Synthesis and Reactivity of Medium-Bridged Twisted Lactams

by

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Abstract

The research presented herein describes the development of synthetic methods to one-carbon bridged twisted amides and the study of properties of one-carbon bridged lactams.

Initial investigations focused on electrostatic cation–π and cation–n interactions as regiochemistry controlling feature of the intramolecular Schmidt reaction to provide access to one-carbon bridged amides. In cases where the reactive conformation of the azidohydrin intermediate is locked, the selectivity of the reaction depends on the electron density of an aromatic ring oriented in 1,3-diaxial relationship with regard to the diazonium cation. However, a placement of a heteroatom in the α-position to the ketone permits the synthesis of otherwise unsubstituted bridged amides from conformationally flexible ring systems. Also, described is the development of a general method of synthesis of one-carbon bridged amides relying on a transannular cyclization strategy.

Next, experiments directed towards investigation of unusual properties of distorted amides are presented. One-carbon bridged lactams display superior to other bridged amides levels of hydrolytic stability. These lactams participate in a number of interesting and potentially useful reactions unknown to traditional amide bonds, including synthesis of remarkably stable tetrahedral intermediates and a direct conversion into bridged spiro-epoxyamines. The influence of the amide bond geometry on reactivity of distorted lactams is also discussed.

For Magda

Acknowledgements

First and foremost, I would like to thank my advisor, Professor Jeffrey Aubé for his advice and support over the past few years. I will always be grateful for the opportunity to work in his laboratory. The satisfaction I experienced as a graduate student is directly related to his scholarly excellence in research, scientific writing and presentation. There is no doubt that any success I may find in my future career will arise from mentorship I received in Jeff's lab.

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I am deeply grateful to my family for all their endless support, love and understanding; they have made this thesis possible, and for that I thank them most wholeheartedly.

Finally, I would like to give my deepest thanks to my wife. Her love and support for me have been limitless. This thesis is dedicated in her honor.

Table of Contents

List of Figures

List of Tables

Chapter 1

Introduction

Amide bonds. The amide bond is one of the most fundamental functional groups in chemistry and biology. Above all, amide bonds provide a linkage between amino acids in peptides and proteins, which are the key building blocks of life. Amide bonds also serve as scaffolds allowing molecular association and recognition through hydrogen bonding, and are vital structural units in a number of synthetic polyamides and pharmaceuticals.[1]

The amide bond properties are commonly explained by Pauling resonance theory introduced almost 70 years ago.[2] In general, amide bonds can be regarded as a hybrid of two major resonance canonical structures with ~40% double bond character of the N–C(O) bond (Figure 1).

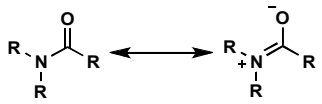


Figure 1. Electron delocalization in amides.

The amide bond resonance results in a number of unique properties of amide bonds, such as: (1) short N–C bonds, (2) high rotational barrier around the N–C(O) bond of ca. 15-20 kcal/mol, (3) planar geometry in which all six atoms of the amide bond lie in one plane, (4) resistance of the carbonyl towards nucleophilic attack and

hydrolysis, (5) minimized coordination at nitrogen (manifested in the predominant protonation of amides at oxygen), and (6) spectroscopic characteristics including lower C=O infrared stretching frequencies and more upfield shifts in ^{13}C NMR as compared to other carboxylic acid derivatives.[1]

Distorted amide bonds. Although the importance of the delocalization of π electrons in amide bonds (with the resulting planarity of amides) is a generally accepted property, it has been found that not all of the peptidic amide bonds are perfectly planar.[3-6] In 1968, Ramachandran recognized the need for non-planar geometry of amide bonds in cyclic peptides.[7] In 1996, MacArthur and Thornton carried out a survey of peptide torsion angles in the Cambridge Structural Database, concluding that flexibility is an important property of amide bonds; for a set of cyclic and linear peptides a standard deviation of 6° was found (from the ideal value of 180° for planar bonds).[8] Subsequent X-ray protein data suggested even larger deviations, up to 20°.[9] Even Pauling, by estimating the strain energies for distortion of amide bonds (0.9 kcal/mol for 10 degree distortion, 3.5 kcal/mol for 20 degree distortion), alluded to the ability of amide bonds to adopt non-planar geometry (Figure 2).[10]

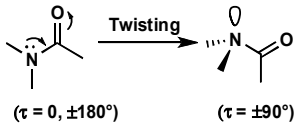


Figure 2. Twisting of the amide bond by rotation around the N–C(O) bond. Note the accompanying pyramidalization of the nitrogen atom.

An implication of the flexibility of amide bonds is its effect on stability and reactivity. For example, upon distortion, amide bonds are expected to undergo facile nucleophilic attack and hydrolysis. This distortion also increases the sp^3 character and therefore the basicity of the amide bond nitrogen, so that it is now available for coordination and protonation.[11]

A number of examples exist in which a twist around the N–C(O) bond plays a critical role in enzymatic catalysis, including enzymatic hydrolysis of amide bonds (a vital process for all living organisms)[12-15] and a family of enzymes catalyzing cis-trans isomerization of amide bonds (a process crucial to protein folding and maturation).[16-18] The latter enzymes operate through distortion of amide bonds via a stabilized twisted transition state, with an intramolecular hydrogen bond engaging the amidic nitrogen and assisting the isomerization.

Distorted amides are key elements of β-lactam antibiotics. The very selective acylation of bacterial peptidoglycan transpeptidase by β-lactams (the first effective, broad-spectrum antibiotics) arises from the fine tuning of the increased reactivity of moderately distorted amide bonds contained in β-lactam systems. It is worth mentioning that since the Second World War β-lactams have saved the lives of millions of people and were the first step towards the elimination of some infectious diseases from society.[19-22]

In organic chemistry the potential flexibility of amide bonds leads to a number of fundamental and intriguing questions: What is the distortion barrier that marks the amide and the keto–amine-like reactivity of amide bonds?[23-26] What are the effects of

distortion of amides on their properties? Can distorted amides benefit from the border-like reactivity and be used as versatile synthetic intermediates?[27-30] Is it possible to selectively functionalize distorted amide bonds, and if so, to then translate these effects into their planar counterparts?[31-36] What types of reactivity are yet to be found in distorted amides? In addition to providing chemists with a better understanding of amide bonds[26] and supplying them with novel synthetic tools, answering these questions may have significant biological implications. For example, non-traditional amides could be useful in the design of novel enzyme inhibitors with new mechanism of action.[11]

However, the study of effects arising from the distortion of amide bonds is challenging, and given the prevalence of planar amide bonds, there are very few examples of their distorted analogues described in the literature. In general, enzymes enforce deformation of amide bonds by forming stabilized enzyme-substrate complexes. Of course, this type of intermolecular steric interaction cannot be utilized for probing strain influence on properties of amide bonds beyond biological systems. Deformation of amide bonds can be also achieved by intramolecular steric effects, such as steric repulsion or conformational restriction (Figure 3).[37]

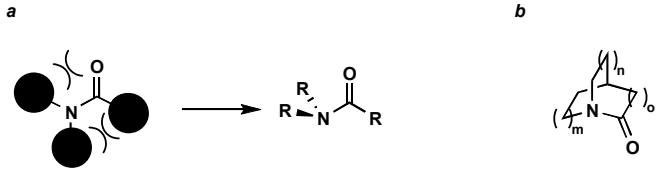


Figure 3. a) Steric repulsion and b) conformational restriction of amide bonds.

Types of distorted amides. In the steric repulsion approach, the amide bond is substituted with a relatively large group, so that the C–N(O) bond rotates to avoid the steric repulsion at the expense of the resonance stabilization. In other words, the twisted amide bond is more stable than the planar amide bond.[38]

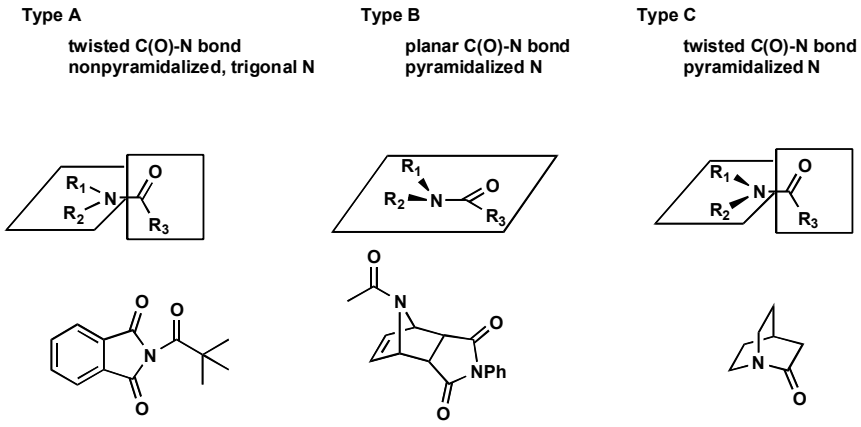
In the conformational restriction approach, the amide bond is contained in a rigid ring system that prohibits the amide bond from adopting its usual planar geometry. This class of amides is represented by small and medium-bridged cyclic lactams, which contain nitrogen at the bridgehead position.[39-41]

To allow for quantitative description of distortion of amide bonds, Winkler and Dunitz introduced three independent parameters, τ (twist angle), χ_N (pyramidalization at nitrogen) and χ_C (pyramidalization at carbon).[42] Twist angle describes the magnitude of rotation around the N–C(O) bond, χ_N and χ_C define the tetragonal character of the corresponding atoms. A twist angle of 0° corresponds to a planar amide bond and of 90° corresponds to fully orthogonal bonds, χ_N and χ_C are 0° for planar bonds and 60° for fully pyramidalized amide bonds. Since in distorted amides changes in χ_C are minimal, this value is often not reported. In addition, pyramidalization at nitrogen is sometimes quantified by the sum of three bond angles at nitrogen (for an ideally sp^3 hybridized atom $\theta = 328.4°$, for sp^2 atom $\theta = 360.0°$).[43]

To allow for qualitative description of distorted amides, Yamada has suggested a useful classification of amide bonds based on twist angle (τ) and pyramidalization at nitrogen (χ_N) (Scheme 1).[37] Type A includes amides with perpendicularly twisted N–C(O) bonds and virtually non-pyramidalized nitrogen

atoms, for example *N*-pivaloylphtalimide (τ = 83.2°, χ_N = 14.9°). Type B features amides with planar N–C(O) bonds and sp^3 hybridized nitrogen atoms, for example N-acetylaziridine and the N-acyl-7-azabicyclo[2.2.1]heptanes (τ = 18.9°, χ_N = 39.9° for the example in Scheme 1). Type C contains amides with perpendicular amide bonds and pyramidalized nitrogen atoms, for example 2-quinuclidone (τ = 90.9°, χ_N = 59.5°).

Scheme 1



Geometrical deformations of amide bonds occur typically by rotation around the N–C(O) bond (Figure 2). As a result of rotation, the $n_N \rightarrow \pi^*$ C=O donation is progressively removed, and this effect is accompanied by the change of hybridization at nitrogen.[43-45] Although much less common, nitrogen inversion can also lead to geometrical transformations of amide bonds. For example, amides in which nitrogen is substituted with electronegative atoms (XXN–CO) exhibit large negative anomeric

effects within the XNX system, leading to pyramidalized amide bonds.[46] These compounds belong to Type B in Yamada's classification.

Rotation of N–C(O) bond affects bond lengths and spectroscopic properties of amide bonds. Only a limited number of structurally characterized distorted amides are available;[40] however, inspection of their X-ray structures indicates that upon rotation the length of N–C(O) significantly increases, while the C=O bond is barely affected. This tendency is explained by resonance theory, and reflects the change of pyramidalization at nitrogen from sp^2 to sp^3 (for examples of bond lengths in planar and distorted amides see Table 1, page 14).

Infrared C=O stretching frequencies and carbonyl shifts in ^{13}C NMR spectrum are very sensitive to changes in the extent of lone pair resonance stabilization of the amide bond and to changes in the charge density of the carbonyl carbon, respectively. Due to the reduced resonance contribution from the zwitterionic canonical form, distorted amides are characterized by increased $\nu_{C=O}$ values and more downfield ^{13}C=O resonances as compared to traditional amides,[47] typically lying in the range between isolated ketones and planar amides (examples are provided in Table 19, Chapter 2).

Other examples of distorted amides arising from geometrical repulsion include *N*-acylpyrroles,[48] *N*-acylthiazolidine-2-thiones,[49] *N*-acyl-2,5-dithioglycoluril[50] and *N*-acylamides[51] (Figure 4). As expected, these compounds are characterized by unusual amide bonds properties. For example, Evans discovered a family of remarkably stable tetrahedral intermediates based on *N*-acylpyrrole scaffold,[52] while

Yamada has shown that the increased reactivity of *N*-thiazolidine-2-thiones depends on the degree of twist of the amide bond.[53]

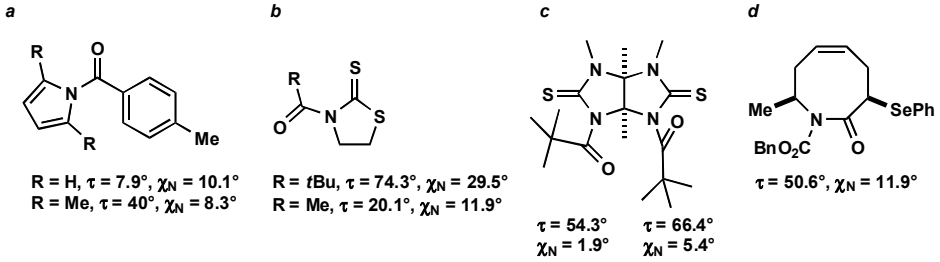


Figure 4. Examples of distorted amides resulting from steric repulsion. a) *N*-acylpyrroles, b) *N*-acylthiazolidine-2-thiones, c) 2,5-dithioglycoluril, d) *N*-benzyloxycarbonylamide.

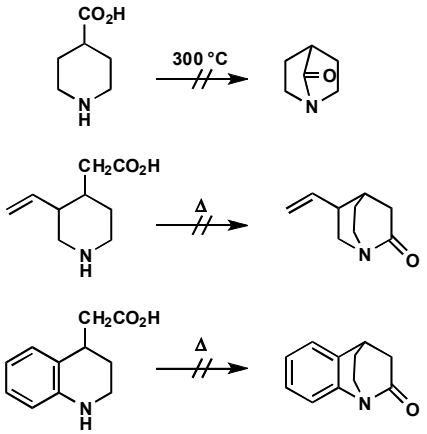
Although a steric repulsion approach has been successful in the preparation and investigation of properties of a number of distorted amides, these compounds suffer from excessive steric hindrance around the amide bonds, a feature which likely changes their properties in and of itself.[11] Delocalization of nitrogen electrons onto the aromatic ring in the pyrrole derivatives or the attachment of a second C=O (or analogous) group to the amide bond significantly reduces the rotational barrier around the amide bonds, also influencing their character.[37]

In contrast, geometrically restricted amides offer a certain advantage in determining the influence of rotation on properties of amide bonds. For example, bridged amides lacking a steric hindrance around the amide bond can readily be imagined.[11] Bridged amide scaffolds can also be more easily modified and

diversified, when compared to sterically hindered amides.[54] The hurdle prohibiting a widespread use of bridged amides in chemistry and biology is their lability towards hydrolysis.[12]

Synthesis of bridged amides. Chemists have been intrigued by bridged amides for more than 70 years; the first mention of a bridged lactam dates back to 1938 (the same time as the origin of Pauling's resonance theory). In that year, Lukeš proposed that incorporating a nitrogen at a bridgehead position in a bicyclic ring system would result in a violation of Bredt's rule by the amide zwitterionic resonance structure.[55] Being unsuccessful in preparing three bridged amides by cyclizations (Scheme 2), Lukeš concluded that such amides are "sterically impossible"[56] and if they were ever made they would exhibit properties of ketones rather than amides.

Scheme 2



It is worth noting that despite the commonly invoked analogy of bridged amides to bridgehead olefins, the major difference between two classes of compounds is that the diradical formed from a bridgehead olefin violates the octet rule, while the apolar resonance structure of a bridgehead amide does not (Scheme 3).[56-59] Nonetheless, the increased reactivity of bridged amides (leading to hydrolytic instability and tendency to polymerization) has prevented the successful synthesis and isolation of some of these compounds to this day.

Scheme 3

In 1941, R. B. Woodward initiated a research program directed towards the problem of synthesizing 2-quinuclidone (Figure 5).[25] Although Woodward was unsuccessful in this endeavor, the experience gained in the synthesis of anti-Bredt amides allowed him to point correctly at the structure of penicillins. Sir Robert Robinson had argued that penicillin antibiotics containing a β-lactam bond would be too reactive to hydrolysis to have an amide bond. However, Woodward, aware that bridged and related amides can exhibit the reactive properties of more or less isolated carbonyl groups, predicted exactly the strained β-lactam structure.

