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Synthesis of Medium-Bridged Twisted Lactams via Cation−π Control of the Regiochemistry of the Intramolecular Schmidt Reaction

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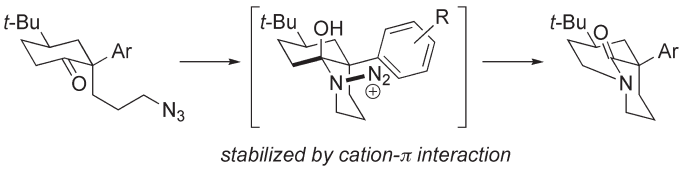


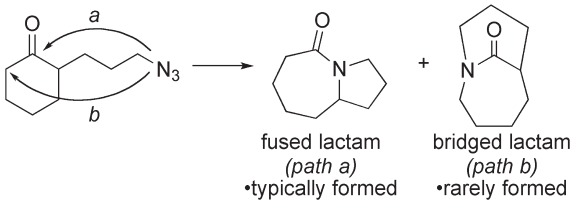
Medium-bridged twisted amides can be synthesized by the intramolecular Schmidt reaction of 2-azidoalkyl ketones. In these reactions, the regiochemistry of the Schmidt reaction is diverted into a typically disfavored pathway by the presence of an aromatic group at the α-position adjacent to the ketone, which stabilizes the predominantly reactive conformation of the azidohydrin intermediate by engaging in a nonbonded cation−π interaction with the positively charged diazonium cation. This results in the rarely observed rearrangement of the C−C bond distal to the azidoalkyl chain. This reaction pathway also requires the azide-containing tether to be situated in the axial orientation in the key azidohydrin intermediate. Examination of the effect of substitution of aromatic rings on the regiochemistry of the Schmidt reaction shows an increase in the migratory selectivity with more electron-rich aromatic groups. The selectivity is lower when an electron-withdrawing substituent is placed on the aromatic ring. The ability of cation−π interactions to act as a controlling element decreases when Lewis acids coordinate to substituents on the aromatic ring. The developed version of the Schmidt reaction provides a direct access to a family of medium-bridged twisted amides with a [4.3.1] bicyclic system, compounds which are very difficult to access with use of other currently available methods.

Introduction

The intramolecular Schmidt reaction effectively permits the synthesis of ring systems featuring a nitrogen atom at the ring fusion position.[1] This sequence is a valuable tool in the preparation of natural products[2] and other biologically relevant compounds.[3] In most applications of this chemistry, ketones[4] and carbocations[5] (typically generated from tertiary alcohols and olefins) are employed as electrophilic components; however, applications of epoxides,[2j,k] alkynes,[3e,f] enones,[6] sulfonium ions,[2r] and boranes[2s,t] have also appeared in the last two decades.

Two regiochemical outcomes can be envisioned from 2-azidoalkyl ketone substrates (Scheme 1).[4a] Formal insertion

SCHEME 1



of the azide into the proximal C−C bond of the reactive electrophile would give a fused structure (path a), while the insertion into the distal C−C bond would give a bridged system (path b). In the vast majority of cases, products resulting from the migration of the proximal C−C bond (path a) have been observed.

In a related reaction, Pearson and co-workers[5b] obtained a ca. 2:1 mixture of bridged bicyclic enamines upon treatment of 3-(2-azidoethyl)-1-phenylcyclopentanol with protic and

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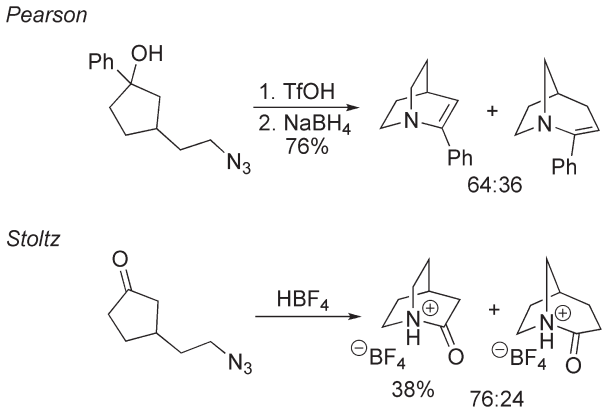
Lewis acids (Scheme 2, top). This reaction proceeds via an α-amino carbocation that undergoes rapid deprotonation to afford the twisted enamine-containing products shown. More recently, Tani and Stoltz[7] demonstrated that a structurally related β-substituted azidoalkyl ketone provided a ca. 3:1 mixture of bridged amides resulting from the migration of both α-keto bonds (Scheme 2, bottom). Recrystallization allowed for isolation of 2-quinuclidone as its protonated derivative in 38% yield. This sequence was particularly noteworthy because it permitted the isolation and characterization of the iconic twisted amide for the first time after more than 60 years of attempts to prepare this compound,[8] confirming that the loss of N_2 is a powerful driving force for the formation of unstable ring systems.

SCHEME 2



Our group has been interested in properties of medium-bridged twisted amides bearing a carbonyl group at the shortest one-carbon bridge in bicyclic ring systems.[9] Similar to 2-quinuclidone, these compounds contain heavily pyramidalized nitrogen atoms, and display properties divergent from planar amides. We have reported unprecedented cleavage reactions of the C−N bond adjacent to the bridged amide bond in a series of tricyclic and bicyclic twisted amides.[10] We have also examined the hydrolytic behavior of one-carbon bridged lactams, demonstrating that these compounds offer superior levels of stability compared to the twisted amides based on the 2-quinuclidone scaffold.[11] Since one-carbon bridged amides are significantly twisted, as evidenced by their substantial twist values of ca. 50° as well as their spectral and chemical properties,[10−12] these compounds can provide a useful platform for investigation of biological and chemical properties of unconventional amide linkages. For example, bridged lactams could facilitate the study of nonplanar amide bonds that are commonly encountered during cis/trans isomerization of amides in peptides.[13] Nonplanar amides have also been proposed as high-energy intermediates in enzymatic cleavage reactions of peptides.[14] In addition, bridged amides can be used to experimentally examine

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the effect of the bond rotation on properties of amide bonds.[15] However, the synthesis of bridged amides is complicated by their tendency to undergo rapid hydrolysis,[9c] and very few methods allowing their efficient synthesis exist.[12b]

