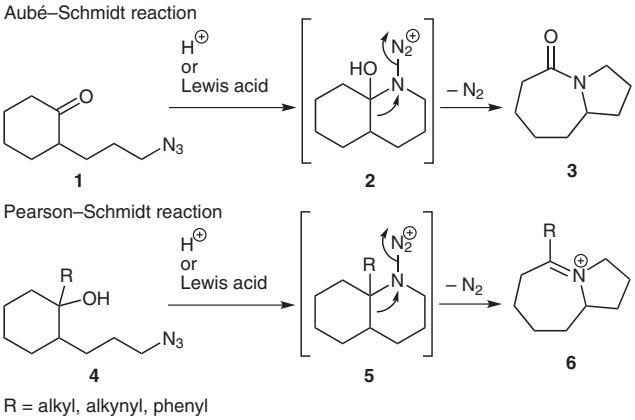
Dedicated to Professor Gerry Pattenden on the occasion of his 70th birthday

Abstract: 2-(2-Azidoethyl)cycloalkanones afford bridged lactams in the Aubé–Schmidt reaction, sometimes in excellent yield, and solvolysis yields derivatives of medium-ring amines. Attempts to divert the Schmidt reaction with an arene-mediated fragmentation of the normal Schmidt intermediate have led to an initial example.

Key words: Aubé, Schmidt, rearrangement, azide, heterocycle, bridged amide, medium-ring amine, medium-ring amide

Over the past two decades, Aubé[1] and Pearson[2] have developed the scope of the Schmidt reaction[3] remarkably into an extremely useful reaction for synthesis.[4] Aubé concentrated largely on the reaction of alkyl azides with ketones, for example, **1** (Scheme 1) and aldehydes,[5] while Pearson and co-workers explored the Schmidt reaction of alkyl azides with tertiary carbocations generated from the corresponding alcohol or alkene, for example, **4** in a process that yields an iminium salt **6** which can then be reduced or deprotonated.



Scheme 1

The Aubé–Schmidt reaction proceeds via a cyclic intermediate **2** that undergoes rearrangement with loss of nitrogen, N_2. As shown in Scheme 2, two pathways are open for the rearrangement involving migration of different bonds and, when starting from a cycloalkanone, these lead to fused amide or bridged amide, respectively, the outcome being determined by stereoelectronic effects. Normally the major product is the fused amide (as in Scheme 1) but a recent discovery by Aubé illustrates how to change the selectivity.[6] Scheme 2 shows that when two related substrates **7** and **10** react, the outcome can be strongly influenced by an appropriately placed arene substituent in the substrate. The principal product from substrate **7** is the fused heterocycle **8**, resulting from a reactive intermediate where the aminodiazonium group, $R_2N–N_2^+$ is equatorial (see inset in Scheme 2). Migration of the antiperiplanar ring-junction bond leads to expulsion of N_2 and formation of **8** (the breaking and migrating bonds are shown as bold lines in the reactive intermediates shown in Scheme 2). In substrate **10**, the bridged product **12** is the major product and arises from a reactive intermediate with an axial aminodiazonium group. The preference for the axial orientation arises from attractive interactions between the $R_2N–N_2^+$ cation and the electron-rich arene. Migration of the antiperiplanar bond leads to the bridged amide **12** in this case. The proposals for cation-π interactions have been backed by computational studies by Aubé.[7]

Very recently, this strategy has been extended beyond arene groups to sulfide groups.[8] This use of electron-rich substituents can drive these reactions towards preferential or exclusive formation of bridged amide products.

Bridged amides have also been produced selectively in some other special cases, notably in the preparation of highly strained quinuclidine salt **14** by Stoltz et al.[9] In this case, the placement of the side chain β to the carbonyl group in substrate **13** ensures that only bridged amide products **14** and **15** could form, regardless of which bond migrates.