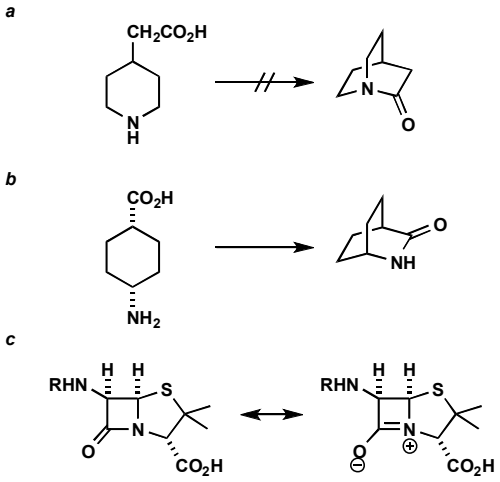
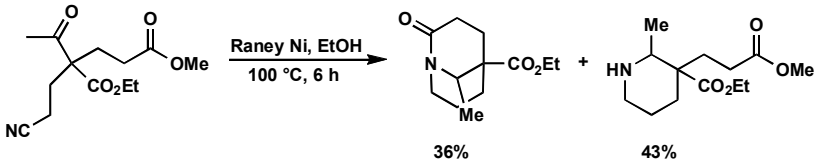


Figure 5. a) Difficulties in cyclization to a bridged amide. b) Ease of synthesis of its geometrical isomer. c) Resonance structures in strained penicillin antibiotics.

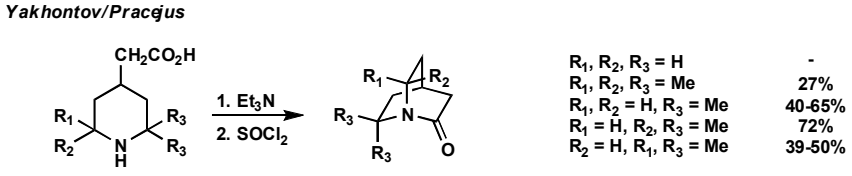
In 1949, Albertson reported[60] the first successful synthesis of a bridged lactam (Scheme 4) (curiously, this pioneering example has been regularly omitted in literature regarding bridged amides). The feasibility of Albertson's synthesis suggested that the stability of amides with C=O bond placed on a 3-carbon bridge is much higher than when the C=O bond is located at a 2-carbon bridge.

Scheme 4



Between 1956 and 1973 the research groups of Yakhontov[61-65] and Pracejus[66-68] studied a family of quinuclidone derivatives prepared by the condensation of amines and acyl chlorides (Scheme 5). These researchers also examined properties of methyl substituted 2-quinuclidones, suggesting that these structures behave as isolated amino ketones (see Scheme 25 for details). It should be noted that the isolation of the parent 2-quinuclidone as reported by Yakhontov and Rubitsov has been questioned in the literature. Given the vigorous conditions utilized for the synthesis and the lack of any characterization data save elemental analysis it is possible that these researchers had obtained a polymerized material.[61] However, it is rarely mentioned that Yakhontov converted 2-quinuclidone into its oxime, and compared its properties with the compound obtained from an independent synthesis.[61]

Scheme 5



In the early 1980s Blackburn[69] and Brown[70-79] engaged independently in a very important study addressing the increased rate of hydrolysis of bridged amides (Scheme 6 and Table 1). Blackburn observed an increase of seven and nine orders of magnitude in the rate of basic and acidic hydrolysis of the stabilized 2-quinuclidone as compared to planar amides. Brown measured the rate of hydrolysis of four 2-

quinuclidone derivatives characterized by different distortion parameters, finding a good relationship between the rate of hydrolysis and twist angles. For two of these amides, the correlation was better when pyramidalizations at nitrogen were considered (Table 1).[12, 77] Brown has pioneered another application of distorted amides by using bridged lactams as model systems for activated peptide units in acylation of serine,[75] aspartate[73] and cysteine[78] proteases.

Scheme 6

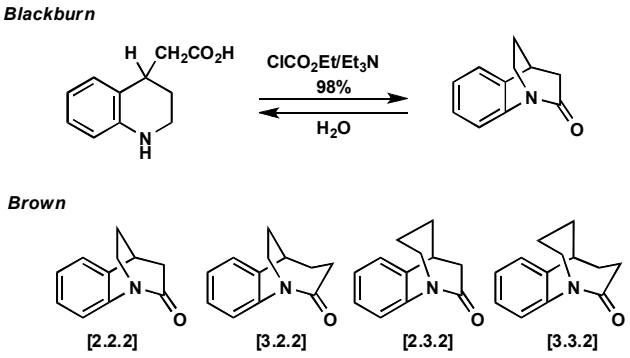


Table 1. Structural parameters and hydrolysis rate constants of 2-quinuclidone derivatives.[12, 77]

entry	system	N–C(O) [Å]	C=O [Å]	τ^a [deg]	$\chi_N{}^a$ [deg]	$\chi_C{}^a$ [deg]	$k_3{}^b$ [$M^{-1}s^{-1}$]	$k_1/K_3{}^c$ [$M^{-1}s^{-1}$]
1	[2.2.2]	1.423[d]	1.179[d]	90.0[d]	63.4[d]	0.0[d]	2.6×10^2	2.3×10^4
2	[3.2.2]	1.401	1.216	30.7	57.2	9.0	6.0×10^1	5.6×10^1
3	[2.3.2]	1.413	1.225	33.2	52.8	11.0	1.7×10^1	3.0×10^1
4	[3.2.2]	1.370	1.233	15.3	38.6	6.7	5.1×10^{-4}	1.2×10^{-4}
5	planar acetanilide[e]	1.338	1.235	1.3	3.7	-1.5	2.2×10^{-5}	2.2×10^{-7}

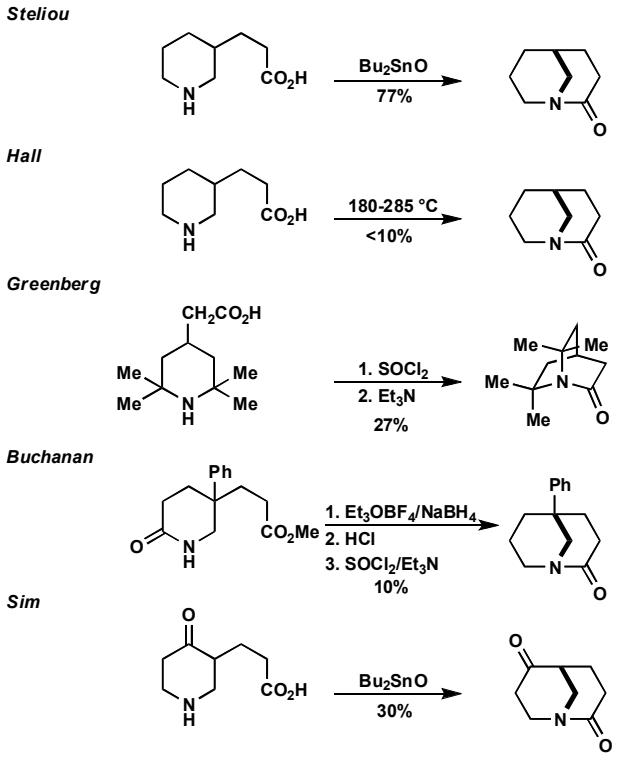
[a] Obtained by X-ray crystallography unless otherwise noted. [b] Constant for base hydrolysis. [c] Constant for acid hydrolysis. [d] Calculated values. [e] N-(4-bromo-2-methylphenyl)-N-methylacetamide.

Although the half-life for hydrolysis of a typical planar amide bond is measured in hundreds of years at rt and pH = 7, the half-life of a stabilized 2-quinuclidone was determined to be ~ 5 min at rt and neutral pH (Table 1, entry 1). Interestingly, even a much less distorted amide with [3.2.2] scaffold (entry 2) was hydrolytically labile and characterized as having a $t_{1/2}$ ~ 1.5 days at neutral pH, and $t_{1/2}$ ~11 min at pH = 4.5.[70] These values correspond to a faster hydrolysis of moderately distorted amides when compared to the hydrolysis of β-lactam antibiotics (for example, hydrolysis of benzylpenicillin occurs with: $t_{1/2}$ ~ 2 weeks at neutral pH,

$t_{1/2}$ ~ 3 h at pH = 9 and $t_{1/2}$ = 3 min at pH = 1),[80] a fact that underscores the difficulty in synthesis and handling of bridged lactams.

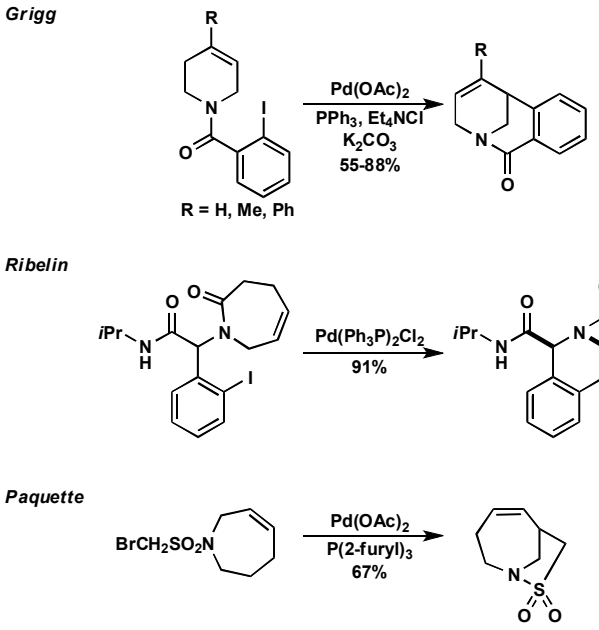
In the 1980s and early 1990s other sporadic reports regarding synthesis of bridged amides appeared in literature. Most synthetic methods for preparation of bridged amides focused on amine condensation with acyl chlorides (e.g. Blackburn),[69, 81] however Brown noticed the advantage of DCC as the coupling reagent in the synthesis of stabilized or relaxed systems based on the 2-quinuclidone scaffold.[70] In addition, Steliou and Pouppart introduced Bu_2SnO as an efficient promoter for difficult lactamizations,[82, 83] Hall reported preparation of bridged amides,[84, 85] ureas[86, 87] and urethanes[88, 89] under flash vacuum pyrolysis, and Greenberg[90] optimized conditions for synthesis of tetramethyl 2-quinuclidone (Scheme 7). Two additional bridged amides with [3.3.1] scaffold were structurally characterized (Buchanan,[91-93] χ_N = 48.8°, τ = 20.8° and Sim,[94] χ_N = 49.1°, τ = 16.3°), confirming that the placement of the C=O at one of the largest bridges results in a large pyramidalization at nitrogen and much smaller twist angles (type B according to Yamada's classification).

Scheme 7



Metal-catalyzed reactions and thermal cycloadditions were also applied to preparation of bridged amides. The use of the Heck reaction in this end was pioneered by Grigg, delivering a number of lactams featuring the C=O on the external bridge.[95-98] This method was also employed for synthesis of analogous bridged sulfonamides.[96-98] A similar cyclization was subsequently used by Paquette[99-102] and Ribelin.[103] Currently the Heck reaction is one of the most popular methods for synthesis of this type of bridged lactams (Scheme 8).

Scheme 8



Paquette also used a Heck reaction to prepare a family of bridged bicyclic sultams[104-106] (typically prepared by intramolecular cyclization of α-sulfonyl radicals). In a sharp contrast to the amide analogues, it was determined that incorporation of a sulfonamide bond in a bridged structure does not result in its hyperreactivity (Figure 6).

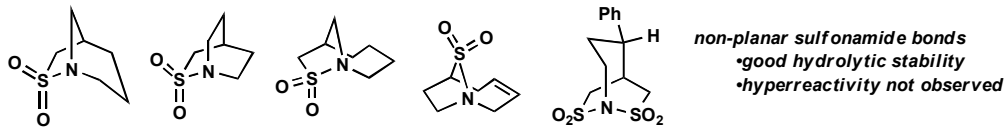
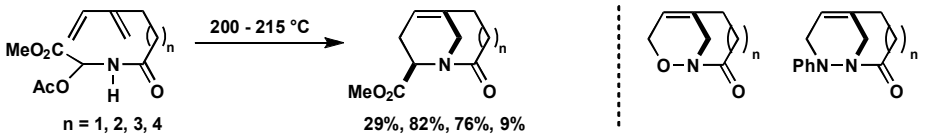


Figure 6. Bridged bicyclic sultams.

Shea applied a type II intramolecular imino Diels-Alder reaction for synthesis of unusual bridged amides that also contained bridgehead olefins in the same molecules (Scheme 9).[40, 59, 107] Interestingly, these bridged olefins were found to be more reactive than bridged amides. This methodology was recently extended by Shea's group to the synthesis of structurally related oxazinolactams[108-110] and 1,2-diazines[111] and was also applied as a key step in synthetic studies towards stenine.[112]

Scheme 9

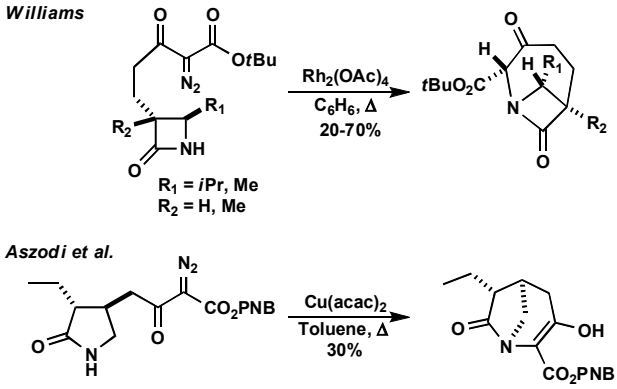


Williams utilized Rh-catalyzed carbenoid insertion for the synthesis of a number of very strained bridged β-lactam analogues possessing [4.1.1] ring system.[113, 114] A similar insertion was recently used by chemists at Sanofi-Aventis for synthesis of bridged carbapenems.[115] In both cases, the rationale included the potential antibacterial activity of bridged amides, however, these lactams proved to be too unstable for biological testing (Scheme 10).

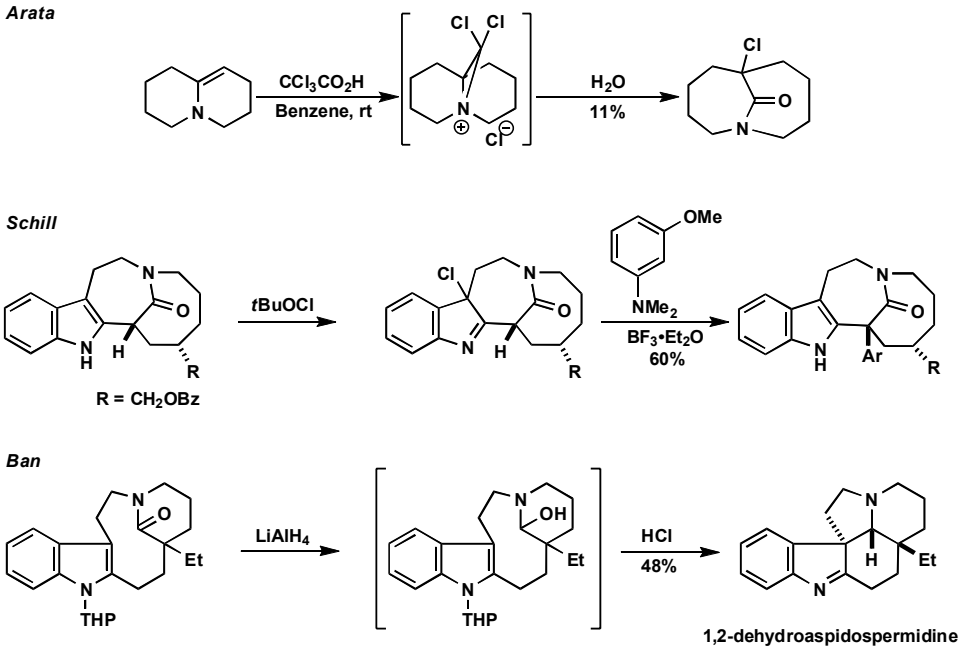
In an interesting approach to bridged lactams, Arata utilized an aziridinium rearrangement to prepare a bridged amide with [4.4.1] scaffold.[116-119] Also, noteworthy is a study of the chemistry of indole-derived bridged amides as potential precursors for higher analogues of vinblastine alkaloids by Schill[29, 30, 120-123] and the

use of a more relaxed bridged lactam as the key precursor in the total synthesis of aspidospermidine by Ban[27, 28, 124, 125] (Scheme 11).