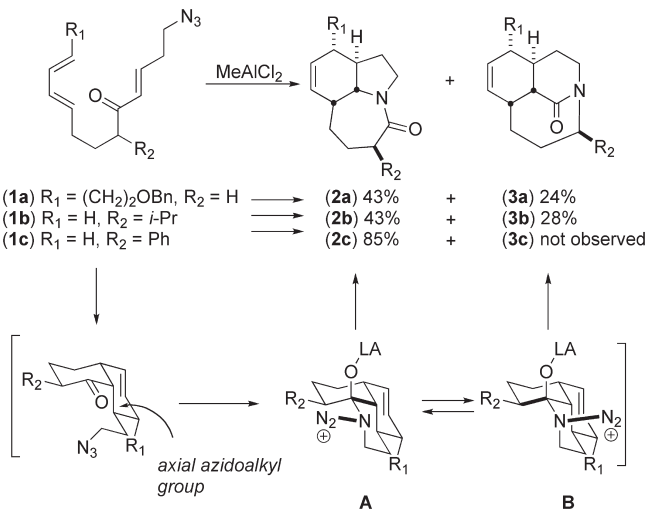
Following our interest in bridged amides and aware of Pearson's and Stoltz's work (Scheme 2), we recently set out to obtain a new class of bridged lactams that would be formed by the intramolecular Schmidt ring expansion reaction proceeding by a formal azide insertion into the distal C−C bond of an α-azidoalkyl ketone (Scheme 1, path b). In this paper, we present a full account[9m] of the study regarding the development of this version of the intramolecular Schmidt reaction, which allows for the direct and efficient formation of one-carbon bridged amides featuring a [4.3.1] bicyclic skeleton. In our approach, the vital regiochemistry-controlling element is a nonbonded electrostatic interaction between an electron-rich aromatic ring and the positively charged diazonium cation in the azidohydrin intermediate. This stabilizing interaction diverts the course of the Schmidt reaction into the migration of the C−C bond distal to the reactive ketone. The mechanism, structural requirements, scope, and coordination effects encountered during the development of this reaction will be discussed.

Results and Discussion

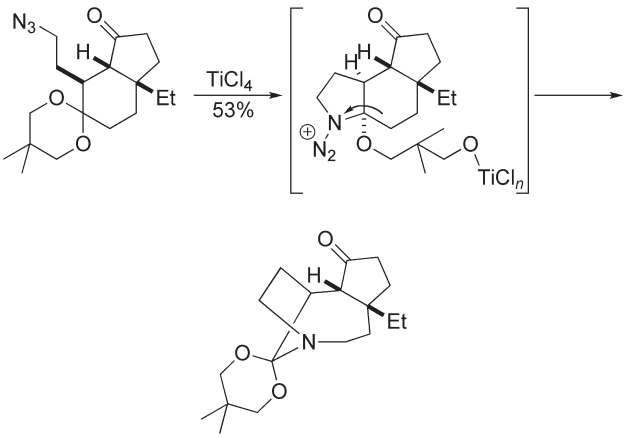
The first example of an intramolecular Schmidt reaction to afford one-carbon bridged bicyclic lactam was encountered during a total synthesis of stenine (Scheme 3).[2e] Thus, triene **1a** underwent intramolecular Diels−Alder reaction to provide the ketone, which further reacted in situ to give a mixture of the fused lactam **2a** and the bridged isomer **3a**. We had earlier proposed that the regiochemistry of the Schmidt reaction involves the selective migration of the C−C bond antiperiplanar to the leaving diazonium cation (Scheme 3, **A** and **B**, bold bonds).[4a] In this scenario, chairlike cyclohexanones can only afford bridged products when two conditions are satisfied: (1) the azidoalkyl chain occupies an axial orientation and (2) a diazonium cation is placed in the pseudoaxial position (see the SI for additional details of this published argument). Accordingly, the antiperiplanar migration of the C−C bond anti to the equatorial N_2^+ group in **A** would afford the fused isomer **2a**, whereas the axially disposed leaving group in **B** is necessary for the formation of the bridged isomer **3a**.

The formation of the bridged product **3a** was unexpected. Despite the very extensive use of the intramolecular Schmidt reaction over the last two decades, the only example of the intramolecular Schmidt reaction with the azidoalkyl chain placed in the α position to the electrophile affording a bridged product had occurred during synthetic studies toward aspidospermidine (Scheme 4).[2g] However, this rather specific case involved the reaction of the azidoalkyl chain with a ketal, providing a bridged orthoaminal product. We had earlier proposed that in typical Schmidt reactions the transition state leading to the bridged product is much less favorable than the alternative transition states affording the fused lactam, in part due to the steric penalties paid by the azidoalkyl chain placed in axial orientation and the diazonium cation occupying the pseudoaxial position.

SCHEME 3



SCHEME 4



Motivated by the formation of bridged amide **3a**, we first attempted to affect the equilibrium by disfavoring isomer **A** through the placement of a bulky group at the R_2 position (Scheme 3). Toward this end, the isopropyl-containing isomer **1b** was prepared and subjected to the reaction conditions; however, essentially the same ratio of bridged/fused adducts was obtained. Conversely, the analogue bearing a phenyl group at the same position afforded a dramatically different result. In this case, fused isomer **2c** was formed exclusively in 85% yield, making this reaction the most efficient example of this domino sequence observed to date (Scheme 3). Since the phenyl group has a larger *A* value (2.8) than the isopropyl group (2.2),[16] we wondered if the apparently exclusive intermediacy of **A** might be explained by an attractive through-space interaction between the positively charged diazonium cation and the phenyl substituent.[17]

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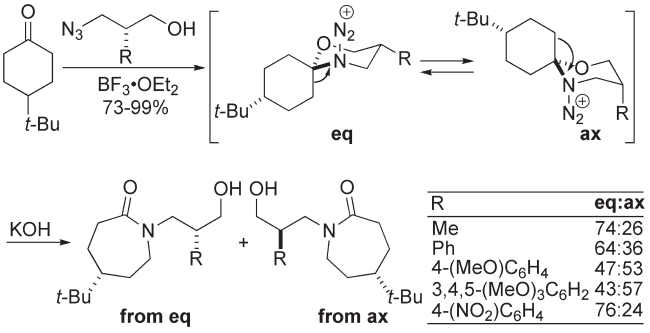
SCHEME 5



R	eq:ax
Me	74:26
Ph	64:36
4-(MeO)C_6H_4	47:53
3,4,5-(MeO)$_3C_6H_2$	43:57
4-(NO_2)C_6H_4	76:24