We now suggest an alternative strategy for accessing medium-ring amides, and medium-ring amine derivatives resulting from their solvolyses. Medium-ring amines are present in a large number of biologically important compounds.[10] Some of the bridged amides formed so far in Schmidt reactions are highly strained and undergo solvolysis to form medium-ring amine derivatives, while others are less strained and need more vigorous conditions for solvolysis.[8,11]

The substrates chosen for Schmidt reaction are very often δ-azidoketones, as in the examples in Schemes 1 and 2 above. It has been shown[12] that when the azide group is placed γ and δ to two potentially competing reactive ke-

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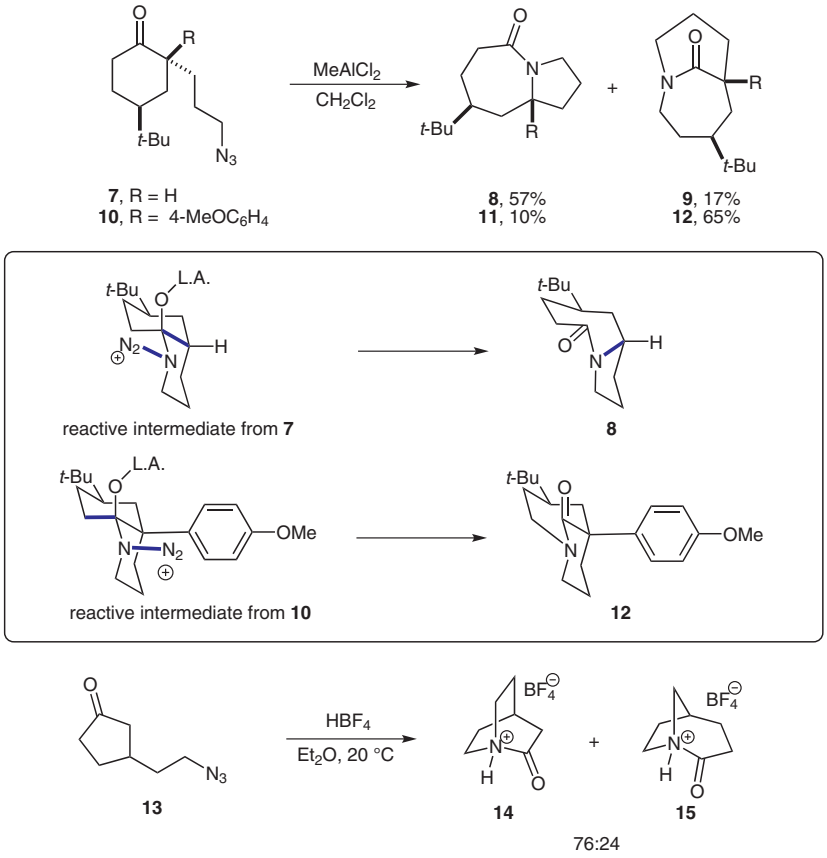
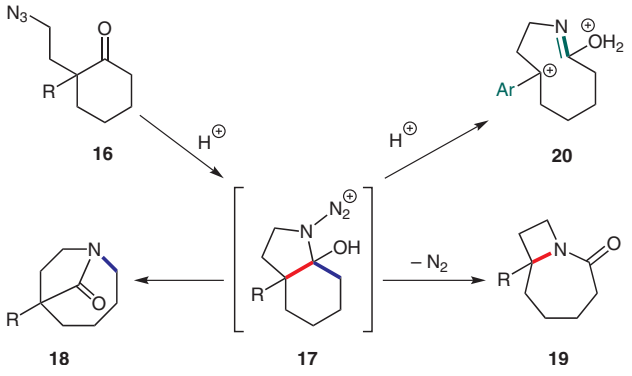