Scheme 10

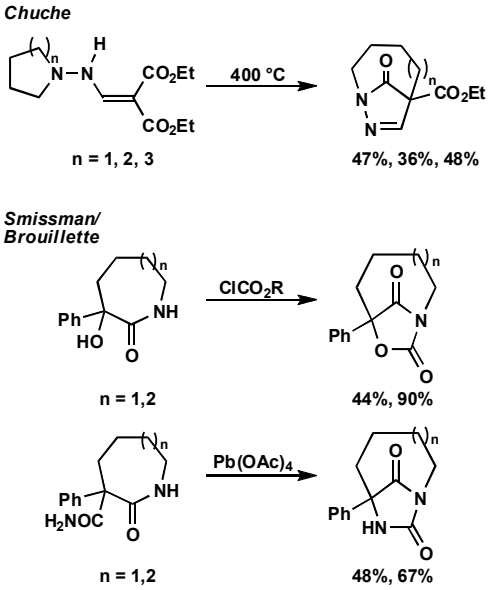


Scheme 11



A number of heteroatom-substituted bridged lactams have also been investigated (Scheme 12). They include pyrazoline-5-ones prepared by Chuche[126] and hydantoins and oxazolidinediones first suggested by Smissman[127-134] and ultimately prepared by Brouillette[135-138] (see also Scheme 9). However, these compounds are significantly easier to prepare than their carbon counterparts due to the conjugation of the amide bond with a heteroatom.

Scheme 12



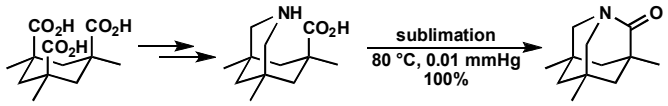
Despite the above developments, until 1998 the area of bridged amides remained rather unexplored. While a relatively large number of bridged lactams have been reported (it should be noted that except for the above mentioned examples, the remaining bridged amides are limited to very specific cases,[139-145] unconfirmed structures[146-149] and more relaxed ring systems[150-162]), besides Blackburn's and

Brown's investigation of hydrolysis, there were no systematic studies addressing the properties of bridged lactams. The geometries of the majority of bridged lactams were close to typical amides, and most of the reports focused on isolated structures rather than families of compounds, thus prohibiting their thorough investigation.

The last decade has witnessed major developments addressing the challenges of versatile synthesis of bridged amides, and conceptually new lactams marked by large distortions of N–C(O) bonds have been prepared.

In 1998, Kirby studying the reverse anomeric effect synthesized 1-aza-2-adamantanone,[163-166] which he subsequently described as the "most twisted amide" (Scheme 13). This perfectly perpendicular amide (τ = 90.5°, θ = 325.7°) displayed some very unusual keto–amine-like reactivity (see page 35), including instantaneous hydrolysis in water ($t_{1/2}$ < 50 s), high basicity of amide nitrogen (pK_a ~5.2) and spectroscopic properties typical of an amino ketone (IR ν_{CO} = 1732 cm^{-1}, δ ^{13}C NMR = 200.0 ppm).

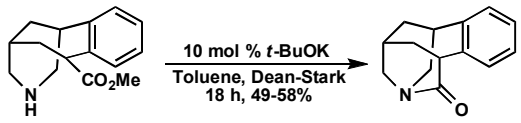
Scheme 13



In 2003, Coe utilized a one-carbon higher homologue of 1-aza-2-adamantanone[167] as an intermediate in the synthesis of nicotinic receptor ligands by subjecting it to an unprecedented Wolff-Kishner reduction (Scheme 14; see page 36

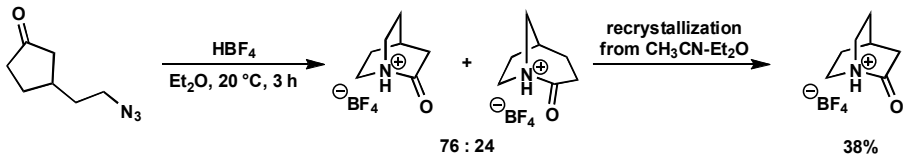
for details). It should be noted that in both of the studies by Kirby and Coe the proximity of the amino and the carbonyl groups, enforced by rigid adamantane-type structures, facilitated their synthesis and influenced the properties of these lactams.

Scheme 14



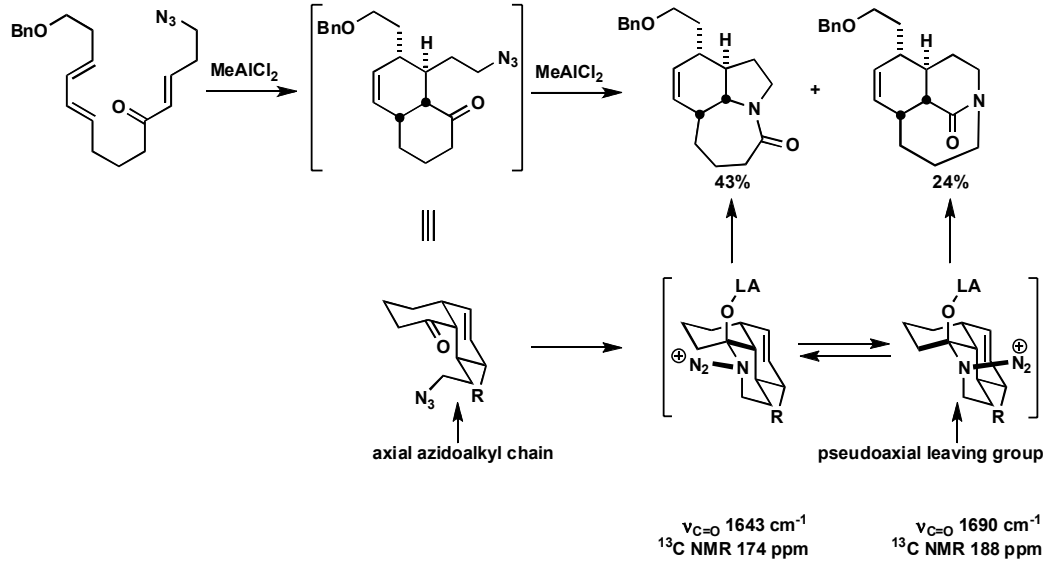
In 2006, Tani and Stoltz synthesized the iconic twisted amide, 2-quinuclidone[26, 168] (isolated as its tetrafluoroborate salt), utilizing an intramolecular Schmidt ring expansion reaction (Scheme 15). This method differs significantly from the classical amide bond formation but it allowed for the scrupulously anhydrous conditions required for isolation of 2-quinuclidone. The X-ray structure of the protonated amide indicated a fully orthogonal amide bond ($\tau = 90.9°$ and $\chi_N = 59.5°$). As expected, 2-quinuclidone was found to be extremely unstable to hydrolysis conditions (in water $t_{1/2} < 15$ s); even other nucleophilic solvents (including DMSO, pyridine and MeOH) led to its rapid decomposition.

Scheme 15



Schmidt reaction and bridged lactams. Stoltz's synthesis was preceded by the Aubé's group findings regarding the Schmidt reaction. In 2002, in the context of a total synthesis of stenine, Golden and Aubé reported a synthesis of a tricyclic bridged amide utilizing a domino Diels-Alder/Schmidt reaction (Scheme 16).[169] Mechanistically, the endo Diels-Alder reaction locked the azido-alkyl chain in the axial orientation in the *cis*-decalin-type system. The subsequent migration of the bond antiperiplanar to the diazonium cation located in the pseudoequatorial position led to the fused lactam, while the migration of the bond antiperiplanar to the N_2^+ in the pseudoaxial orientation afforded the bridged analogue. The amides could be easily distinguished based on their spectroscopic properties.

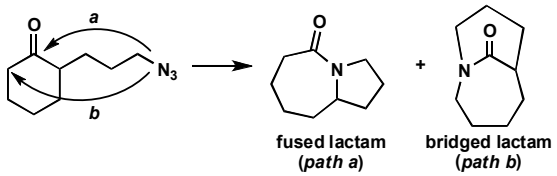
Scheme 16



This reaction was significant since it demonstrated for the first time that a bridged lactam could be prepared from an intramolecular Schmidt reaction and that the loss of nitrogen is a powerful driving force enabling the preparation of strained amides. However, the formation of the bridged product was unexpected. Despite the very extensive use of the intramolecular Schmidt reaction by Aubé and other groups for more than a decade,[170-172] all previous examples of similar Schmidt reactions led exclusively to fused amides.

In the intramolecular Schmidt reactions when the azide-containing side chain is placed at the carbon adjacent to the electrophile, in theory two regiochemical outcomes can be envisioned (Scheme 17).[173] Formal insertion 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).

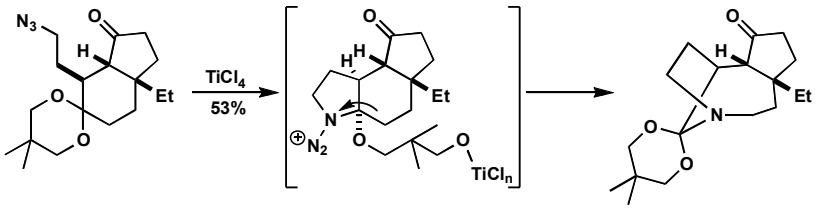
Scheme 17



Before the stenine synthesis, 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 18).[174, 175] However, this involved the reaction of the

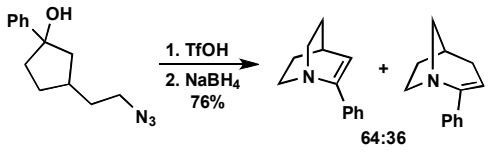
azidoalkyl chain with a ketal, affording a bridged orthoaminal product. It is very likely that in this rather specific case, the fused ring system containing a four-membered ring did not form due to strain, and that the azido-Schmidt reaction of the ketal better accommodates formation of the bridged product than the ketone version. Furthermore, similar variants of the Schmidt reaction utilizing epoxides,[176, 177] olefins, [178-180] diketones[181, 182] and carbocations (generated in semipinacol rearrangement)[183, 184] as electrophiles did not afford bridged systems resulting from the migration of the C–C bond distal to the electrophile.

Scheme 18



By contrast, in the related versions of the Schmidt reaction, when the azide-containing side chain is placed at the carbon non-adjacent to the ketone, products resulting from the azide insertion into both bonds have been observed. In particular, in 1993 Pearson *et al*. showed that tertiary alcohols react intramolecularly with alkyl azides to afford ca. 2:1 mixture of bridged bicyclic enamines after treatment with protic and Lewis acids (Scheme 19).[178] Due to the limited overlap of the lone pair of electrons at nitrogen and the p orbital of the carbocation, the bridgehead iminium ion was not formed.

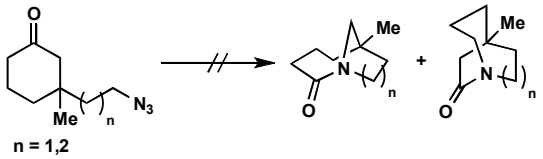
Scheme 19



It should be noted that with the β-positioned tether, the migration of either of the bonds leads to bridged structures: bridged enamines when olefins are utilized as electrophiles (Scheme 19)[178] and bridged amides, when ketones serve as electrophilic components (Scheme 15).[26] In addition, the crucial difference between the Schmidt reaction utilizing α- and β-alkyl tethers is a type of the bridged structure that is obtained. As will be seen in the following sections, one-carbon bridged amides,[169] prepared from α-azidoalkyl tethers offer distinct advantages over bridged amides in which C=O bond is placed on a larger bridge (obtained from β-alkyl tethers).[26]

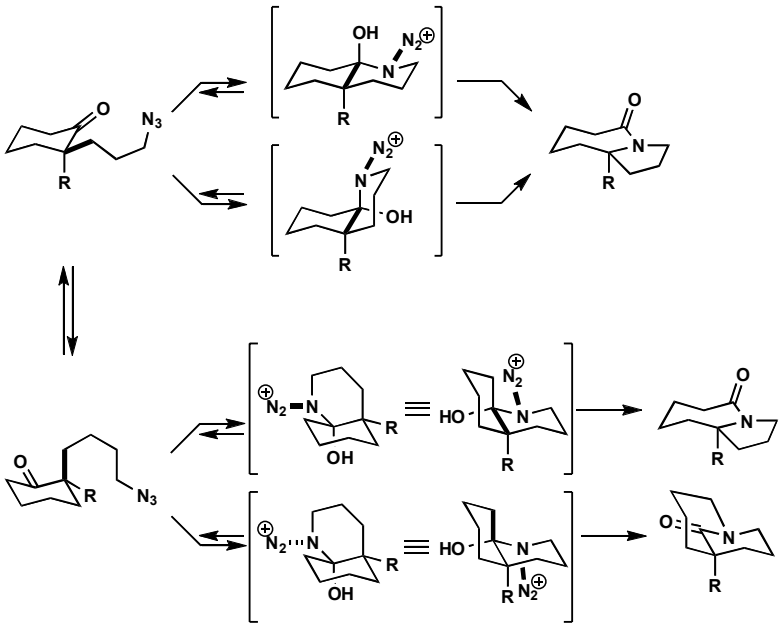
Interestingly, as early as in 1996 Morton and Aubé subjected two β-azidoalkyl cyclohexanones to the intramolecular Schmidt reaction.[185] These azides would provide amides analogous to the Stoltz's 2-quinuclidone after the rearrangement. However, only starting materials were recovered despite forcing reaction conditions, thus emphasizing the difficulty in synthesizing bridged amides (Scheme 20).

Scheme 20

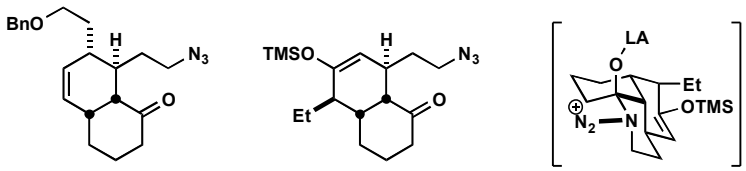


The generally accepted mechanism of the intramolecular Schmidt reaction with an azidoalkyl chain placed in the α position to the ketone involves formation of chair-like azidohydrins followed by the selective migration of the C–C bond antiperiplanar to the leaving diazonium group (Scheme 21).[173, 178] In this scenario, a bridged lactam can only be obtained from the azidohydrin intermediate, in which: (1) the azide-containing chain occupies a pseudoaxial orientation and (2) the leaving diazonium cation is placed in the pseudoaxial position. *Both of these conditions must be satisfied in order to form a bridged amide.* It is likely that this intermediate is energetically unfavorable, which explains why bridged lactams had not been observed as products of the intramolecular Schmidt reaction before the stenine synthesis.

Scheme 21



Very interestingly, during a second generation approach to stenine a similar *cis*-decalin-type intermediate was formed by Diels-Alder reaction. However, the migration of the bond antiperiplanar to the diazonium cation in the pseudoaxial orientation was not observed, suggesting that subtle stereoelectronic factors dramatically influence the outcome of Schmidt reactions (Figure 7).[186, 187]



first generation intermediate *second generation intermediate* *exclusive reactive conformation*

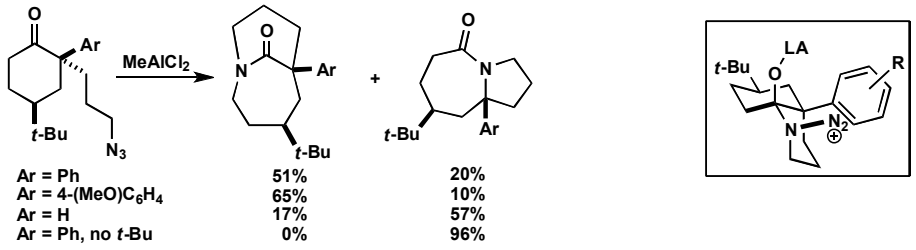
Figure 7. Comparison of reactive intermediates in the first and the second generation syntheses of stenine.

In 2005, Yao, Wrobleski, and Aubé reported the synthesis and novel reactions of several other tricyclic amides based on the Diels-Alder/Schmidt sequence.[31] Importantly, the structure of bridged amides was confirmed by X-ray crystallography, indicating that these compounds contain amide bonds from a previously unknown distortion range (τ = ~50°, see Table 35 for details), and offer very attractive possibilities for investigating the properties of half-way rotated amide bonds.

Schmidt reaction and electrostatic interactions. In 2007, Yao and Aubé obtained a bridged amide as the major product of the intramolecular Schmidt reaction

for the first time (Scheme 22).[188] In this study, the regiochemical control was achieved by combining two effects: (1) axial orientation of the azide-containing tether and (2) a stabilizing cation-π interaction between an aromatic group and the leaving diazonium cation in the key azidohydrin intermediate (Scheme 22, box). Control reactions demonstrated that both the *tert*-butyl substituent and the aromatic ring were necessary for the efficient formation of the bridged products. The fact that the bridged/fused ratio increased with a more electron-rich aromatic ring system provided a strong support for cation–π interactions operating in this system.