Electrostatic through-space interactions have been commonly invoked in small-molecule/protein-binding interactions.[18] However despite the great utility of such effects in synthesis, their potential as stereocontrolling elements in selective organic reactions is yet to be fully realized.[19] In earlier work, we proposed such an interaction as a controlling feature of certain asymmetric Schmidt reactions of symmetrical ketones with chiral hydroxyalkyl azides (Scheme 5).[20] The diastereoselectivity of this reaction was explained by the stabilization of the reactive intermediate **ax** by cation$-\pi$ interaction between the aromatic group and the diazonium cation. Moreover, the selectivity could be correlated with the electron density of the aromatic substituents,[21] leading us to propose that the stabilization of the diazonium cation by aromatic rings increased along the expected electrostatic trend: 3,4,5-trimethoxyphenyl > 4-methoxyphenyl > phenyl > 4-nitrophenyl (Scheme 5, box).

Accordingly, we hypothesized that in the currently investigated intramolecular Schmidt reaction (Scheme 3), an appropriately situated aromatic group might be able to stabilize the isomer **B** and provide a direct route to bridged lactams. Since for an effective cation$-\pi$ interaction the aromatic ring and the diazonium cation must be placed in a 1,3-diaxial relationship, we considered tricyclic intermediates **C**, **D**, and **E** that could in theory provide access to bridged amides (Scheme 6, Ar = electron-rich aromatic ring). Having determined that the removal of the cyclohexene ring in the intermediate **E** would significantly facilitate the synthesis of the required keto-azide precursor, we

SCHEME 6

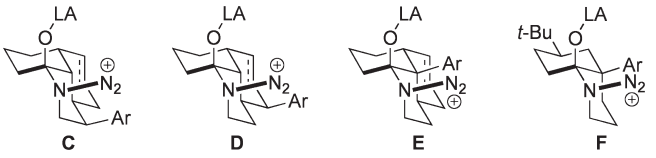
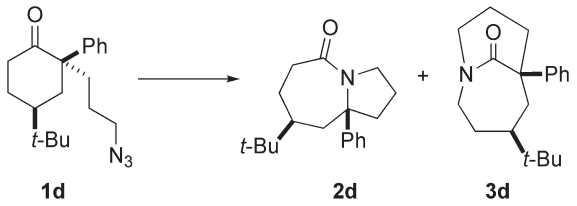


TABLE 1. Optimization of Product Distribution in the Schmidt Reaction with Azide 1d[a]



entry	acid	equiv	t (h)	**2d**:**3d**[b]
1	$MeAlCl_2$	1.0	48	28:72[c]
2	$EtAlCl_2$	1.1	18	50:50
3	TfOH	5.0	1	63:37
4	$TiCl_4$	5.0	1	50:50
5	$SnCl_4$	1.1	18	71:29
6	$BF_3 \cdot Et_2O$	1.1	6	60:40
7[d]	$MeAlCl_2$	1.1	6	26:74
8[e]	$MeAlCl_2$	2.2	18	47:53
9[f]	$MeAlCl_2$	2.0	24	71:29
10[g]	$MeAlCl_2$	2.0	24	47:53
11[h]	$MeAlCl_2$	2.0	24	26:74
12[i]	$MeAlCl_2$	2.0	24	37:63

[a]0 °C to rt, c = 0.05−0.15 M in CH_2Cl_2 unless otherwise noted. [b]Determined by ^{1}H NMR. [c]Based on isolated yields; **2d** isolated in 20%, **3d** isolated in 51%. [d]−78 °C to rt. [e]Reflux, 1.1 equiv added after 2 h. [f]c = 0.0007 M. [g]c = 0.007 M. [h]c = 0.05 M. [i]c = 0.23 M.

designed a potential cation$-\pi$ stabilized intermediate **F**. Here, a *tert*-butyl group would serve to lock the conformation of the azidohydrin intermediate, reducing the number of reactive intermediates.

Indeed, exposure of the 2-phenyl-substituted azidoalkyl cyclohexanone **1d** to Lewis and protic acids afforded the bridged amide **3d** in an excellent yield (Table 1, entry 1). Modification of the reaction conditions revealed that a number of Lewis and protic acids led to the desired bridged lactam (entries 1−6). Changes in temperature did not improve the bridged/fused ratio (entries 7 and 8). Interestingly, the product distribution proved to be dependent on the concentration of the reaction, with ideal results obtained at c = 0.05 M (entries 9−12).

We propose that Lewis acid treatment of **1d** afforded an equilibrium mixture of **G** and **H** (Scheme 7). In this scenario, the cation$-\pi$ stabilized intermediate **H** rearranges to furnish the bridged amide **3d**. Formation of the fused analogue **2d** is explained by the rearrangement of the azidohydrin intermediate **G** placing the diazonium cation in the pseudoequatorial orientation. This intermediate could be formed by nitrogen inversion or by reversion to keto azide. Although the cation$-\pi$ interaction with a phenyl substituent can divert the reaction pathway into the predominant migration of the distal C−C bond, the pathway leading to the fused analogue cannot be completely blocked.

Control experiments probing the structures of keto-alkylazides required for the synthesis of bridged amides utilizing

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(21) (a) Mecozzi, S.; West, A. P.; Dougherty, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 2307–2308. (b) Mecozzi, S.; West, A. P.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10566–10571.

SCHEME 7

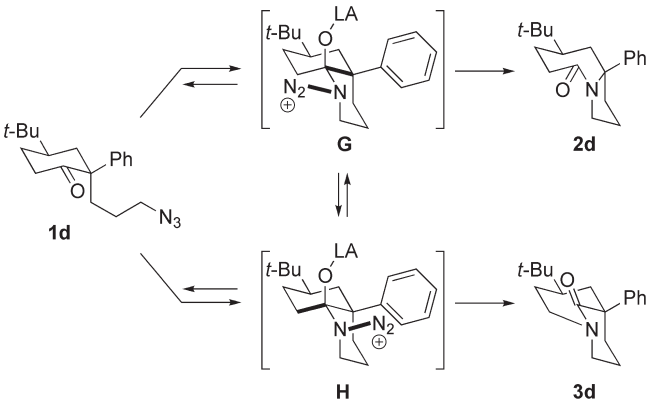
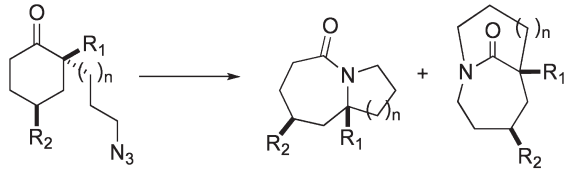