Scheme 2

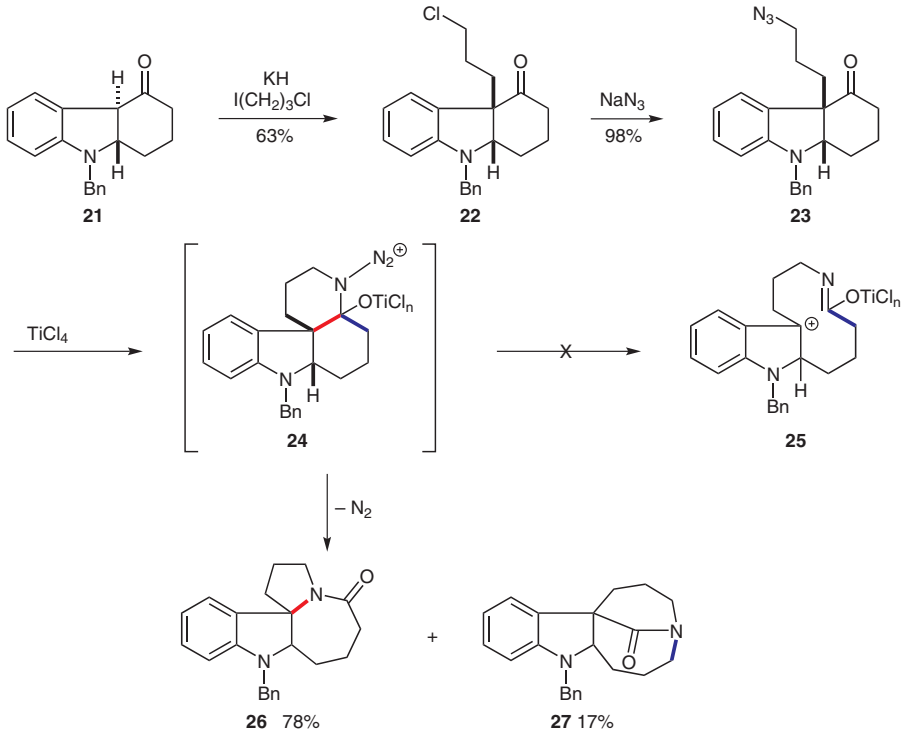
tones, then the δ-azidocarbonyl grouping preferentially reacts. Aubé pointed out that γ-ketoazides derived from cycloalkanones fail to give the normal Schmidt product, probably due to the fact that that product would contain a strained *N*-acylazetidine.[1b] Scheme 3 illustrates the point: substrate **16** would afford reactive intermediate **17**. Assuming that access to the appropriate conformation is available, migration of the ring-junction bond (shown in red) would afford an *N*-acylazetidine **19**.



Scheme 3

With this information, we wondered about alternative outcomes for the reaction of substrates like **16**. Does the blue bond migrate to form bridged amide **18**? Our studies below were undertaken for two types of substrate (i) with R = H, and (ii) with R = Ar. In the latter case, we wished to explore also whether in intermediates like **17** (R = Ar) the electronic push of the hydroxyl group that triggers the migration could be diminished, perhaps through further protonation of the hydroxyl group in triflic acid or through association with a sufficiently strong Lewis acid. If the push were sufficiently diminished, it might allow the electron-rich arene (R = Ar) to divert the normal course of the Schmidt rearrangement in favor of a fragmentation to a macrocyclic dication **20** that could then be transformed to a neutral amide product, for example, by tautomerism and deprotonation.[13] Dications like **20** might look like high energy intermediates, but recent reports suggest that dications may be more prevalent in organic chemistry than previously recognized.[14]