Scheme 22



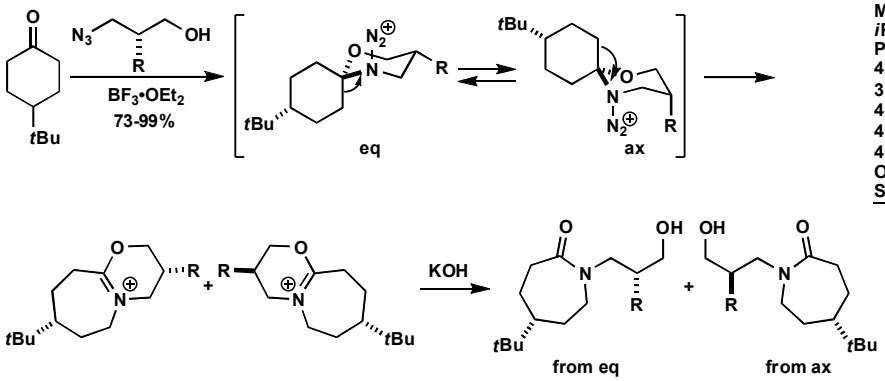
Ar = Ph	51%	20%
Ar = 4-(MeO)C_6H_4	65%	10%
Ar = H	17%	57%
Ar = Ph, no *t*-Bu	0%	96%

Interestingly, the (2*R*,4*S*)-2-(3-azidopropyl)-4-*tert*-butylcyclohexanone (see Scheme 33 for details) had already been subjected to a Schmidt reaction using $TiCl_4$, but the bridged amide was not obtained under these reaction conditions.[173] This suggested that the regiochemistry of the Schmidt reaction is promoter-dependent, and suggested an attractive possibility to control the outcome of the reaction by the appropriate choice of reaction conditions.

These studies allowed for a very efficient preparation of one-carbon bridged amides, requiring only four steps from commercially available materials as opposed to the much longer syntheses of triene precursors for the Diels-Alder/Schmidt sequence.[189] This investigation also represented a rare example of utilizing an electrostatic cation–π interaction to control the outcome of chemical reactions.

Although cation–π interactions have been commonly invoked as key forces in ligand recognition and binding, these effects are highly underutilized in organic synthesis.[190-193] In one related case, Katz and Aubé proposed cation–π interactions as a controlling feature of certain asymmetric Schmidt reactions of symmetrical ketones with chiral hydroxyalkyl azides (Scheme 23).[194, 195] Diastereoselectivity in this reaction was explained by the stabilization of the reactive intermediate **ax** by cation–π interactions between the aromatic group and the diazonium cation. In addition, it was found that the selectivity could be correlated with the electron density on aromatic systems. The stabilization of the diazonium cation by aromatic rings followed the expected electrostatic trend: 3,4,5-trimethoxyphenyl > 4-methoxyphenyl > phenyl > 4-nitrophenyl.

Scheme 23



R	eq:ax
Me	74:26
*i*Pr	88:12
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
4-BrC_6H_4	68:32
4-FC_6H_4	69:31
OMe	4:96
SMe	1.8:98.2

In a similar study of the Schmidt ring expansion reaction, Ribelin and Aubé,[196] utilized heteroatoms placed on hydroxyalkyl azides to function as electronegative components in the electrostatic interactions with diazonium cations (Scheme 23, two last examples). In this study, these cation–n interactions were found to be more effective in inducing diastereoselectivity in this reaction than cation–π effects.

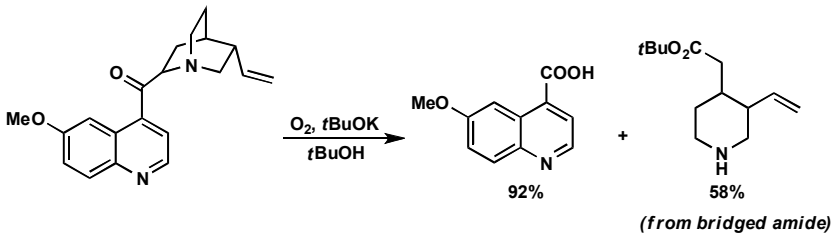
In Chapter 2, I discuss a thorough study of the cation–π effects in the context of regiochemical control in the intramolecular Schmidt reaction leading to one-carbon bridged amides. This section also describes the discovery of a heteroatom directed variant of the Schmidt reaction, which obviates the need for a locked conformation of the reactive azidohydrin to afford bridged lactams. Chapter 2 culminates in the development of a general methodology for the synthesis of one-carbon bridged amides, based on a transannular cyclization strategy.

Reactivity of bridged amides. As mentioned earlier, due to limited $n_N \rightarrow \pi^*_{C=O}$ overlap, bridged amides are expected to display reactivity divergent from traditional amides.[41] In the most distorted amide bonds, the carbonyl group is more electrophilic and its properties are more closely related to those of isolated ketones rather than amides. Meanwhile, the lone pair of electrons at nitrogen is not engaged in conjugation with the C=O system and participates in amine-like reactivity.

There are very few prior studies addressing the reactivity of bridged amides. Accordingly, the potential to utilize the unique properties of distorted amide bonds in organic synthesis has largely been overlooked. Two major factors preventing study on the reactivity of bridged amides are hydrolytic instability of bridged lactams, which complicates their handling and significantly limits the number of potential reaction types that can be examined, and the fact that most of the bridged amides known exist in geometries resembling traditional amides.[11]

The first example of a reaction of a bridged amide was reported in 1946 by Doering and Chanley during the oxidation of a quininone-derived enolate (Scheme 24).[197] In this transformation, *tert*-butyl alcohol (used a solvent) led to a rapid alcoholysis of the corresponding amide to the amino ester, a reaction forecasting the increased reactivity of twisted amide bonds.

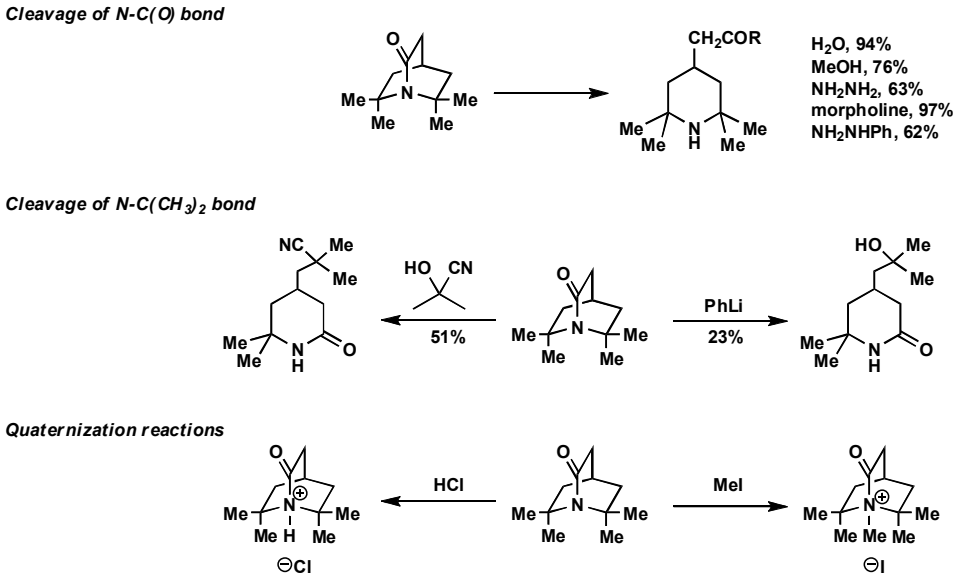
Scheme 24



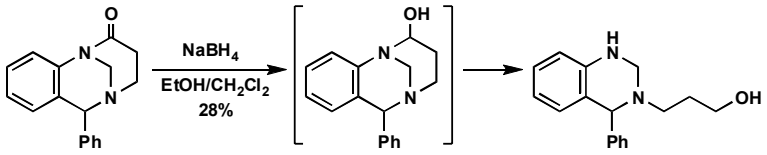
Yakhontov has studied the chemistry of a tetramethyl-substituted 2-quinuclidone, finding that this amide participates in three types of reactions (Scheme 25).[62, 64, 65] Despite the perpendicular amide bond, this compound does not serve as a good model for reactivity of bridged amides due to a steric hindrance around the amide bonds and the ease of formation of the tertiary carbocation. Using related compounds, Pracejus suggested that 2-quinuclidones behave as reactive amino–ketones.[66-68] He also determined the pKa of 2,2-dimethylquinuclidone to be 5.33,[66] which was the first quantitative evaluation of a high electron density at nitrogen in bridged amides.

An interesting example was reported by Denzer and Ott,[81] who found that the reduction of the bridged amide can be performed with $NaBH_4$, a reagent that typically is unreactive with amides (Scheme 26). The resulting hemiaminal collapsed to the aldehyde and was further reduced to the alcohol.

Scheme 25

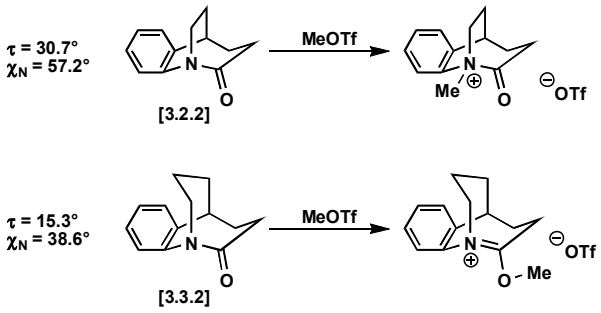


Scheme 26



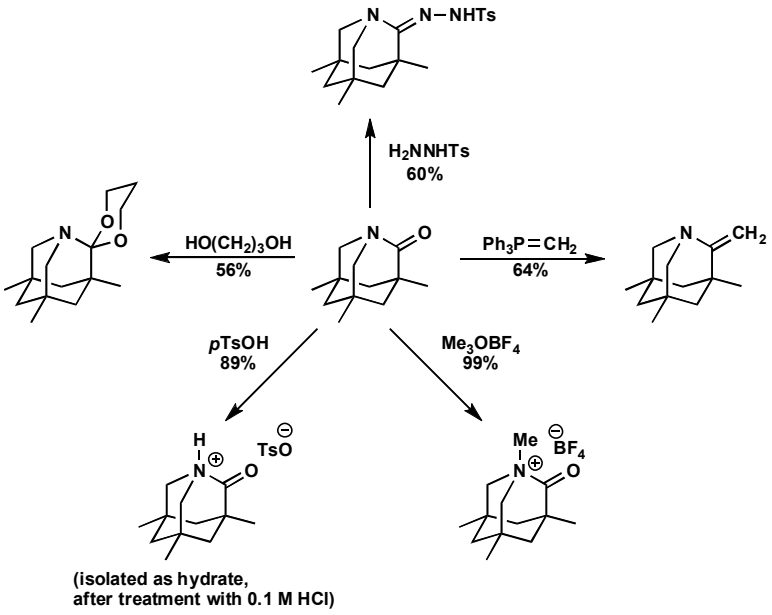
In an important study, Brown demonstrated that the methylation of the amide with [3.2.2] ring system takes place at nitrogen, while in the less distorted [3.3.2] system the oxygen is the reactive site (Scheme 27).[198] These results had been predicted by *ab initio* calculations by Greenberg,[23, 24] which indicated that similar bridged substrates had a greater degree of electron density on nitrogen relative to typical amides.

Scheme 27



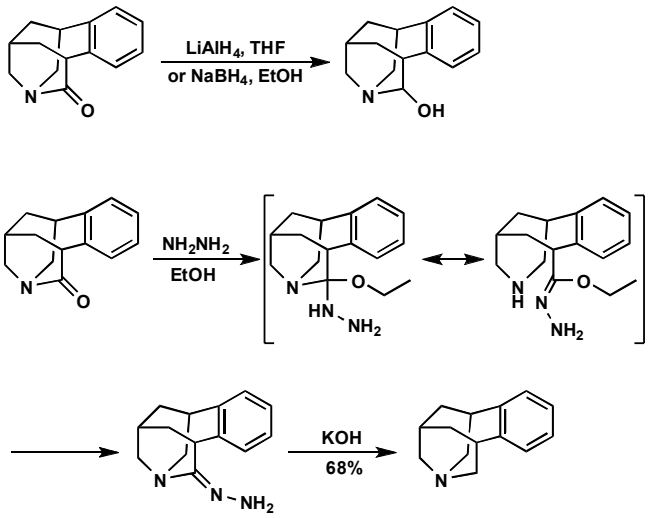
By converting 1-aza-2-adamantanone into the ketal, hydrazide and enamine, as well as into quaternary ammonium salts, Kirby has unambiguously demonstrated that this compound displays keto amine like properties, which are, however, expected for this perfectly perpendicular amide (Scheme 28).[166, 199]

Scheme 28



Coe found the one-carbon higher homologue of Kirby's amide to be one of the very few examples of a twisted amide which is reactive and stable in alcoholic solvents.[167] The reduction of this compound terminated at the hemiaminal stage; the iminium ion was not formed due to the geometrical constraints imposed by the rigid adamantane-like structure. Furthermore, the twisted amide underwent hydrazone formation and full reduction to the amine under Wolff-Kishner conditions. Coe also observed (MS analysis) that after addition of hydrazine the mixed ethanol-aminohydrazine intermediate (which probably exists in equilibrium with the open form amino-hydrazonate) is formed (Scheme 29).

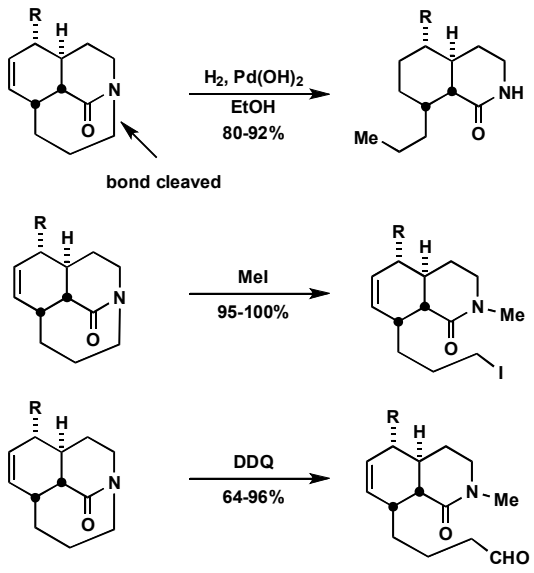
Scheme 29



In a breakthrough study, Lei, Wrobleski, Golden and Aubé demonstrated that one-carbon bridged amides undergo unprecedented C–N bond cleavage reactions under very mild reaction conditions (Scheme 30).[31] It was determined that the

hydrogenolysis is completely regioselective, a fact suggested to arise from a decreased overlap of the bond that is being cleaved with the C=O system. In this reaction, N-activation of amides by hydrogen bond with alcoholic solvents was proposed. Furthermore, tricyclic amides were found to undergo novel functionalization reactions on treatment with DDQ and MeI. Thus, for the first time it was shown that distorted amides can display unique reactivity reaching far beyond the enhanced rate of hydrolysis or ketone-like reactions of amides. Importantly, the amide bond does not need to be fully orthogonal to participate in these novel reactions.

Scheme 30

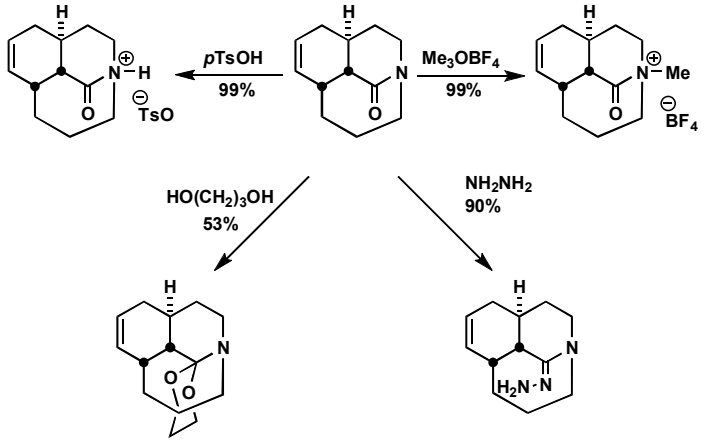


Lei and Aubé extended the above study to the nitrogen and carbonyl reactivity of tricyclic and bicyclic one-carbon bridged amides (Scheme 31).[189] Importantly, a

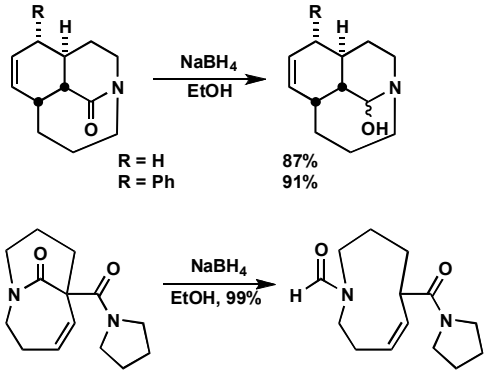
number of N-protonated and N-methylated amides were prepared. In contrast to Kirby's amide, the N-protonated amides could be isolated before undergoing hydration and their structures were confirmed by X-ray crystallography. It was also found that N-protonation of amide bonds results in a dramatic increase in the magnitude of rotation around the N–C(O) bond.