TABLE 2. Structural Requirements for the Cation−π Directed Schmidt Reaction



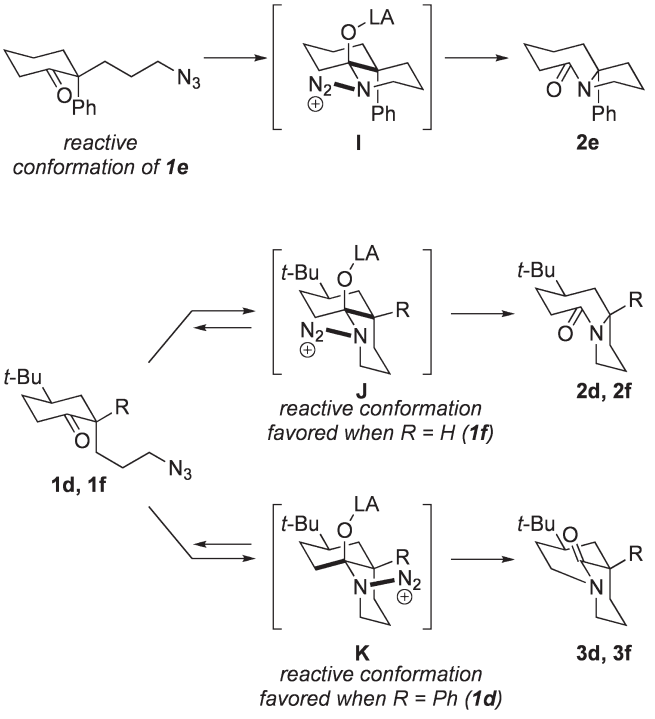
						yield (%)	
entry	azide	R1	R2	*n*	acid	**2**	**3**
1	**1e**	Ph	H	1	$MeAlCl_2$	96	
2	**1e**	Ph	H	1	TfOH	85	
3	**1f**	H	*t*-Bu	1	$MeAlCl_2$	57	17
4	**1f**	H	*t*-Bu	1	$TiCl_4$	91	
5	**1g**	Ph	*t*-Bu	2	$MeAlCl_2$		

cation−π interactions are shown in Table 2. Results obtained with azides **1e** and **1f** indicate that neither placement of the phenyl group at the α carbon (Table 2, entries 1 and 2) nor the axial orientation of the side chain (entries 3 and 4) alone is sufficient to steer the reaction toward bridged lactam product. However, the combination of an axial azide-containing tether and an aromatic group in a 1,3-diaxial relationship with the leaving diazonium cation in the intermediate azidohydrin diverts the reaction so that the bridged product predominates (**3d**, Table 1). In addition, a ketone in which the azide-containing side chain was lengthened to four carbons did not lead to any productive reaction (Table 2, entry 5). Such compounds are known to be recalcitrant substrates for the intramolecular Schmidt reaction.[4a]

The relevant intermediates are shown in Scheme 8. The fact that the **1e** affords only fused product **2e** rules out any effect arising from differences in intrinsic migratory aptitudes. In this case the thermodynamically favored conformation of **1e** affords a reactive intermediate **I** that can lead to only **2e**. Interestingly, the alternative conformation bearing an axial side chain that could in principle afford the bridged isomer does not appear to react in this example. However, it very likely exists in the ground state, suggesting the possibility that conformation **I** is simply more reactive than the alternative. The comparison of hydrogen and phenyl group placement in the conformationally locked systems is depicted in the bottom part of Scheme 8.

The product distribution in the Schmidt reaction of azide **1f** appeared to be very dependent on the conditions applied to promote the rearrangement (Table 2, entries 3 and 4). These results indicated that the regiochemistry of the Schmidt reaction is promoter-dependent and suggest that it may be possible to control reaction regiochemistry by the appropriate choice of reaction conditions.

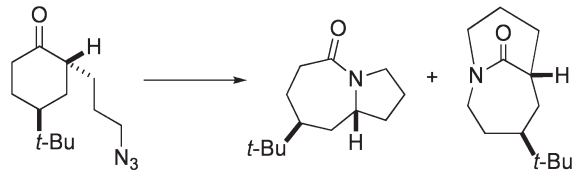
SCHEME 8



The effect of reaction conditions on the product distribution in the Schmidt reaction of the non-phenyl group-containing azide **1f** is summarized in Table 3. The results show that the choice of bond migration in this system, in which the reactive intermediates (Scheme 8, **J** and **K**, R = H) differ only by the orientation of the diazonium cation, depend on the choice of Lewis acid promoter. In general, aluminum containing acids afforded the highest ratio of the bridged to the fused amide (entries 1−5). The migration of the C−C bond proximal to the azidoalkyl chain was favored by the use of sterically demanding Lewis acids (entries 10−13). The product distribution was also influenced by changes in the reaction temperature (entries 14 and 15). However, the highest ratio of the bridged to the fused amide that could be obtained in this system (bridged/fused = 29:71) was much lower than that in the reaction of the azide **1d** (bridged/fused = 74:26), underscoring the importance of the cation−π interaction in enhancing the migration of the distal C−C bond.

Next, we probed the electronic nature of the aromatic substituent in the α position to the ketone on the outcome of the Schmidt reaction (Table 4). In these experiments the bridged amide **3** arises from the cation−π stabilized intermediate, bearing the diazonium cation in a pseudoaxial orientation (Scheme 7, type **H** intermediate), whereas the fused lactam **2** arises from a competing pathway involving the pseudoequatorial diazonium cation (Scheme 7, type **G**

TABLE 3. Effect of Reaction Conditions on Product Distribution in the Schmidt Reactions of Azide 1f[a]