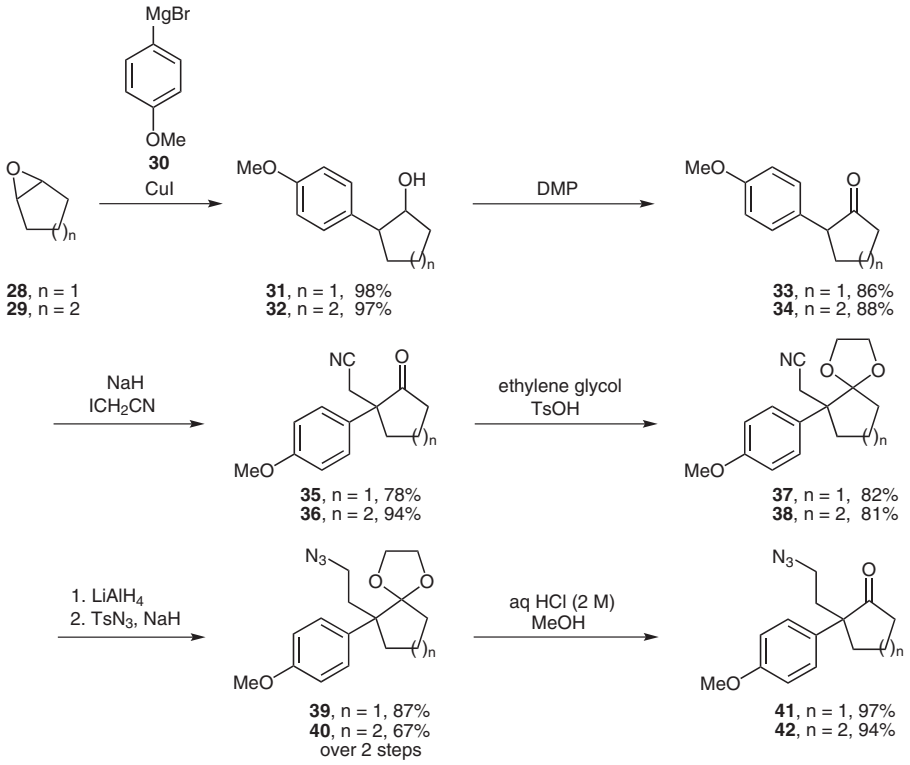
Our search started with an examination of this last point exclusively with substrate δ-azidoketone **23**, easily prepared in two steps from the known indoline **21** (Scheme 4).[15] This substrate bears an azidopropyl side chain, as opposed to the azidoethyl chains in the examples below, and was simply designed to test the relative fragmentation powers of the *N*-benzylindoline versus the titanium-bound oxygen in **24** in this type of substrate. No products resulting from fragmentation to a macrocycle **25** were seen. Instead, a combined 95% yield of the ring-fused product **26** (78%) and the bridged lactam **27** (17%) was formed. As with subsequent examples below, this



Scheme 4

bridged lactam **27** gave a ^{13}C carbonyl resonance (δ = 184 ppm) in the diagnostic 184–192 ppm region.[1b]

We now proceeded to prepare 2-(2-azidoethyl)-cycloalkanones to test the outcomes of their Schmidt reactions. The synthesis of the initial substrates **41** and **42** was initiated by epoxide opening with aryl bromide **30** in the presence of a catalytic portion of CuI (Scheme 5). The resulting alcohols **31** and **32** were oxidized with Dess–Martin periodinane (DMP) to give ketones **33** and **34** that were alkylated by sequential treatment with NaH and iodoacetonitrile. The carbonyl groups in **35** and **36** were



Scheme 5

protected as the corresponding ketals and the nitrile groups reduced with $LiAlH_4$ to give amines that were converted into the corresponding azides **39** and **40**. Finally, deprotection of the ketals afforded the desired substrates **41** and **42**.

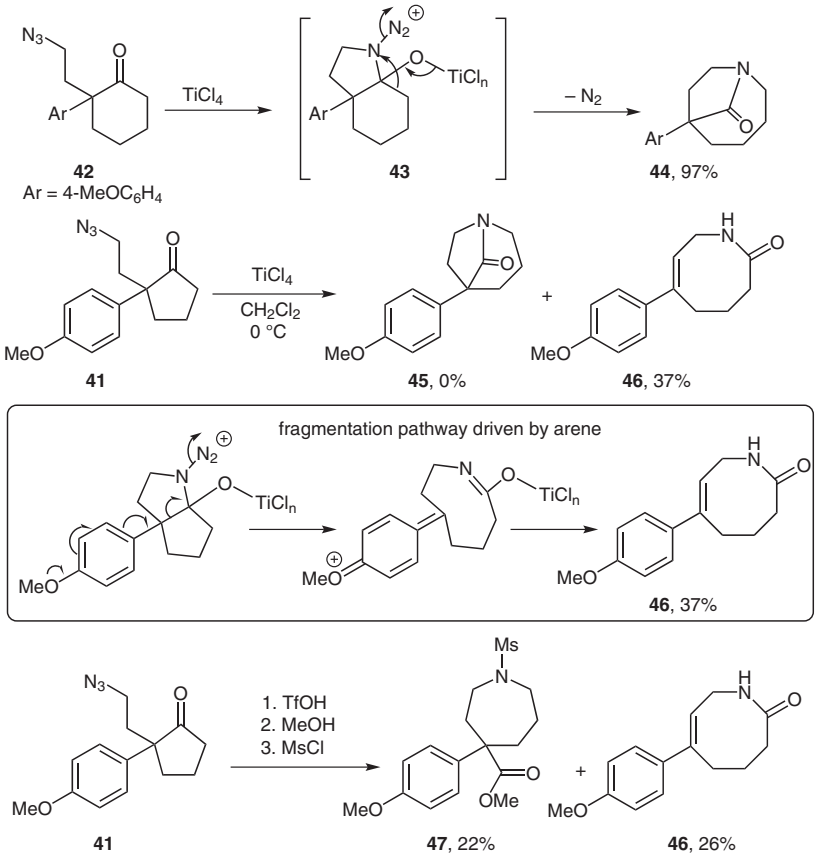
Treatment of ketoazide **42** with $TiCl_4$ in CH_2Cl_2 afforded bridged lactam **44** (97%) exclusively (Scheme 6). Evidently, the incorporation of an azidoethyl side chain had indeed blocked formation of a fused bicyclic product. As with example **23**, no product resulting from fragmentation of the inter-ring bond, driven by the electron-releasing aryl ring, was seen.