Similar to Kirby's amide, these tricyclic lactams were also found to react with ethylene glycol and hydrazine (Scheme 31). The reduction of bridged amides was facile with $NaBH_4$ and the resulting hemiaminals were stable to the isolation conditions (compare with Schemes 26 and 29). Interestingly, a bicylic amide substituted with an electron-withdrawing group in the α position collapsed to the formamide (Scheme 32). In a preliminary study it was also found that incubation of tricyclic amides at different pH conditions resulted in the recovery of the parent amides, suggesting unprecedented levels of hydrolytic stability in the distorted amides.

Scheme 31



Scheme 32



In Chapter 2, I report the study of reactivity of one-carbon bridged amides. First, the hydrolytic stability of one-carbon bridged amides is investigated. These amides are shown to display superior hydrolytic profile as compared to other bridged lactams, allowing for a number of unique transformations. Next, nucleophilic addition reactions to twisted amides, resulting in formation of exceptionally stable hemiaminals, are reported. Lastly, bridged amides are demonstrated to undergo the Corey-Chaykovsky reaction to afford isolable aminoepoxides. Other aspects of the reactivity of one-carbon bridged amides are also discussed.

Transannular amine-carbonyl interactions. Transannular interactions between the amine and carbonyl groups are relevant to this study of one-carbon bridged amides. For example, interactions between amines and electrophilic ketones or aldehydes can lead to a pseudo-tetrahedral hemiaminal-type carbon, adopting a hybridization state between sp^2 and sp^3, and which are easily observed by spectroscopic methods (Figure 8a). This type of transannular interaction has been

utilized extensively in conformational analysis,[200] mechanistic physical-organic chemistry,[201, 202] total synthesis projects,[203, 204] medicinal chemistry,[205-207] and in drug design.[208-210] The most widely recognized example of transannular N···C=O interaction is the fundamental study by Bürgi and Dunitz[211] designating the general trajectory of the attack of nucleophiles on C=O bonds. In this investigation, a set of conformationally-frozen tertiary amine and ketone groups was necessary to keep the reactive groups in close proximity to limit the number of unproductive conformations (Figure 8b).

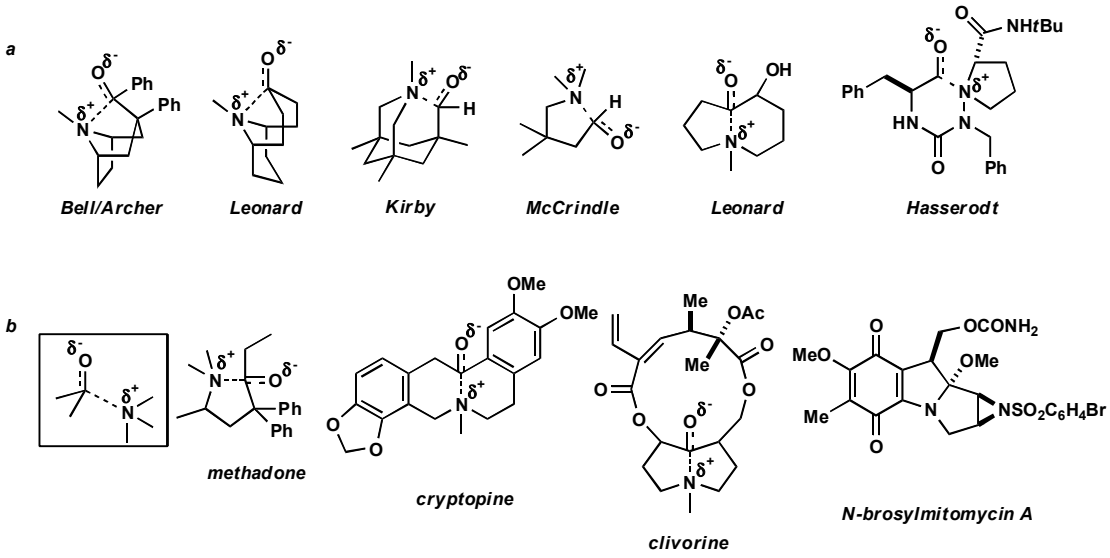


Figure 8. a) Examples of N···C=O interactions.[212-217] b) Compounds whose X-ray structures provided the basis for Bürgi-Dunitz trajectory[211] (the trajectory is shown in the box).

Interestingly, the majority of nitrogen-carbonyl transannular interactions reported so far involve electrophiles placed directly on a ring or otherwise conformationally restricted tropane-type structures. In contrast, the opening of one-carbon bridged amides would provide reasonably flexible systems with the carbonyl moved one-carbon away from the ring. Furthermore, a transannular condensation between a secondary amine and a carbonyl group placed on the other side of the ring can in principle lead to the formation of bridged amides. However, prior to the present study a very limited precedent of such transannular condensation reactions in the synthesis of bridged amides existed.

The synergy between the opening and closing of bridged amides led to the development of a general method for the synthesis of one-carbon bridged lactams discussed in Chapter 2, and also to the observation of the proximity induced transannular effects (Chapter 3).

Tetrahedral intermediates. Condensation of amines and carboxylic acid derivatives affords tetrahedral intermediates.[218] However, typical tetrahedral intermediates formed during nucleophilic addition to carboxylic acid derivatives are unstable. These short-lived species could sometimes be detected[219] but are rarely isolated.[52, 164, 220, 221] When thiol-, alcohol- and amine-based nucleophiles are employed, such species are commonly encountered in enzymatic acylation reactions, where enzymes stabilize the reactive intermediates. In addition to their synthetic value, isolated tetrahedral intermediates would provide models for *in vivo*

transacylation processes.[218] Although, tetrahedral intermediates formed in the reaction of tertiary amides and N-methoxy-N-methylamides with organometallic reagents are relatively stable as their salts, and have been used extensively for synthesis of ketones, the tetrahedral intermediates rapidly decompose upon protonation (Figure 9).

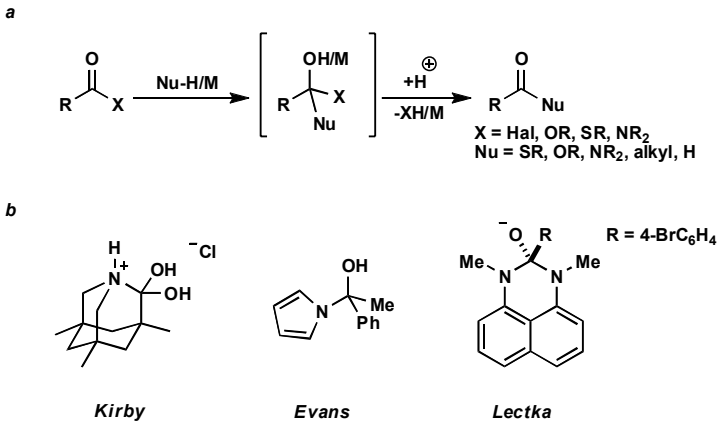


Figure 9. a) Reaction of carboxylic acid derivatives with nucleophiles. b) Examples of isolable tetrahedral adducts (see also N-brosylmitomycin C in Figure 8, and Scheme 18).

Due to the limited conjugation of amide bonds in rigid ring systems, bridged amides offer scaffolds that can be utilized for the isolation of otherwise unstable tetrahedral intermediates. Chapter 3 describes isolation of a number of remarkably stable and structurally diverse tetrahedral intermediates based on one-carbon bridged amide scaffolds. Structural requirements necessary for the isolation of these intermediates are also presented.

Chapter 2

Synthesis of Medium-Bridged Twisted Amides

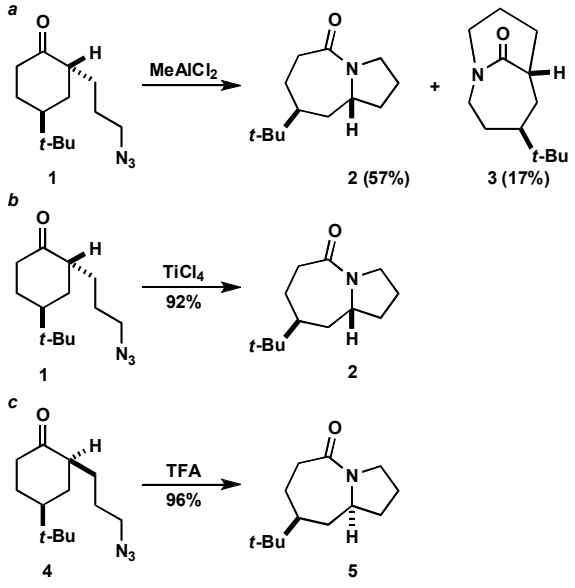
As described in the introductory chapter, the intramolecular Schmidt reaction has emerged as a reliable method for the synthesis of bridged amides. Tani and Stoltz's approach permitted the isolation of the archetypal twisted amide, 2-quinuclidone (after more than 60 years of attempts to prepare this compound), while the research of Aubé's group focusing on α-azidoalkyl azides led to the first examples of half-way rotated lactams, allowing for the initial exploration of their unusual reactivity.

Following these examples, we were interested in broadening the scope of the intramolecular Schmidt reaction in the synthesis of one-carbon bridged amides. In addition to exploring the uncommon rearrangement pathway in the Schmidt reaction of α-azidoalkyl ketones, we wished to prepare a diverse family of bridged lactams to further investigate the chemistry of non-planar amides.

When we began our study, the Schmidt reaction was limited to the synthesis of [4.3.1] ring system of bridged amides.[189] Furthermore, when the conformation of the reactive azidohydrin intermediate was not locked (even in the presence of stabilizing cation–π interactions), only fused lactams could be obtained. Consequently, our goal was to determine whether the Schmidt reaction could be utilized for preparation of other bridged amide scaffolds, and to identify whether flexible ring systems could serve as precursors to bridged amides.

Pyramidalization at nitrogen in Schmidt reaction. One promising example reported by Lei and Aubé[189] was the trans α-unsubstituted azidoketone **1**, which after exposure to $MeAlCl_2$ afforded the fused amide **2** as the major product of the Schmidt reaction, and the bridged analogue **3** in a modest yield (Scheme 33a). The same azide **1**, however, was first utilized a decade earlier in the original investigation of the intramolecular Schmidt reaction[173] to confirm that the reaction proceeds with the retention of configuration at the migrating carbon. Upon exposure to $TiCl_4$, **1** provided the fused lactam **2** as the only product of the Schmidt reaction (Scheme 33b), while the diasteroisomeric **4** cleanly furnished the lactam **5** (Scheme 33c). The acid dependence on the product distribution of the reaction of azide **1** (Scheme 33a vs. 33c) suggested an opportunity to evaluate the effects of reaction conditions on the regiochemical outcome of the Schmidt reaction.

Scheme 33



Importantly, the main factor governing the outcome of the Schmidt reaction with **1** is the configuration at nitrogen. Previous studies indicated that in the aminodiazonium intermediates involved in the Schmidt reaction, the barrier to pyramidal inversion at nitrogen is relatively small (ca. 1 kcal/mol).[178] We reasoned that the appropriate choice of promoters, solvents and temperatures could influence the reactive conformations leading to lactams **2** and **3**. Furthermore, a better understanding of this system would facilitate the extension of the scope of cation–π effects, which we envisioned to pursue afterwards.

It is worthwhile to examine the reactive intermediates in the Schmidt reaction in the α-unsubstituted system (Scheme 34). After activation, the trans azide **1** furnishes two azidohydrin intermediates **1a** and **1b**, which could interconvert through nitrogen inversion (**1a**→**1b** and **1b**→**1a**) or by reversion to the keto azide (**1a**→**1** and **1b**→**1**). The intermediate **1a** with the pseudoequatorially disposed N_2^+ affords the fused lactam while the intermediate **1b** with the N_2^+ in pseudoaxial position gives the bridged isomer.

Although epimerization (by acid mediated enolization, **1**→**4**) is not predicted to be a significant problem in this system, such a side reaction had been noticed in the original study of the Schmidt reaction. If epimerization occurs, the diastereoisomer **4** can undergo azide attack from the equatorial direction to give the intermediate **4a**, or the axial azide attack to give the intermediate **4b**. Rearrangement of either azidohydrin would give the fused lactam **5**. It is important to notice that although the

nitrogen inversion can occur in **4a** and **4b**, it would result in N_2^+ being antiperiplanr to the hydroxyl group (Figure 10); in either case the carbon migration is not possible.

Scheme 34

*Intermediates involved in the Schmidt reaction with α-unsubstitued cyclohexanone **1***

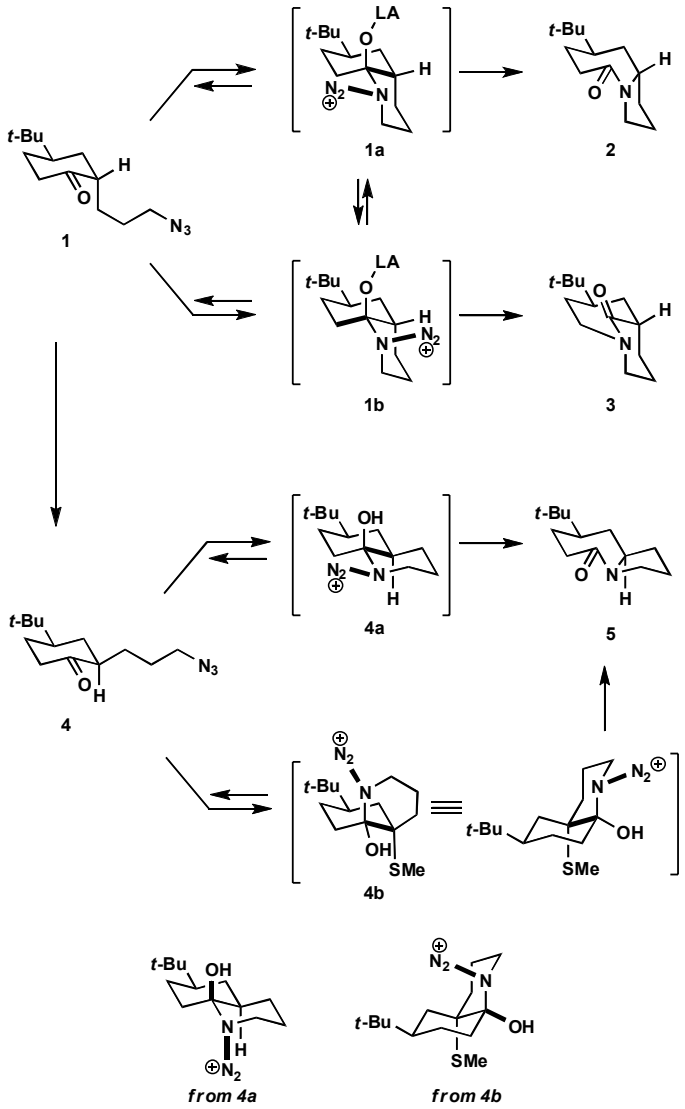


Figure 10. Unproductive azidohydrin intermediates arising from cyclohexanone bearing equatorial azidoalkyl tether (bonds antiperiplanar to N_2^+ marked in bold).

Accordingly, I undertook a detailed study of the rearrangement of keto azide **1**. The effect of different acids, temperatures and solvents on the product distribution in the Schmidt reaction of azide **1** is summarized in Tables 2, 3 and 4.

Table 2. Effect of Lewis Acid on Product Distribution with Azide **1**.[a]

entry	acid	equiv	t [h]	**2**:**3**[b]	conversion[b]	trans/cis lactams[b,c]
1	$MeAlCl_2$	1.1	2	71:29	>95	>95:5
2	$TiCl_4$	5.0	1	>95:5	>95	>95:5
3	TFA	85[d]	2	86:14	>95	70:30
4	$MeAlCl_2$	1.1	24	71:29	>95	>95:5
5	$MeAlCl_2$	25	3	71:29	>95	>95:5
6	$EtAlCl_2$	1.1	8	71:29	>95	>95:5
7	$AlCl_3$	1.1	1	77:23	>95	>95:5
8	Me_2AlCl	1.1	24	75:25	60	71:29
9	Me_3Al	2.2	24	-	<5	-
10	TMSOTf	1.1	2	77:23	>95	57:43
11	$BF_3•Et_2O$	1.1	2	78:22	>95	>95:5
12	TfOH	5.0	1	79:21	>95	>95:5
13	$SnCl_4$	1.1	2	85:15	>95	>95:5
14	$SnBr_4$	1.1	24	>95:5	>95	>95:5
15	$TiBr_4$	1.1	1	90:10	>95	80:20
16	$SbCl_5$	1.1	1	87:13	>95	94:6
17	$YbCl_3$	1.1	24	88:12	>95	>95:5
18	$AgBF_4$[e]	1.1	24	82:18	80	83:17
19	$Sc(OTf)_2$[e]	1.1	6	86:14	>95	96:4
20	$Yb(OTf)_3$[e]	1.1	24	-	<5	-
21	$Ti(O\textit{i}Pr)_4$[e]	5.0	24	-	<5	-
22	$Zn(OTf)_2$[e]	1.1	24	-	<5	-
23	$Cu(OTf)_2$[e]	1.1	24	-	9	-
24	$CuCl_2$[e]	1.1	24	-	<5	-
25	$SnCl_2$[e]	1.1	24	-	17	-

[a] 0 °C to rt, c = 0.05−0.15 M in CH_2Cl_2. [b] Determined by ^1H NMR. [c] Trans/cis lactams ratio indicates **2**,**3**:**5** ratio. [d] Neat. [e] Reflux.