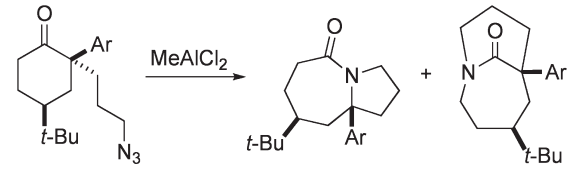


1f **2f** **3f**

entry	acid	equiv	*t* (h)	**2f**:**3f**[b]
1	$MeAlCl_2$	1.1	2	71:29
2	$MeAlCl_2$	25	3	71:29
3	$EtAlCl_2$	1.1	8	71:29
4	$AlCl_3$	1.1	1	77:23
5	Me_2AlCl	1.1	24	75:25
6	TMSOTf	1.1	2	77:23
7	$BF_3 \cdot Et_2O$	1.1	2	78:22
8	TfOH	5.0	1	79:21
9	TFA	85[c]	2	86:14
10	$SnCl_4$	1.1	2	85:15
11	$TiCl_4$	5.0	1	>95:5
12	$TiBr_4$	1.1	1	90:10
13	$SbCl_5$	1.1	1	87:13
14[d]	$MeAlCl_2$	1.1	24	92:8
15[e]	$MeAlCl_2$	1.1	1	79:21

[a]0 °C to rt, c = 0.05−0.15 M in CH_2Cl_2. [b]Determined by ^{1}H NMR. [c]Neat TFA. [d]−78 °C for 6 h to rt. [e]90 °C (MW).

TABLE 4. Synthesis of Fused and Bridged Lactams[a]



1h-m **2h-m** **3h-m**

			yield (%)	
entry	azide	Ar	**2**	**3**
1	**1d**	C_6H_5	22	61
2	**1h**	4-(MeO)C_6H_4	11	71
3	**1i**	4-(NO_2)C_6H_4	38	39
4	**1j**	3,4,5-$(MeO)_3C_6H_2$	19	66
5	**1k**	3,4-$(MeO)_2C_6H_3$	18	65
6	**1*l***	3,4-$(OCH_2O)C_6H_3$	13	72
7	**1m**	3,5-$(MeO)_2C_6H_3$	25	65

[a]1.5 equiv of $MeAlCl_2$, 0 °C to rt, 24 h, 0.05 M in CH_2Cl_2.

intermediate). The observed overall dependence of selectivity is consistent with the ability of aryl rings to stabilize the N_2^+ group in a 1,3-diaxial relationship. Thus, under optimized conditions, the azide **1d** bearing a phenyl in the α position afforded 61% of the bridged lactam **3d** along with 22% of the fused product **2d** (Table 4, entry 1). The azide **1h**, featuring a more electron-rich 4-methoxyphenyl system, led to the increased bridged/fused lactam ratio, delivering the amides in 71% and 11% yields, respectively (Table 4, entry 2). Conversely, the azide **1i** decorated with an electron-withdrawing 4-nitrophenyl substituent decreased the ratio, affording ca. 1:1 distribution of the final products (Table 4, entry 3). This trend is fully consistent with the expectation that the observed selectivities are a direct result

TABLE 5. Influence of Stoichiometry of Lewis Acid on Product Distribution[a,b]

entry	equiv	acid	**2d**:**3d**	**2h**:**3h**	**2j**:**3j**	**2k**:**3k**	**2m**:**3m**
1	1.0	$MeAlCl_2$	26:74	12:88	16:84	15:85	24:76
2	1.5	$MeAlCl_2$	26:74	12:88	21:79	22:78	31:69
3	2.0	$MeAlCl_2$	28:72	14:86	30:70	39:61	42:58
4	3.0	$MeAlCl_2$	30:70	29:71	46:54	52:48	61:39
5	2.0	$BF_3 \cdot CH_3CN$	56:44	32:68	42:58	nd	65:35

[a]0 °C to rt, 24 h, c = 0.05 M in CH_2Cl_2. [b]Product ratio determined by ^{1}H NMR. nd = not determined.

of the axial/equatorial preference of the diazonium cation and the strength of the cation−π interaction.

Interestingly, the introduction of a 3,4,5-trimethoxyphenyl substituent in the α position of the 2-azidoalkyl cyclohexanone afforded the bridged amide in 66% yield and the fused analogue in 19% yield (Table 4, entry 4). The obtained yields correspond to a ratio intermediate between that of azido-ketones **1d** (phenyl-substituted) and **1h** (4-methoxyphenyl-substituted), and do not follow the trend previously observed in the Schmidt reaction with hydroxyalkyl azides (Scheme 5, box).[20] Furthermore, the use of 3,4-dimethoxyphenyl substrate **1k** provided a lactam ratio similar to that obtained from substrate **1j** (Table 4, entry 5), while the 3,4-dioxomethylenephenyl-containing azide **1*l*** (entry 6) increased the selectivity, matching the ratio obtained with azide **1h** (entry 2). In addition, 3,5-dimethoxyphenyl-containing azide **1m** (entry 7) led to a similar ratio of bridged/fused lactams to that obtained from the phenyl keto-azide in entry 1. We reasoned that this unanticipated trend in product distribution could result from coordination of the Lewis acid to oxygen groups situated on the aromatic ring. To probe this hypothesis we carried out a set of experiments in which selected azido-ketones were subjected to a varying number of equivalents of $MeAlCl_2$. These results are summarized in Table 5.

In the case of the azide **1d** the ratio bridged/fused amide remains practically constant, regardless of the stoichiometry of $MeAlCl_2$ (Table 5, entries 1−4, **2d**:**3d**). However, with alkoxy-substituted phenyl rings, the bridged/fused lactam ratio decreases with the increase of equivalents of the Lewis acid used. This trend is more pronounced in substrates capable of coordination of $MeAlCl_2$ to multiple oxygens (Table 5, entries 1−4, series **j**, **k**, **m**). Furthermore, using a monodentate acid to promote the rearrangement affords a similar trend of bridged/fused lactams regardless of aromatic oxygenation pattern (4-methoxyphenyl > 3,4,5-trimethoxyphenyl > phenyl > 3,5-dimethoxyphenyl) (Table 5, entry 5).