Attention was then turned towards the cyclopentanone ketoazide **41**. In this case, the expected product **45** was not observed. As a water workup had been required to remove the titanium byproducts, the suspicion was that any bridged lactam that had formed had been easily hydrolyzed to the corresponding water-soluble amino acid. The greater strain associated with lactam **45** compared with **44** would explain why **45** would undergo solvolysis more readily. However, azocinone **46** was isolated from this reaction (37%). This corresponds to a diversion of the normal Schmidt intermediate to a fragmentation pathway, akin to the proposed conversion of **17** into **20** (see Scheme 6, inset). We have not yet performed a study of the scope of such reactions, but the result clearly shows that the fragmentation pathway driven by the arene can, in some circumstances, compete with the normal Schmidt rearrangement.[16]

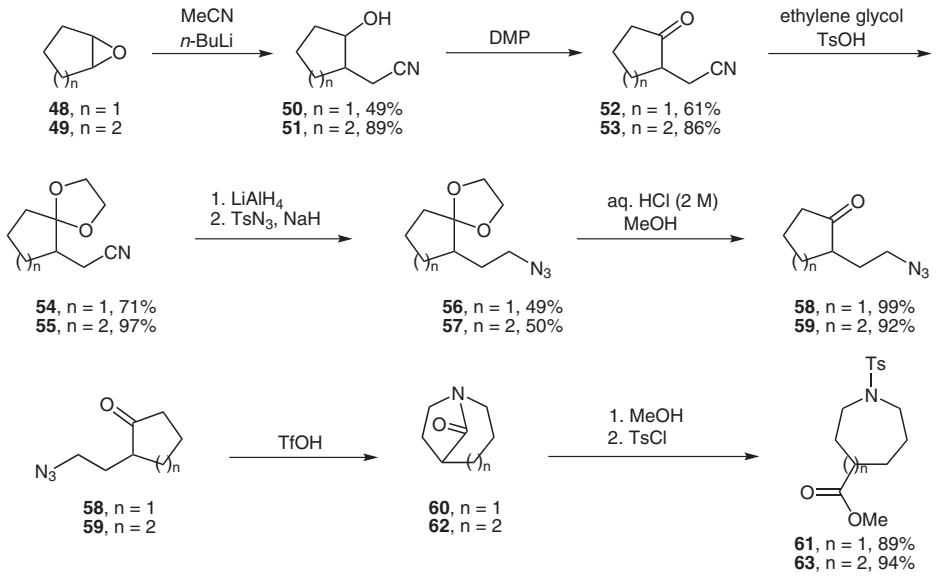
The reaction was repeated in triflic acid, thereby avoiding the need for an aqueous workup. Upon completion of nitrogen evolution, anhydrous methanol was added to the reaction to cleave the lactam bridge and afford an ester that would be easier to handle than the analogous carboxylic acid. A mesylation step was also included to convert the expected amine into a less polar sulfonamide. Pleasingly, this revised protocol resulted in the isolation of azepine **47** (22%) together with the azocinone **46** (26%).