Table 3. Effect of Temperature on Product Distribution with Azide **1**.[a]

entry	acid	temperature	t [h]	**2**:**3**[b]	conversion[b]	trans/cis lactams[b,c]
1	$MeAlCl_2$	0 °C → rt	2	71:29	>95	>95:5
2	$MeAlCl_2$	-78 °C → rt	24	79:21	>95	94:6
3	$MeAlCl_2$	-78 °C (6 h) → rt	24	93:7	55	93:7
4	$MeAlCl_2$	45 °C[d]	1	74:26	>95	>95:5
5	$MeAlCl_2$	90 °C[e]	0.2	80:20	>95	92:8
6	$MeAlCl_2$	110 °C[d, f]	0.5	77:23	>95	>95:5

[a] 1.1 equiv of $MeAlCl_2$, c = 0.05–0.15 M in CH_2Cl_2. [b] Determined by ^{1}H NMR. [c] Trans/cis lactams ratio indicates (**2**+**3**):**5** ratio. [d] $MeAlCl_2$ added at rt, and the reaction vessel was placed in the oil bath preheated to the indicated temperature. [e] MW irradiation. [f] Toluene as a solvent.

Table 4. Effect of Solvent on Product Distribution with Azide **1**.[a]

entry	acid	solvent	t [h]	**2**:**3**[b]	conversion[b]	trans/cis lactams[b,c]
1	$MeAlCl_2$	CH_2Cl_2	2	71:29	>95	>95:5
2	$MeAlCl_2$	Et_2O	24	71:29	>95	51:49
3	$MeAlCl_2$	CH_3CN	6	73:27	>95	93:7
4	$MeAlCl_2$	$PhCH_3$	1	75:25	>95	>95:5
5	$MeAlCl_2$	CCl_4	24	75:25	>95	92:8
6	$MeAlCl_2$	CH_3Cl	24	-	20	-
7	$MeAlCl_2$	MeOH	24	ketal[d]	-	-

[a] 0 °C to rt, 1.1 equiv of $MeAlCl_2$, c = 0.05–0.15 M in indicated solvent. [b] Determined by ^{1}H NMR. [c] Trans/cis lactams ratio indicates **2**,**3**:**5** ratio. [d] 2-(3-Azidopropyl)-4-*tert*-butyl-1,1-dimethoxy cyclohexane was formed.

As noted above, we expected that the bond migration in this simple system, in which the reactive intermediates **1a** and **1b** differ only by the orientation of the diazonium cation (Scheme 34), could be influenced by application of different Lewis acids. Indeed, examination of the reaction conditions confirmed this to be the case. Migration of the bond distal to the azide was regularly observed, and the resulting bridged amide **3** was found to be stable to the reaction conditions (Table 2, entries 1,

4 and 5). In general, aluminum-containing acids afforded the highest ratio of the bridged to the fused amide (entries 4-9). The migration of the proximal C–C bond was favored by sterically demanding Lewis acids (entries 2 and 13-17). The vast majority of acids led to the clean ring expansion reaction; only few of the studied acids did not promote the rearrangement (entries 9 and 20-25). A significant amount of epimerization occurred only in three instances (entries 3, 8 and 10), reflecting the general facility of the intramolecular Schmidt reaction.

We determined that the distribution of lactams formed from azide **1** could also be influenced by changes in the reaction temperature (Table 3). The formation of the bridged amide could be almost entirely suppressed by lowering the temperature (entry 3). Similarly, the bridged/fused amide ratio was decreased when the reaction was performed at the higher temperatures (entries 2 and 6). By contrast, changing solvents had a minor influence on the selectivity of the rearrangement (Table 4).

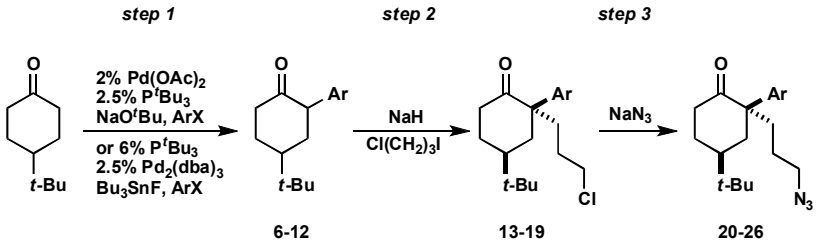
Overall, the regioselectivity of the rearrangement of azide **1** proved to be condition-dependent and a variety of acids were found to promote the formation of the bridged amide. Although, the ratio of the bridged to the fused lactam formed from the azide **1** could not be improved, the above results suggested a possibility of influencing the outcome of Schmidt reactions in more complex systems. The reaction with azide **1** could be easily scaled up to provide gram quantities of lactam **3**, allowing for examination of properties of the α-unsubstitiuted [4.3.1] bridged system (see Chapter 3).

Cation–π control of regiochemistry in the Schmidt reaction. Lei and Aubé discovered a significant increase in the bridged/fused amide ratio when phenyl and 4-methoxy phenyl substituents were placed in the α-position to the ketone in the intramolecular Schmidt reaction (Scheme 22). Cation–π interactions were suggested to be a key controlling feature in this reaction.[188, 189]

In an attempt to improve the synthesis of distorted amides, we wished to further enhance the regioselectivity of the Schmidt rearrangement by utilizing substrates with higher electron density on aromatic rings than 4-methoxy phenyl. We also wanted to confirm the presence of cation–π interactions by using a substrate bearing an electron withdrawing group on the aromatic ring. Following Katz's precedence[194, 195] (Scheme 23), it seemed likely that 3,4,5-trimethoxyphenyl and 4-nitrophenyl groups would fulfill these tasks. Examination of additional substrates bearing aromatic rings with different substitution patterns would provide both insights into this type of the intramolecular Schmidt reaction and further examples of bridged amides.

The selected 2-azidoalkyl-2-arylketones and their synthesis are presented in Table 5. In all cases, diastereomerically pure samples of the required trans diastereoisomers could be obtained after careful chromatography of the intermediate chlorides.

Table 5. Preparation of Azides **20-26**.

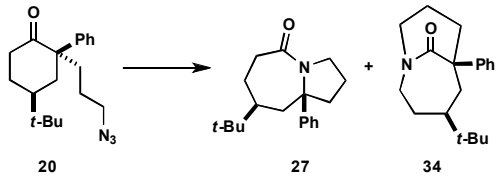


entry	Ar	product (yield, %)		
		step 1	step 2	step 3
1	C_6H_5	**6** (50)	**13** (40)	**20** (89)
2	4-(MeO)C_6H_4	**7** (52)	**14** (45)	**21** (96)
3	4-(NO_2)C_6H_4	**8** (61)[a]	**15** (41)	**22** (88)
4	3,4,5-$(MeO)_3C_6H_2$	**9** (46)	**16** (40)	**23** (99)
5	3,4-$(MeO)_2C_6H_3$	**10** (52)	**17** (45)	**24** (87)
6	3,4-(CH_2OCH_2)C_6H_3	**11** (37)	**18** (37)	**25** (86)
7	3,5-$(MeO)_2C_6H_3$	**12** (62)	**19** (43)	**26** (89)

[a] TMS enol ether used instead of the ketone.

Having determined earlier (Tables 2 and 3) that the regiochemical outcome of the Schmidt rearrangement depends significantly on the reaction conditions, we started the investigation of the cation–π directed version by a short optimization of the reaction conditions, utilizing α-phenyl containing azide **20** as a model substrate (Table 6).

Table 6. Optimization of Product Distribution in Schmidt Reaction with Azide **20**.[a]



20 **27** **34**

entry	acid	equiv	t [h]	**27**:**34**[b]
1	$MeAlCl_2$	1.1	3[i]	26:74
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	$BF_3•Et_2O$	1.1	6	60:40
7[c]	$MeAlCl_2$	1.1	6	26:74
8[d]	$MeAlCl_2$	2.2	18	47:53
9[e]	$MeAlCl_2$	2.0	24	71:29
10[f]	$MeAlCl_2$	2.0	24	47:53
11[g]	$MeAlCl_2$	2.0	24	26:74
12[h]	$MeAlCl_2$	2.0	24	37:63

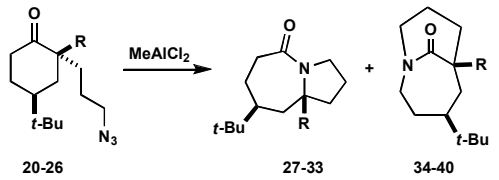
[a] 0 °C to rt, c = 0.05−0.15 M in CH_2Cl_2 unless otherwise noted. [b] Determined by ^1H NMR. [c] -78 °C to rt. [d] Reflux, 1.1 equiv added after 2 h. [e] c = 0.0007 M. [f] c = 0.007 M. [g] c = 0.05 M. [h] c = 0.23 M. [i] The ratio did not change after next 12 h.

These studies revealed that a number of Lewis and protic acids could be used to provide the desired bridged lactam **34** (entries 1−6). Changes in temperature did not improve the bridged/fused ratio (entries 7−8). Interestingly, the product distribution proved to be dependent on the concentration of the reaction, with the ideal results obtained at c = 0.05 M (entries 9−12).

Next, we probed the effect of the electronic nature of the aromatic substituent in the α position on the outcome of the Schmidt reaction (Table 7). In these experiments bridged amides **34-40** arise from cation–π stabilized intermediates,

bearing the diazonium cation in the pseudoaxial orientation (Scheme 35, **ax-cation**), whereas fused lactams **27-33** arise from a competing reaction pathway involving pseudoequatorial diazonium cation (Scheme 35, **eq-cation**).

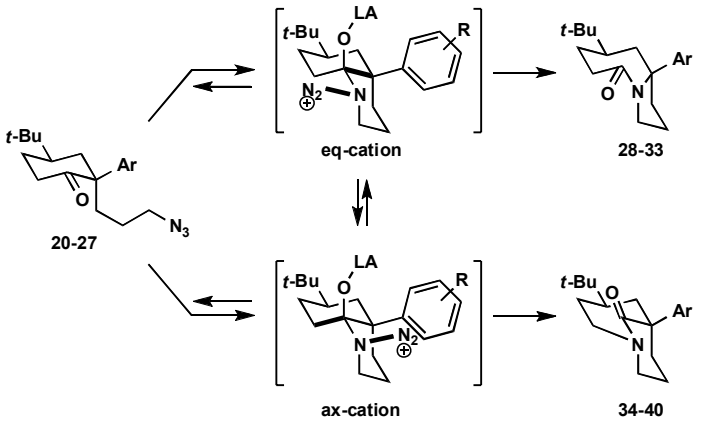
Table 7. Cation–π Directed Synthesis of Fused and Bridged Lactams.[a]



			product (yield, %)	
entry	azide	R	fused	bridged
1	**20**	C_6H_5	**27** (22)	**34** (61)
2	**21**	4-(MeO)C_6H_4	**28** (11)	**35** (71)
3	**22**	4-(NO_2)C_6H_4	**29** (38)	**36** (39)
4	**23**	3,4,5-$(MeO)_3C_6H_2$	**30** (19)	**37** (66)
5	**24**	3,4-$(MeO)_2C_6H_3$	**31** (18)	**38** (65)
6	**25**	3,4-(CH_2OCH_2)C_6H_3	**32** (13)	**39** (72)
7	**26**	3,5-$(MeO)_2C_6H_3$	**33** (25)	**40** (65)

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

Scheme 35



The observed overall dependence of selectivity is consistent with the ability of aryl rings to stabilize the N_2^+ group in 1,3-diaxial relationship.[195] Thus, under the optimized conditions, the azide **20** bearing phenyl in the α position afforded 61% of the bridged lactam **34** along with 22% of the fused product **27** (Table 7, entry 1). The azide **21**, featuring a more electron-rich 4-methoxyphenyl system, led to an increased bridged/fused lactam ratio delivering the amides **35** and **28** in 71 and 11% yield, respectively (Table 7, entry 2). Conversely, azide **22**, decorated with an electron-withdrawing 4-nitrophenyl substituent, decreased the ratio, leading to ca. 1:1 distribution of the final products (Table 7, entry 3). This trend is fully consistent with the expectation that the observed selectivities are a direct result of the axial/equatorial preference of the diazonium cation and the strength of the cation–π interaction.

Interestingly, introduction of the 3,4,5-trimethoxyphenyl substituent in the α position of the azido-alkyl cyclohexanone afforded the bridged amide in 66% and its fused analogue in 19% yields, respectively (Table 7, entry 4). This ratio is intermediate between that of the phenyl and 4-methoxyphenyl substituted azido-ketones. Moreover, it does not follow the trend observed in the Schmidt reaction with hydroxyalkyl azides (Scheme 23), which is a closely related system probing the strength of cation–π interactions between N_2^+ and aromatic rings. Furthermore, the use of 3,4-dimethoxyphenyl substrate **24** provided products having a bridged/fused lactam ratio similar to that of substrate **23** (entry 5), while the 3,4-dioxomethylenephenyl-containing azide **25** (entry 6) increased the selectivity, matching the ratio obtained with azide **21** (entry 2). In addition, 3,5-

dimethoxyphenyl-containing azide **26** (entry 7) gave a ratio similar to the α-phenyl keto-azide from entry 1.

We reasoned that these unanticipated results could be ascribed to coordination of the Lewis acid to the oxygen ethers. To probe this hypothesis we performed a set of experiments, in which the azido-ketones were subjected to varying number of equivalents of $MeAlCl_2$. The results are summarized in Table 8.

Table 8. Influence of Lewis Acid Stoichiometry on Product Distribution in Cation–π Directed Schmidt Reaction.[a,b]

			bridged:fused					
entry	equiv	acid	**27**:**34**	**28**:**35**	**29**:**36**	**30**:**37**	**31**:**38**	**33**:**40**
1	1.0	$MeAlCl_2$	26:74	12:88	50:50	16:84	15:85	24:76
2	1.5	$MeAlCl_2$	26:74	12:88	49:51	21:79	22:78	31:69
3	2.0	$MeAlCl_2$	28:72	14:86	47:53	30:70	39:61	42:58
4	3.0	$MeAlCl_2$	30:70	29:71	nd	46:54	52:48	61:39
5	2.0	BF_3•CH_3CN	56:44	32:68	nd	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 ^1H NMR. nd = not determined.

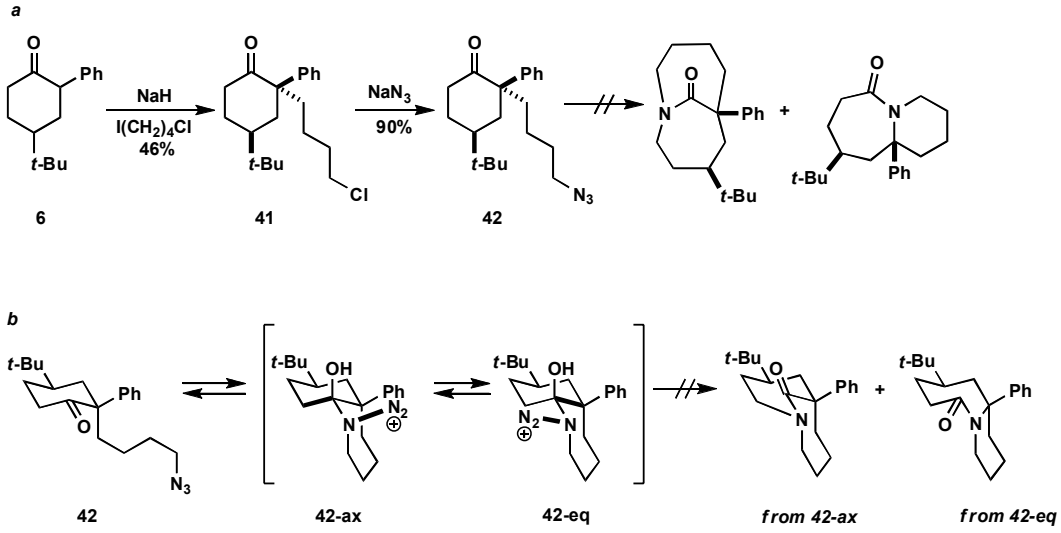
In the case of the α-phenyl-containing azide the bridged/fused amide ratio remains practically constant, regardless of the stoichiometry of $MeAlCl_2$ (Table 8, **27**:**34**, entries 1-4). However, with alkyloxygen-substituted phenyl rings, the ratio significantly decreases with the increase of equivalents of the acid used. In addition, this tendency is more pronounced in substrates capable of coordination of $MeAlCl_2$ to multiple oxygens (Table 8, series **30**:**37**, **31**:**38**, **33**:**40**). Furthermore, the application of a monodentate Lewis acid to promote the rearrangement afforded a similar trend of

bridged/fused lactams to that obtained with $MeAlCl_2$ (4-methoxyphenyl > 3,4,5-trimethoxyphenyl > phenyl > 3,5-dimethoxyphenyl) (Table 8, entry 5).