These results are consistent with coordination of the acid to oxygens on the aromatic ring, resulting in the decrease of the electron density of π-systems and the concomitant weakening of cation−π interactions. The net outcome is an increased amount of the fused lactam formed from the intermediate bearing a N_2^+ group in the pseudoequatorial orientation (Scheme 7, type **G** intermediate). In addition, a steric interaction between the acid coordinated to oxygens on the aromatic ring and diazonium cation in the pseudoaxial orientation might also be responsible for a lower selectivity in the C−C bond migration. It is also possible that the diazonium cation in the pseudoaxial orientation is disfavored by electronic dipoles formed upon coordination of the acid to oxygenated substrates. Finally, it is not possible to completely discard a role of changing the migratory aptitude with

SCHEME 9

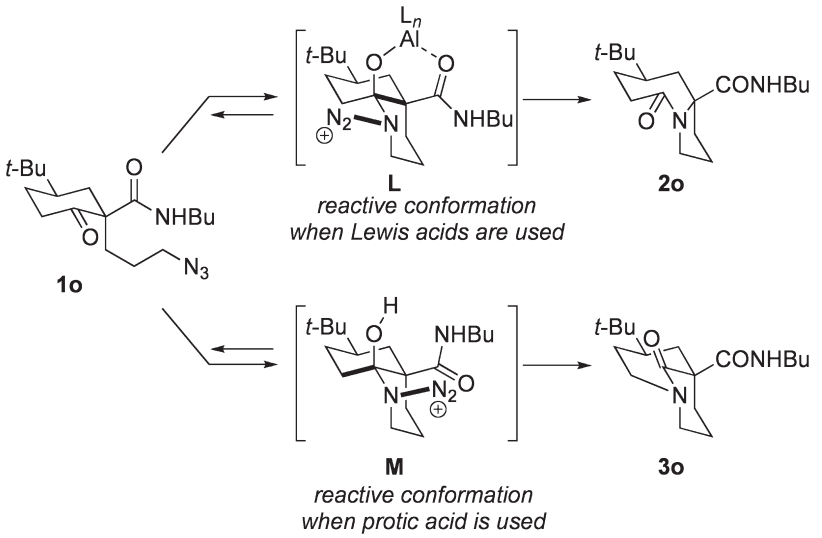
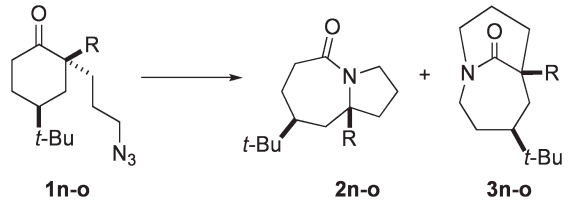


TABLE 6. Schmidt Reactions of α-Carbonyl Substituted Azides



				yield (%)	
entry	azide	R	acid	**2**	**3**
1	**1n**	CO_2Et	$MeAlCl_2$	80	
2	**1n**	CO_2Et	TfOH	92	
3	**1n**	CO_2Et	TFA	88	
4	**1n**	CO_2Et	$BF_3 \cdot Et_2O$	78	
5	**1o**	CONHBu	TfOH	52	13
6	**1o**	CONHBu	$MeAlCl_2$	77	

the modification of the reaction parameters. Overall, these results emphasize the importance of selecting appropriate reaction conditions to obtain maximum cation−π stabilization effects.

Motivated by Yamada et al. finding that carbonyl groups can serve as effective π-systems,[22] we examined the potential of ester and amide functionalities as cation-stabilizing groups in the intramolecular Schmidt reaction (Table 6). However, the presence of an ethoxycarbonyl group in a conformationally locked system afforded only the fused amide in good yields (entries 1−4). The placement of the secondary amide in the α position to the ketone allowed for the formation of the bridged amide **3o** (entry 5). However, the ratio of bridged/fused lactams resembled the outcome obtained with azide **1f** (Table 2, entry 3) rather than cases in which we propose cation−π interactions to be operative. Interestingly, when the reaction of the azide **1o** was promoted by a Lewis acid instead of a protic acid, the formation of the bridged amide was not observed (entry 6). This suggests that the Lewis acid coordinates to the amide group, possibly forming a six-membered chelate, which might reasonably be expected to disfavor the orientation of the diazonium cation in the pseudoaxial position (Scheme 9, intermediate **L**).

(22) Yamada, S.; Misono, T.; Tsuzuki, S. *J. Am. Chem. Soc.* **2004**, *126*, 9862–9872.

Summary

The intramolecular Schmidt reaction of 2-azidoalkyl ketones can be utilized to efficiently prepare medium-bridged twisted amides having a [4.3.1] bicyclic scaffold. Despite the large potential utility of such compounds, they are very difficult to synthesize with use of other currently available methods. Our work shows that electrostatic cation−π interactions can be applied as the key regiochemistry-controlling element, allowing the migration of the typically disfavored C−C bond distal to the reactive α-ketone. This contrasts with the results of Pearson and Stoltz, in which formation of a bridged intermediate occurred but did not suffer the onus of forming a bridged cation or was mandated by the nonadjacent disposition of the ketone and the azide-containing side chain (Scheme 2). In α-aryl-substituted 2-azidoalkyl ketones, cation−π effects are consistent with the dependence of selectivity on the electronic density of α-substituted aryl groups; however, coordination influence cannot be neglected in this system.

Overall, this methodology significantly extends the utility of the intramolecular Schmidt reaction in the synthesis of nontraditional lactams. Furthermore, it demonstrates that cation−π interactions are a very effective conformation-controlling tool, and can be utilized to favor the formation of unstable ring systems. Future work will address the application of cation−π effects to the synthesis of other bridged structures and focus on the use of electrostatic interactions as a stereochemistry-controlling tool. One-carbon bridged amides prepared in this study are currently utilized to investigate the influence of the amide bond distortion on the properties of these compounds.

Experimental Section

General Procedure for Schmidt Reactions in the Tricyclic Series. To a solution of azidoketone **1** (1.0 equiv) in CH_2Cl_2

was added $MeAlCl_2$ (1.0 equiv) dropwise at 0 °C, then the reaction was allowed to reflux for 20 h. The reaction was cooled to 0 °C, partitioned between saturated $NaHCO_3$ and EtOAc, and the organic layer was dried with Na_2SO_4, filtered, and concentrated. Flash chromatography afforded the title lactams. Note: Typically, bridged lactams **3** are less polar and more UV active than fused lactams **2**. This is yet another consequence of the decreased conjugation of the lone pair of electrons at nitrogen with the amide C=O system.

Lactams 2b and 3b. The reaction of azidotriene **1b** (0.87 g, 3.3 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M in hexanes, 3.3 mL, 3.3 mmol) in CH_2Cl_2 afforded after chromatography **2b** (0.33 g, 43%) as an oil and **3b** (0.22 g, 28%) as an oil.