Until now, the study had involved ketones substituted with aryl groups in the α-position. Bearing in mind the findings of Aubé on the key role of aryl groups in dictating the outcome of Schmidt reactions, as discussed above,[6a] our next substrates were simple 2-(2-azidoethyl)cycloalkanones **58** and **59** (Scheme 7); the synthesis of the desired ketoazides was completed using the same methodology as had been employed for ketoazides **41** and **42**.

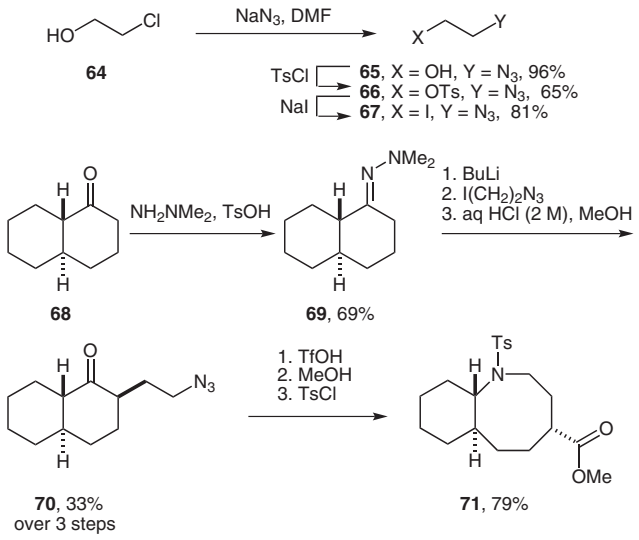
2-(2-Azidoethyl)cyclopentanone (**58**) was treated with TfOH in CH_2Cl_2 at 0 °C using the same conditions used for the isolation of azepine **47**. This gave sulfonamide **61** in an excellent 89% yield (Scheme 8). Similarly, 2-(2-azidoethyl)cyclohexanone (**59**) afforded sulfonamide **63** (94%). Accordingly, it seems that an aryl-ring substituent was not needed for success in the formation of the bridged lactams and their methanolysis products.



Scheme 6



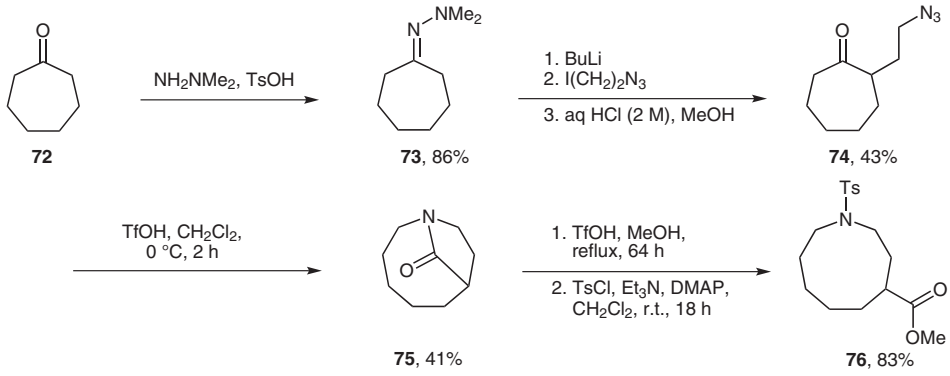
Scheme 7



Scheme 8

With this success in forming an eight-membered ring product from a simple azidoethylcyclohexanone, we explored whether similar success could be found in a more complex example. Ketoazide **70** was identified as a suitable target. The desired substrate was readily prepared by elaboration of *trans*-decalone **68** into the desired ketoazide using methodology developed by Vaultier and coworkers,[17] who have previously demonstrated that carbanions derived from *N*,*N*-dimethylhydrazones[18] can be alkylated with β-iodoazides (Scheme 8). The iodoazide **67**, required for the subsequent alkylation step, was prepared in three steps: the azido alcohol **65** was formed by reaction of 2-chloroethanol (**64**) and NaN_3 in DMF. Conversion of **65** into tosylate **66** and treament with NaI gave iodoazide **67**. Alkylation of the *N*,*N*-dimethylhydrazone **69**, derived from *trans*-1-decalone (**68**), afforded the azidoethyl product. Hydrolysis of the hydrazone group gave the substrate **70** (33% over 3 steps). Reaction with triflic acid, followed by methanolysis and tosylation provided the expected eight-membered-ring product **71** in 79% yield.[19]