These results are consistent with coordination of the acid to oxygens placed on the aromatic ring, leading to the decrease of the electron density of π-systems, and weakening of cation–π interactions. The net outcome is the increased amount of the fused lactam formed from the intermediate bearing N_2^+ group in the pseudoequatorial orientation (Scheme 35, **eq-cation**). A steric interaction between the acid coordinated to aromatic ring oxygens and diazonium cation in the pseudoaxial orientation might also be responsible for a lower selectivity in the C–C bond migration. Overall, these results emphasize the importance of selecting appropriate reaction conditions to obtain maximum cation–π stabilization effects.

We also subjected azide **42** bearing a four-carbon tether to the above Schmidt reaction conditions (Scheme 36a). However, lengthening of the azide-side chain did not lead to any productive reaction, even under very forcing reaction conditions ($Sc(OTf)_3$, 0.5 equiv, H_2O, 180 °C, 3 h or $TiCl_4$, 5.0 equiv, toluene, 105 °C, 18 h). It is very likely that in this case the azidohydrin intermediates **42-ax**/**42-eq** are formed, however the α-phenyl substitutent slows down the migration of the C–C bond (Scheme 36b). A deleterious effect of electron-withdrawing substituents on the rate of the reaction was observed earlier in a number of azido-Schmidt substrates.[173, 222, 223]

Scheme 36



Motivated by Yamada *et al.* findings that carbonyl groups can serve as effective π-systems,[224] we examined the potential of ester and amide functionalities as cation-stabilizing groups in the intramolecular Schmidt reaction (Scheme 37 and Table 9).

Scheme 37

Preparation of azides with α-carbonyl groups

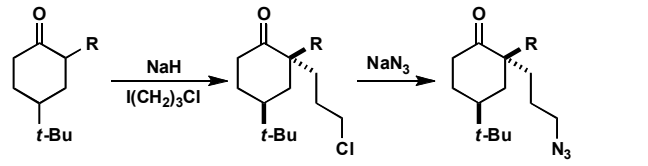
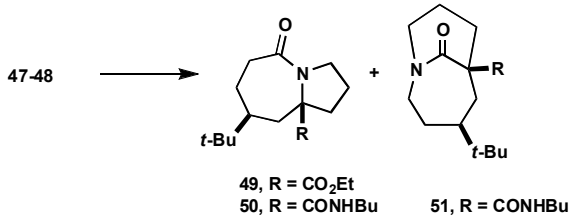


Table 9. Schmidt Reactions of α-Carbonyl Substituted Azides.



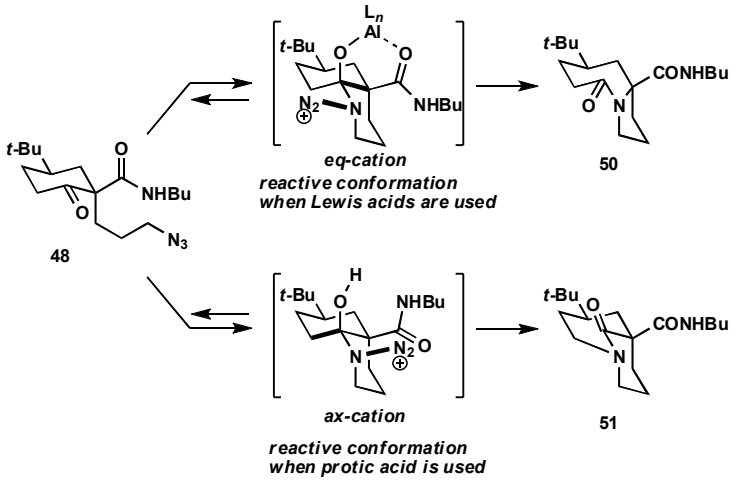
				product (yield, %)	
entry	azide	R	acid	fused	bridged
1	**47**	CO_2Et	$MeAlCl_2$	**49** (80)	-
2	**47**	CO_2Et	TfOH	**49** (92)	-
3	**47**	CO_2Et	TFA	**49** (88)	-
4	**47**	CO_2Et	$BF_3•Et_2O$	**49** (78)	-
5	**48**	CONHBu	TfOH	**50** (52)	**51** (13)
6	**48**	CONHBu	$MeAlCl_2$	**50** (77)	-

However, the α-ethoxycarbonyl group embedded in a conformationally-locked system afforded only the fused amide, albeit in good yields (Table 9, entries 1-4). The placement of a secondary amide in the α position permitted the formation of the bridged amide **51** (entry 5), but the bridged/fused lactam ratio resembled the outcome obtained with the azide **1** rather than cases in which cation–π interactions were operative. Interestingly, when the reaction of the azide **48** was promoted by the Lewis acid, the formation of the bridged amide was not observed (entry 6). This suggests that the Lewis acid coordinates to the amide, possibly forming a six-membered chelate, which might disfavor the placement of the diazonium cation in the pseudoaxial position (Scheme 38, **eq-cation**).

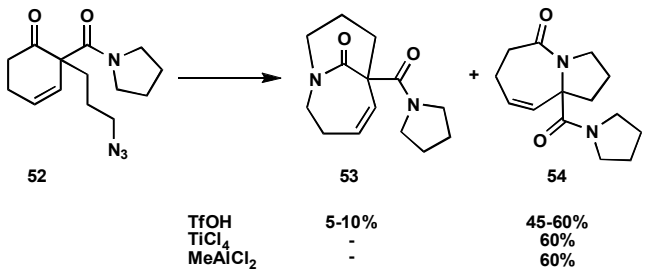
The behavior of azide **48** is reminiscent of another α-amide-containing azidoketone (**52**, Scheme 39), which affords the fused and the bridged amide when

subjected to TfOH, however it gives only the fused analogue in reactions mediated by $TiCl_4$ or $MeAlCl_2$ (described by Wrobleski and Aubé).[225]

Scheme 38



Scheme 39



Distortion parameters of [4.3.1] bridged amide ring system. Bridged amides prepared by cation–π directed intramolecular Schmidt reaction contain nitrogen atoms at a bridgehead position in [4.3.1] ring system. This arrangement prohibits the nitrogen and the carbonyl group from adopting co-planarity.

Consequently, the nitrogen lone pair is partially orthogonal to the amide C=O bond, and unable to participate in full conjugation with the C=O π* orbital. This results in keto amine-like character of these compounds. The X-ray structure of **38** confirms that the amide bond is significantly distorted (Figure 11).[226] Dunitz-Winkler distortion parameters show that in **38**, the N–C(O) bond has $\tau = 43.2°$, $\chi_N = 33.8°$, and $\chi_C = 16.3°$. This indicates that the N–C(O) bond is halfway rotated, and that the hybridization at nitrogen is nearly halfway between sp^2 and sp^3 in character. In contrast, the carbon of the amide bond is nearly planar; this property has also been observed in other distorted amides.[37] The N–C(O) bond length of 1.363 Å in **38** is longer than the typical N–C(O) bond in planar amides and the C=O bond length of 1.234 Å is slightly shorter than the average C=O bond in traditional lactams. These values are consistent with a significantly distorted amide bond resulting from incorporation of the nitrogen in the bicyclic [4.3.1] ring system.

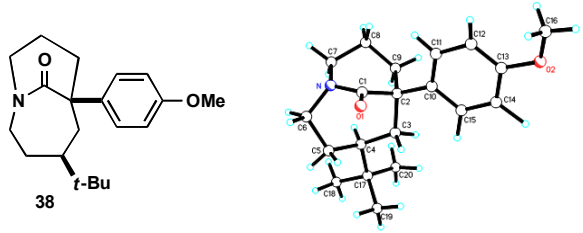


Figure 11. X-ray structure of bridged amide **38**.

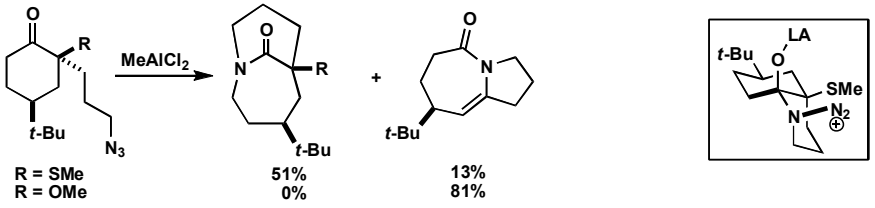
The comparison of distortion parameters of **38** and **53** along with tricyclic bridged amides obtained in the Schmidt reaction and representative other distorted

lactams is presented in Table 35, Chapter 3. The X-ray structure of **38** provides key evidence to explain the differences in reactivity between distorted amides.

Cation–n control of regiochemistry in Schmidt reaction. Although cation–π interactions have proven to be a very efficient method for synthesis of one-carbon bridged amides, a major limitation of this approach is the necessity for a locked conformation of the reactive azidohydrin intermediate to form a twisted amide (Scheme 22). In addition, only the [4.3.1] ring system could be prepared utilizing the cation–π directed Schmidt reaction (Scheme 36). These limitations could be partially overcome by applying cation–n interactions as a controlling feature of the Schmidt reaction.

Lei and Aubé have found that the bridged amide is formed as the major product of the Schmidt reaction when a thiomethyl group is placed in the α-position in the conformationally locked 2-azidoalkylcyclohexanone, (Scheme 40).[189] By contrast, the methoxy group led exclusively to the fused lactam. It was proposed that attractive cation–n interactions between the N_2^+ leaving group and n electrons on the polarizable sulfur atom could be responsible for the formation of the bridged lactam (Scheme 40, box). These experiments were preceded by realization that the spectroscopic properties reported earlier by Aubé and coworkers[173] for the fused α-thiophenyl-containing lactam are likely to correspond to a bridged rather than fused structure (see Experimental Section for details).

Scheme 40



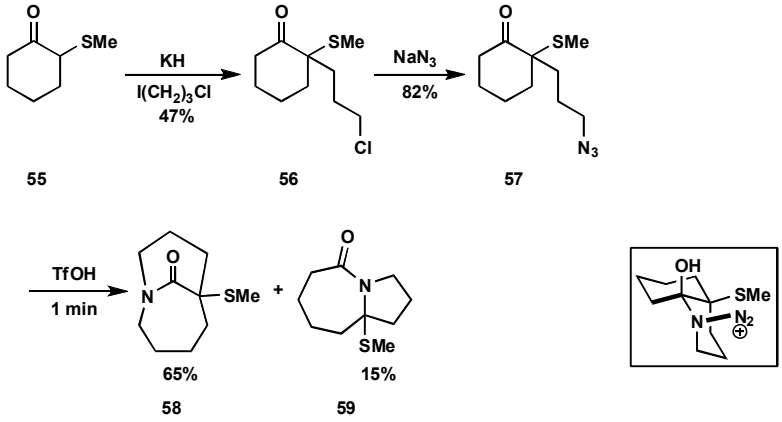
We wondered if a similar cation–n effect could be utilized for the *synthesis of bridged amides in a system in which the conformation of the reactive azidohydrin intermediate is not locked*. We hypothesized that a thiomethyl group might have a beneficial effect on the rearrangement of the distal C–C bond in the Schmidt reaction. Firstly, similar to the phenyl group, an electron-withdrawing SR group should slow down the rearrangement step. Importantly, this will also disfavor the migration of the C–C bond proximal to the azide. Secondly, due to a similar A value to the azidoalkyl tether (1.1 kcal/mol of SMe vs. 1.79 kcal/mol of C_2H_5),[227] it is possible that the required conformation of the azidohydrin bearing the azidoalkyl chain in the axial orientation will be present not only in the ground state but also during the reaction. In this arrangement, the diazonium cation in the axial orientation could be stabilized by the interaction with sulfur.

It should be noted that despite a relatively large A value of the phenyl group (2.8 kcal/mol), this substituent does not always occupy the equatorial orientation predicted by steric requirements.[195] For example, in 1-methyl-2-phenylcyclohexane the phenyl preferentially occupies an axial orientation, since after rotation it can avoid steric interactions with adjacent hydrogens that are unavoidable when the phenyl is

equatorial. Phenyl rotation is likely to be one of the major factors contributing to the exclusive formation of the fused lactam from the unlocked α-phenyl azidoalkyl cyclohexanone (Scheme 21).

After a two-step synthesis of the required precursor, we were delighted to discover that the azide **57** with a thiomethyl placed in the α position to the ketone afforded a bridged bicyclic lactam *without relying on the locked conformation of cyclohexanone* (Scheme 41).[228] Given the original hypothesis for the mechanism of the intramolecular Schmidt reactions (Scheme 20), we hypothesized that the lactam **58** is formed from the azidohydrin intermediate (Scheme 41, box) subjected to a stabilizing electrostatic 1,3-diaxial interaction between the cation and the thiomethyl.

Scheme 41



Control experiments demonstrated that the axial orientation of the azide-containing side-chain is required for the formation of bridged lactams (Scheme 42 and Table 10, entries 2 and 3). In this particular case, the preparation of azides was

complicated due to the difficulties in separation of the diastereoisomers (Scheme 42a). Despite extensive investigation of methods based on reduction of the ketone or oxidation of the sulfur to increase the polarity of intermediates, direct alkylation followed by careful chromatography still afforded the best results.

The use of thiomethyl is crucial to the outcome of the reaction (Table 10, entries 1, 4 and 5). The selectivity observed with the conformationally locked azide **61** equals the highest selectivity obtained in the previous study (entries 2 and 6). Thus, in the cyclic intermediates involved in the Schmidt reaction the strength of thiomethyl cation–n interactions is comparable with the well-established cation–π interactions. *However, the remarkable advantage is that when the thiomethyl occupies the α position to the ketone the reactive intermediate contains the azide chain in the axial orientation (entries 1 and 6), allowing for the synthesis of otherwise unsubstituted bridged lactams.*

Scheme 42

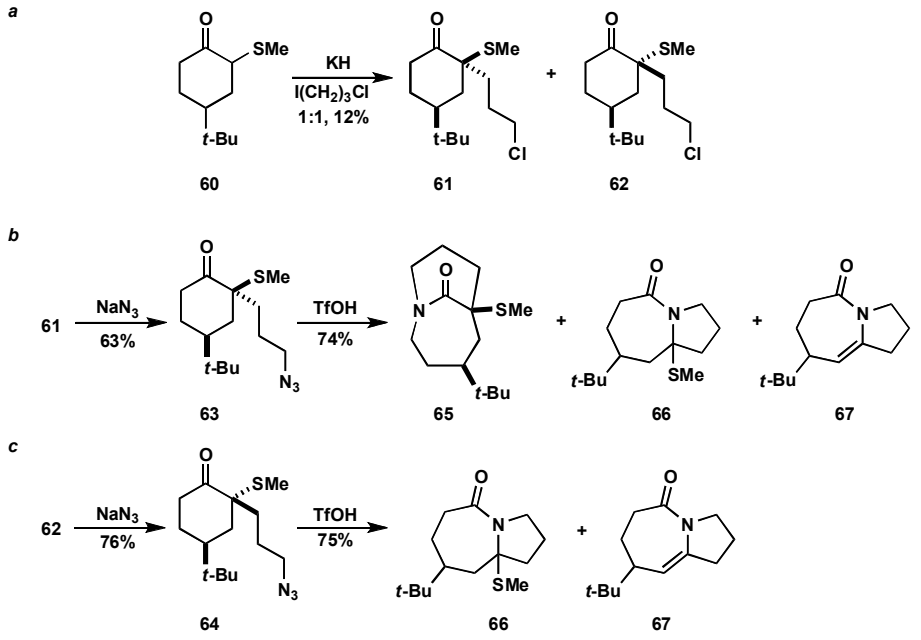
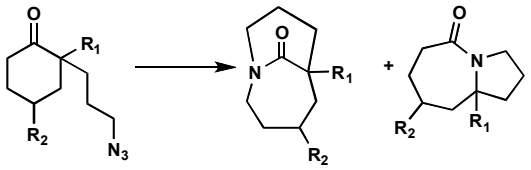


Table 10. Synthesis of Bridged and Fused Lactams Utilizing Cation–n Effects.