Compound 2b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.93 (m, 6H), 1.32−1.44 (m, 2H), 1.50−1.55 (m, 1H), 1.61−1.84 (complex, 4H), 1.95−2.01 (m, 2H), 2.13−2.19 (m, 2H), 3.22−3.27 (m, 1H), 3.40−3.45 (m, 1H), 3.56−3.64 (m, 1H), 5.45−5.49 (m, 1H), 5.62−5.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 22.5, 24.3, 26.1, 27.6, 29.1, 29.5, 37.6, 38.5, 46.6, 54.6, 62.2, 125.8, 130.8, 173.2; IR (neat) 1623 cm^{-1}; HRMS calcd for $C_{15}H_{24}NO$ ($M^+ + H$) 234.1858, found 234.1855.

Compound 3b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.93 (m, 6H), 1.50−1.62 (m, 2H), 1.61−1.84 (complex, 8H), 2.30−2.51 (complex, 3H), 3.02−3.10 (m, 1H), 3.71−3.75 (m, 1H), 5.64−5.67 (complex, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.4, 27.8, 28.5, 30.5, 32.4, 33.2, 36.1, 41.4, 56.2, 57.4, 73.7, 128.4, 132.4, 187.6; IR (neat) 1695 cm^{-1}; HRMS calcd for $C_{15}H_{24}NO$ ($M^+ + H$) 234.1858, found 234.1878.

(3*R*,7a*S*,10a*R*,11*S*)-1,2,3,6,7,7a,8,10a-Octahydro-3-phenylazepino[3,2,1-*hi*]indol-4(11*H*)-one (2c). The reaction of azidotriene **1c** (2.9 g, 10 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M in hexanes, 10 mL, 10 mmol) in CH_2Cl_2 afforded after chromatography **2c** (2.3 g, 85%) as a white solid (mp 132−134 °C). Bridged lactam **3b** was not detected by TLC and NMR analysis of the crude reaction mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49−1.75 (complex, 5H), 2.10−2.19 (m, 2H), 2.20−2.36 (m, 2H), 2.50−2.56 (m, 1H), 2.88−2.94 (m, 1H), 3.69−3.75 (m, 2H), 4.10−4.16 (m, 1H), 5.32−5.36 (m, 1H), 5.56−5.59 (m, 1H), 7.19−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 26.9, 28.1, 30.0, 35.5, 38.4, 46.8, 50.4, 62.8, 125.9, 126.4, 126.5, 129.2, 131.0, 140.5, 171.9; IR (neat) 1623 cm^{-1}; HRMS calcd for $C_{18}H_{22}NO$ ($M^+ + H$) 268.1709, found 268.1701.

General Procedure for the Cation−π Directed Schmidt Reaction in the Bicyclic Series. To a solution of azidoketone **1** (1.0 equiv) in CH_2Cl_2 (0.05 M) was added $MeAlCl_2$ (1.5 equiv) dropwise at 0 °C, then the reaction was allowed to slowly warm to rt and stirred for 24 h. The reaction was cooled to 0 °C, quenched with water (10 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with brine (1 × 20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography afforded the title lactams.

(8*S*,9a*R*)-8-*tert*-Butyl-9a-phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2d) and (4*R*,6*R*)-4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-one (3d). The reaction of azide **1d** (0.0904 g, 0.29 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M in hexanes, 0.43 mL, 1.5 equiv) in CH_2Cl_2 (5.4 mL, 0.05 M) for 24 h afforded after chromatography (1/3 hexanes/EtOAc−EtOAc) lactam **2d** (0.0185 g, 0.065 mmol, yield 22%) as an oil (R_f 0.40, 1/1 EtOAc/hexanes) and lactam **3d** (0.0502 g, 0.0176 mmol, yield 61%) as an oil (R_f 0.70, 1/1 EtOAc/hexanes).

Compound 2d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.31−1.42 (complex, 3H), 1.52−1.58 (m, 1H), 1.71−1.73 (m, 1H), 1.90−1.92 (m, 1H), 2.11−2.18 (complex, 3H), 2.28−2.32 (m, 1H), 2.50−2.54 (m, 1H), 3.60−3.73 (m, 2H), 7.13−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 24.6, 27.1, 32.6, 33.0, 39.3, 41.4, 43.0, 47.5, 68.6, 124.8, 126.8, 128.5, 147.1, 172.4; IR (neat) 1635 cm^{-1}; HRMS calcd for $C_{19}H_{28}NO$ ($M^+ + H$) 286.2165, found 286.2173.

Compound 3d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.53−1.55 (m, 1H), 1.64 (t, J = 11.6 Hz, 1H), 1.84−2.12 (complex, 6H), 2.53−2.56 (m, 1H), 2.60−2.68 (m, 1H), 3.33−3.41 (m, 1H), 3.71−3.74 (m, 1H), 3.92−3.97 (m, 1H), 7.17−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 26.1, 28.0, 34.1, 37.6, 43.1, 44.1, 50.2, 54.8, 56.2, 126.1, 126.2, 128.5, 147.6, 184.4; IR (neat) 1685 cm^{-1}; HRMS calcd for $C_{19}H_{28}NO$ ($M^+ + H$) 286.2165, found 286.2173.

(8*S*,9a*R*)-8-*tert*-Butyl-9a-(4-methoxyphenyl)hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2h) and (4*R*,6*R*)-4-*tert*-Butyl-6-(4-methoxyphenyl)-1-azabicyclo[4.3.1]decan-10-one (3h). The reaction of azide **1h** (0.0841 g, 0.25 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M in hexanes, 0.37 mL, 1.5 equiv) in CH_2Cl_2 (4.5 mL, 0.05 M) for 24 h afforded after chromatography (1/2 hexanes/EtOAc−EtOAc) lactam **2h** (0.0090 g, 0.028 mmol, yield 11%) as an oil and lactam **3h** (0.0556 g, 0.0177 mmol, yield 71%) as a white solid (mp 135−136 °C).

Compound 2h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 9H), 1.31−1.55 (complex, 4H), 1.71−1.73 (m, 1H), 1.90−1.92 (m, 1H), 2.06−2.18 (complex, 3H), 2.27−2.32 (m, 1H), 2.46−2.50 (m, 1H), 3.42−3.71 (m, 2H), 3.82 (s, 3H), 6.87−6.91 (m, 2H), 7.15−7.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 24.7, 27.1, 32.6, 33.0, 39.5, 41.4, 43.0, 47.5, 55.3, 68.1, 113.8, 125.9, 139.2, 158.4, 172.3; IR (neat) 1625 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO_2$ ($M^+ + H$) 316.2277, found 316.2278.