Finally, we explored this methodology for the formation of a nine-membered-ring product. Cycloheptanone hydrazone (**73**) was treated with base and alkylated with iodoazide **67** to form ketoazide **74**, following hydrolysis of the hydrazone under mildly acidic conditions.



Scheme 9

On treatment of **74**, bridged lactam **75** was isolated in 41% yield. Returning to efforts to solvolyze this bridged amide, **75** was heated in methanol under reflux in the presence of TfOH for a period of 64 hours, followed by a tosylation step afforded nine-membered-ring product **76** in 83% overall yield (Scheme 9).

In summary, it has been demonstrated that the normal mechanistic pathway of the Aubé–Schmidt reaction can be diverted to selectively form bridged lactams in an efficient manner when a 2-(2-azidoethyl)cycloalkanone is used. In this case, the normal fused ring product would incorporate an azetidine, and the strain associated with the formation of this small ring renders the alternative pathway to the bridged amide product more efficient.

Experimental Section (see Supplementary Information file for details of other experimental procedures and supporting data).

Typical Procedure for Schmidt Reactions

To a solution of 2-(2-azidoethyl)-2-(4-methoxy-phenyl)cyclohexanone (**42**) (0.10 g, 0.37 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise $TiCl_4$ (0.08 ml, 0.74 mmol, 2.0 equiv). This mixture was stirred allowed to warm to r.t. and was stirred for 16 h. The reaction was diluted by the addition of CH_2Cl_2 (15 mL) and NaOH solution (2 M, 10 mL). This mixture was stirred vigorously for 30 min. The organic phase was separated, washed with NaOH solution (2 × 10 mL) and with sat. brine solution (2 × 20 mL). The organic extracts were combined, dried over anhyd Na_2SO_4, filtered, and concentrated at reduced pressure. The crude product was purified by column chromatography (PE and EtOAc in a 10:1 ratio and increasing level of EtOAc during elution before changing to CH_2Cl_2 and MeOH in a 50:1 ratio and gradually increasing level of MeOH during elution).

6-(4-Methoxyphenyl)-1-azabicyclo[4.2.1]nonan-9-one (**44**) was isolated as a colorless oil (0.09 g, 97%). ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}N_1O_2$: 246.1489; found: 246.1488. IR (neat): 3040 (m), 2945 (s), 2901 (s), 2838 (m), 1705 (s), 1611 (m), 1519 (s), 1443 (s), 1380 (s), 1295 (s), 1251 (s), 1205 (m), 1185 (s), 1087 (m), 1032 (s), 890 (m), 835 (s), 761 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.80–1.99 (6 H, m, CH_2), 2.23–2.39 (2 H, m, CH_2), 2.83 (1 H, m, CH_2), 3.30 (1 H, dt, *J* = 10.9, 8.8 Hz, CH_2), 3.57 (1 H, ddd, *J* = 10.9, 9.5, 1.8 Hz, CH_2), 3.83–3.86 (4 H, m, CH_2 and OCH_3), 6.89 (2 H, m, ArH), 7.46 (2 H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2 (CH_2), 24.9 (CH_2), 32.2 (CH_2), 40.1 (CH_2), 47.4 (CH_2), 48.3 (CH_2), 53.4 (C), 55.5 (CH_3), 113.9 (CH), 128.2 (CH), 135.1 (C), 158.4 (C), 187.7 (C). LRMS (CI): *m/z* (%) = 263 (38) $[M + NH_4]^+$, 246 (100).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) These compounds were isolated as single isomers. The most likely stereochemistry of alkylation of the decalone enolate would afford **70** and methanolysis would convert this into **71**.