Compound 3h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.51−1.54 (m, 1H), 1.61 (t, J = 11.5 Hz, 1H), 1.83−2.08 (complex, 6H), 2.48−2.51 (m, 1H), 2.61−2.67 (m, 1H), 3.32−3.37 (m, 1H), 3.69−3.72 (m, 1H), 3.81 (s, 3H), 3.91−3.95 (m, 1H), 6.88−6.90 (m, 1H), 7.27−7.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 26.1, 28.0, 34.1, 37.6, 43.1, 44.4, 50.2, 54.8, 55.3, 55.6, 113.8, 127.1, 140.0, 157.8, 184.6; IR (neat) 1685 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO_2$ ($M^+ + H$) 316.2277, found 316.2278.

(8*S*,9a*R*)-8-*tert*-Butyl-9a-(4-nitrophenyl)hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2i) and (4*R*,6*R*)-4-*tert*-Butyl-6-(4-nitrophenyl)-1-azabicyclo[4.3.1]decan-10-one (3i). The reaction of azide **1i** (0.0872 g, 0.24 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M in hexanes, 0.37 mL, 1.5 equiv) in CH_2Cl_2 (4.4 mL, 0.05 M) for 24 h afforded after chromatography (1/2 hexanes/EtOAc−EtOAc) lactam **2i** (0.0301 g, 0.091 mmol, yield 38%) as a white solid (mp 177−178 °C, R_f 0.53, 1/1 EtOAc/hexanes) and lactam **3i** (0.0312 g, 0.095 mmol, yield 39%, R_f 0.84, 1/1 EtOAc/hexanes) as a white solid (mp 135−136 °C).

Compound 2i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 9H), 1.24−1.43 (m, 3H), 1.49−1.56 (m, 1H), 1.74−1.81 (m, 1H), 1.88−1.95 (m, 1H), 2.07 (dt, J = 6.0, 12.8 Hz, 1H), 2.12−2.26 (m, 2H), 2.34 (dd, J = 4.3, 12.6 Hz, 1H), 2.53 (d, J = 13.9 Hz, 1H), 3.64−3.77 (m, 2H), 7.40 (d, J = 8.8 Hz, 2H), 8.22 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 24.5, 27.0, 32.7, 33.0, 39.0, 41.4, 43.2, 47.6, 68.5, 123.9, 126.0, 147.0, 154.7, 172.2; IR (neat) 2961, 2870, 1636, 1597, 1518, 1452, 1421, 1348, 731 cm^{-1}; HRMS calcd for $C_{19}H_{27}N_2O_3$ ($M^+ + H$) 331.2022, found 331.2008.

Compound 3i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.53−1.72 (m, 2H), 1.81−2.04 (m, 6H), 2.56 (d, J = 11.7 Hz, 1H), 2.62−2.72 (m, 1H), 3.40 (m, 1H), 3.74 (d, J = 10.2 Hz, 1H), 3.93 (dd, J = 5.9, 13.4 Hz, 1H), 7.52 (d, J = 6.8 Hz, 2H), 8.21 (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 25.9, 28.0, 34.1, 37.0, 43.0, 44.2, 50.1, 54.6, 56.3, 123.8, 127.3, 146.3, 154.8, 183.1; IR (neat) 2957, 2876, 1666, 1603, 1518, 1348, 1317, 1186, 1177, 732 cm^{-1}; HRMS calcd for $C_{19}H_{27}N_2O_3$ ($M^+ + H$) 331.2022, found 331.2044.

(8*S*,9a*R*)-8-*tert*-Butyl-9a-(3,4,5-trimethoxyphenyl)hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2j) and (4*R*,6*R*)-4-*tert*-Butyl-6-(3,4,5-trimethoxyphenyl)-1-azabicyclo[4.3.1]decan-10-one (3j). The reaction of azide **1j** (0.0779 g, 0.19 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M in hexanes, 0.29 mL, 1.5 equiv) in CH_2Cl_2 (3.6 mL, 0.05 M) for 24 h afforded after chromatography (1/1 hexanes/

EtOAc−EtOAc) lactam **2j** (0.0136 g, 0.036 mmol, yield 19%) as an oil (R_f 0.28, 1/1 EtOAc/hexanes) and lactam **3j** (0.0473 g, 0.126 mmol, yield 66%, R_f 0.53, 1/1 EtOAc/hexanes) as a solid (mp 158−159 °C).

Compound 2i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 9H), 1.22−1.52 (m, 3H), 1.58 (t, J = 13.2 Hz, 1H), 1.66−1.78 (m, 1H), 1.86−1.97 (m, 1H), 2.05−2.19 (m, 2H), 2.21−2.36 (m, 2H), 2.42 (d, J = 14.0 Hz, 1H), 3.58−3.74 (m, 2H), 3.86 (s, 9H), 6.37 (d, J = 3.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 24.7, 27.1, 32.7, 32.9, 39.2, 41.6, 43.0, 47.6, 56.3, 60.8, 68.8, 102.2, 136.9, 143.0, 153.2, 172.4; IR (neat) 2960, 1630, 1580, 1500, 1445, 1405, 1325, 1235, 1120 cm^{-1}; HRMS calcd for $C_{22}H_{34}NO_4$ (M^+ + H) 376.2488, found 376.2477.

Compound 3j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.50 (m, 1H), 1.54−1.63 (m, 1H), 1.85−1.97 (m, 5H), 2.07 (m, 1H), 2.49 (d, J = 11.9 Hz, 1H), 2.59−2.67 (m, 1H), 3.30−3.38 (m, 1H), 3.70 (d, J = 11.0 Hz, 1H), 3.83 (d, J = 4.0 Hz, 3H), 3.87 (d, J = 3.8 Hz, 6H), 3.90−3.97 (m, 1H), 6.55 (d, J = 3.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 25.9, 28.0, 34.1, 37.6, 43.1, 44.3, 50.3, 54.6, 56.2, 56.4, 60.8, 103.7, 136.6, 143.4, 153.1, 184.2; IR (neat) 2950, 1660, 1580, 1405, 1325, 1245, 1120 cm^{-1}; HRMS calcd for $C_{22}H_{34}NO_4$ (M^+ + H) 376.2488, found 376.2482.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.