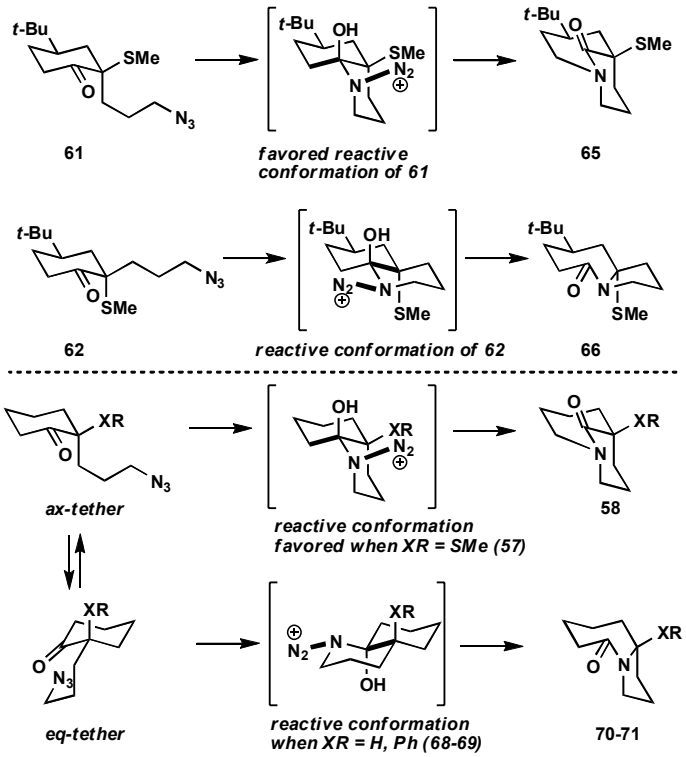


entry	azide	R_1	R_2	bridged:fused ratio[a]	yield (%)[b]
1	**57**	SMe	H	80:20	80
2	**61**	SMe, cis to R_2	*t*-Bu	86:14	74
3	**62**	SMe, trans to R_2	*t*-Bu	>5:95	75
4	**68**	H[c]	H	>5:95	85
5	**69**	Ph[d]	H	>5:95	96
6	**21**	4-(MeO)C_6H_4, cis to R_2[d]	*t*-Bu	87:13	75

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Combined yield, see the Experimental Section for full details. [c] Reference 173.[d] Reference 188.

The reactive intermediates are shown in Scheme 43. The fact that the isomer **61** leads primarily to the bridged product while the isomer **62** affords only the fused product provides the first experimental support for the hypothesis that the intramolecular Schmidt reaction requires the azidoalkyl chain to adopt an axial orientation to give a bridged lactam. Here, we suggest that the bridged isomer **65** is formed due to stabilizing cation–n interaction favoring the orientation of diazonium cation in pseudoaxial position in the azidohydrin intermediate. The effect of an α substituent is shown in the bottom part of Scheme 43. In **57**, the thermodynamically favored conformation **ax-tether** affords the azidohydrin intermediate that leads to **58**. It is very likely, however, that the alternative conformation with the azidoalkyl chain in equatorial orientation **eq-tether** exists in the ground state.

Scheme 43



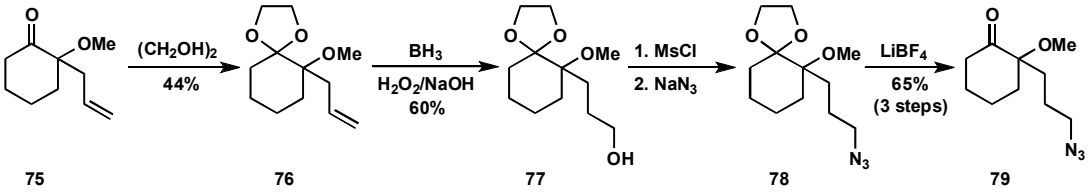
We also probed the effect of heteroatom substituents and ring sizes on the outcome of the reaction (Schemes 44 and 45, Table 11). Thiophenyl and methoxy groups allowed for the synthesis of bridged lactams, albeit in lower yield. Sulfur substitution with either an electron-withdrawing group (entry 2) or a less polarizable heteroatom (entry 3) led to diminished cation–n interactions. Sulfonyl was also found to be an efficient directing group, however in this case the interaction takes place between cation and oxygen and a cation–π component cannot be excluded.

Examination of different ring sizes revealed that bridged lactams are formed efficiently from six and seven membered rings in which the azide is separated from

the ring by a three-carbon tether. Extending the ring size or the tether length decelerated the reaction and decomposition of azide to aldehyde was the only reaction pathway observed (entries 7 and 8). As determined earlier for other intramolecular Schmidt reactions, substitution with an electron-withdrawing substitutent slows down the rate of reaction.[173] This effect is similar to that seen in the reaction of azide **42** (Scheme 36), which was found unable to undergo the rearrangement.

Scheme 44

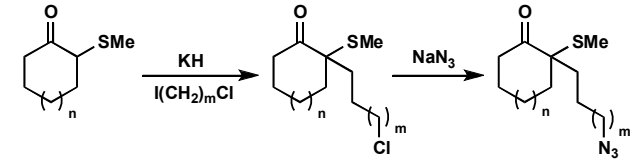
*Preparation of azide **79***



75 76 77 78 79

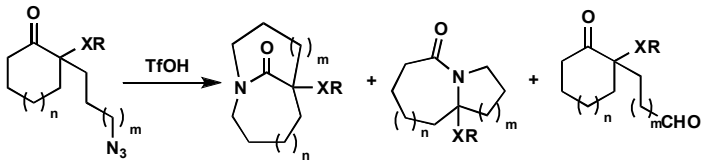
Scheme 45

*Preparation of azides **88**, **92**, **98** and **101***



n = 0, m = 1, (86)	37%, (87)	77%, (88)
n = 2, m = 1, (90)	64%, (91)	85%, (92)
n = 3, m = 1, (96)	75%, (97)	90%, (98)
n = 1, m = 2, (55)	67%, (100)	86%, (101)

Table 11. Effect of Substituent and Ring Size on Cation–n Directed Schmidt Reactions.



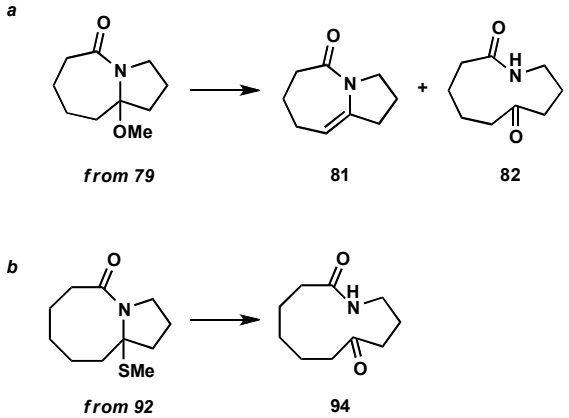
					yield (%)		
entry	azide	XR	n	m	bridged	fused	aldehyde
1	**57**	SMe	1	1	**58** (65)	**59** (15)	-
2	**72**	SPh	1	1	**73** (35)	**74** (32)	-
3	**79**	OMe	1	1	**80** (23)	**81**+**82** (52)[a]	-
4	**83**	SO_2Me	1	1	**84** (48)	**85** (13)	-
5	**88**	SMe	0	1	-	**89** (43)	-
6	**92**	SMe	2	1	**93** (62)	**94** (11)[b]	**95** (20)
7	**98**	SMe	3	1	-	-	**99** (30)
8	**101**	SMe	1	2	-	-	**102** (53)

[a] Combined yield of **81** and **82** (see below). [b] Keto amide (see below).

Some of the α-heteroatom-substituted fused lactams were found to be unstable. For example, the Schmidt reaction of azide **79**, instead of the expected lactam, afforded elimination and ring-opening products in ca. 1:1 ratio (Scheme 46a). Mechanistically, this involves protonation of the methoxy group, N-acyliminum ion formation, and deprotonation or hydrolysis. Similarly, the azide **92** afforded the 11-

membered keto amide (Scheme 46b). Additionally, lactams **85** and **89** were found to eliminate readily upon exposure to acids and mild heating. Analogous ring opening of bicyclic systems had been observed earlier in the Schmidt reaction with hydroxyl alkylazides.[229]

Scheme 46



Interestingly, cation–n directed Schmidt reactions were found to be very dependent on the acid used for rearrangement, suggesting the importance of coordination effects on the product distribution (Table 12).

Table 12. Acid Influence on Bridged/Fused Lactam Ratios in Cation–n Directed Schmidt Reactions.

entry	azide	XR	acid	equiv	time	bridged:fused lactam[a]	bridged:fused products
1	**57**	SMe	TfOH	5.0	60 s	80 : 20	**58** : **59**
2	**57**	SMe	HBF_4	5.0	5 min	75 : 25	**58** : **59**
3	**57**	SMe	BF_3•CH_3CN	2.0	2 h	76 : 24	**58** : **59**
4	**57**	SMe	$MeAlCl_2$	1.0	4 h	77 : 23	**58** : **59**
5	**57**	SMe	$TiCl_4$	2.0	2 h	27 : 73	**58** : **59**
6	**72**	SPh	TfOH	5.0	60 s	53 : 47	**73** : **74**
7	**72**	SPh	HBF_4	5.0	5 min	33 : 67	**73** : **74**
8	**72**	SPh	BF_3•CH_3CN	2.0	2 h	44 : 56	**73** : **74**
9	**72**	SPh	$MeAlCl_2$	1.0	4 h	27 : 73	**73** : **74**
10	**72**	SPh	$TiCl_4$	2.0	2 h	>5 : 95	**73** : **74**
11	**79**	OMe	TfOH	5.0	60 s	32 : 68	**80** : **81**+**82**
12	**79**	OMe	BF_3•CH_3CN	2.0	6 h	37 : 63	**80** : **81**+**82**
13	**79**	OMe	$MeAlCl_2$	2.0	6 h	22 : 78	**80** : **81**+**82**
14	**79**	OMe	$TiCl_4$	2.0	6 h	16 : 84	**80** : **81**+**82**

[a] Determined by ^{1}H NMR of crude reaction mixtures.

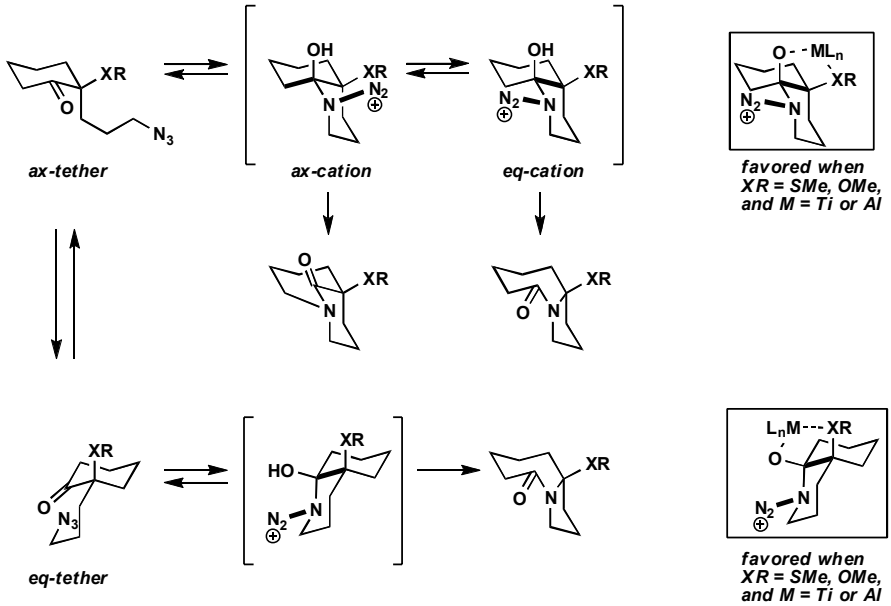
With the α-thiomethyl azide **57** the bridged/fused amide ratio (**58**:**59)** drops significantly only when $TiCl_4$ is used to promote the reaction (Table 12, entry 5). Other acids gave a comparable **58**:**59** ratio (entries 1-4). However, in the case of **72**, HBF_4 and $MeAlCl_2$ led to a significantly decrease in the **73**:**74** ratio (entries 7 and 9),

while $TiCl_4$ does not lead to the bridged amide at all (entry 10). In the case of **79**, a trend similar to **72** was observed, with TfOH and BF_3•CH_3CN (entries 11 and 12) giving superior results to $MeAlCl_2$ and $TiCl_4$ (entries 13 and 14).

The product distribution with a seven-membered azidoketone **93** was also dependent on the acid used to promote the rearrangement. Thus, TfOH gave **93**, **94** and **95** in 62%, 11% and 20% yields, respectively (Table 11, entry 6). Similar to the examples in Table 12, $TiCl_4$ afforded **93** and **94** in the opposite ratio (22% and 43% yield), while BF_3•CH_3CN gave comparable results to TfOH (71% and 13% yield). The aldehyde was not detected in reactions mediated by $TiCl_4$ and BF_3•CH_3CN.

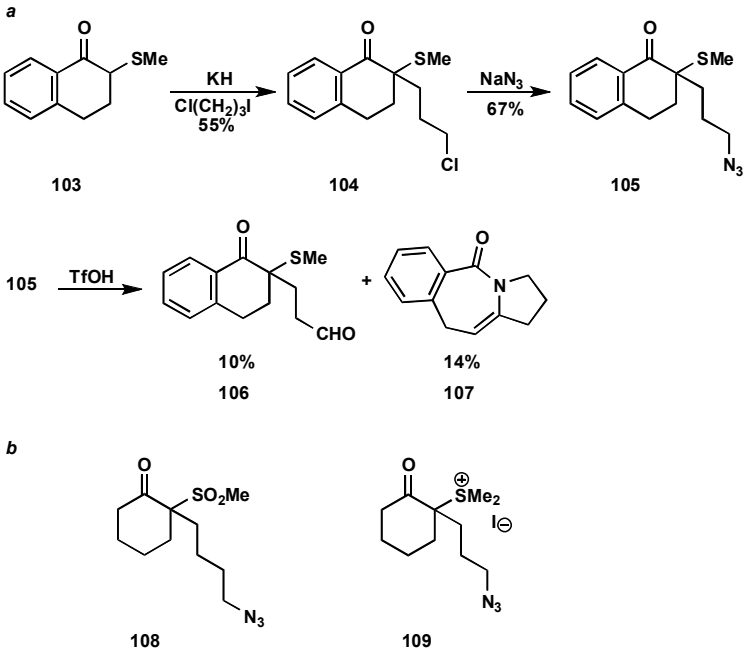
The increased formation of fused lactams can be caused either by favoring the reactive conformation in which the leaving diazonium cation is placed in the pseudoequatorial orientation (Scheme 47, **eq-cation**) or by favoring the reactive conformation of cyclohexanone in which the azidoalkyl chain occupies the equatorial position (**eq-tether**). $MeAlCl_2$ and $TiCl_4$ may favor **eq-cation** by formation of stable 5-membered chelates between the carbonyl oxygen and the α-heteroatom (Scheme 47, top box). Alternatively, metal chelation may favor placing the tether in the pseudoequatorial orientation (**eq-tether**, bottom box). As a consequence, the formation of bridged amides is minimized. This dependence resembles the stoichiometry relationship in the cation–π directed Schmidt reaction (Table 8), and the Schmidt reactions of α-amide-substituted azidoalkyl ketones (Schemes 38 and 39).

Scheme 47



In addition to the substrates presented in Table 11, we attempted the Schmidt reaction with three other α-thiomethyl substituted azido ketones. However, **105** afforded only the fused lactam and the aldehyde in very low yields (Scheme 48a), while **108** and **109** decomposed under the Schmidt reaction conditions (Scheme 48b). The results with **105** may reflect the difficulty of the migration of benzylic C–C bond combined with a slower rate of the rearrangement of the α-thiomethyl-substituted proximal C–C bond.[173]

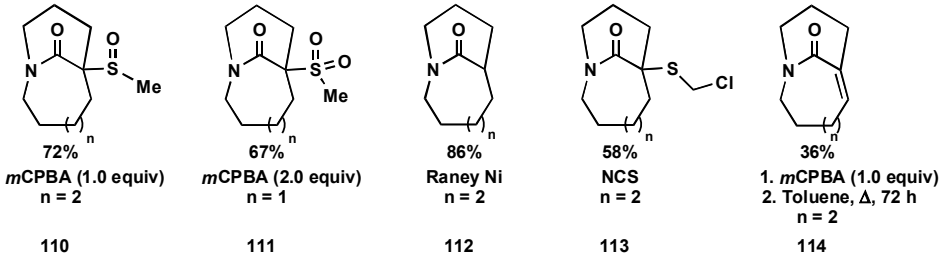
Scheme 48



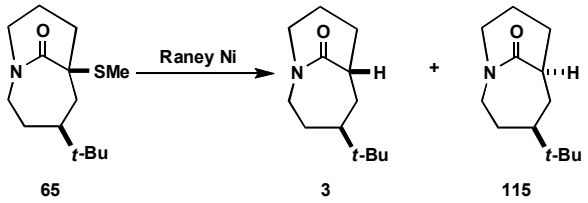
Thiomethyl ethers are valuable synthetic intermediates.[230] We demonstrated the utility of the thiomethyl-substituted lactams to obtain a family of structurally related bridged amides (Scheme 49, only products shown). Noteworthy is the chemoselective oxidation of the thiomethyl in the presence of sensitive twisted amide functionalities (**110**, **111**, **113**), reductive thiomethyl removal proceeding via generation of a bridgehead radical (**112**), and isolation of the bridged amide **114** containing a bridgehead olefin in the same molecule. In addition, Raney Ni reduction of the *tert*-butyl substituted amide **65** led to the formation of two diastereoisomeric amides, confirming the intermediacy of the bridgehead radical (Scheme 50). Interestingly the amide bond in **115** (IR $\nu_{C=O}$ = 1697 cm^{-1}, ^{13}C NMR δ = 188.9 ppm)

is more distorted than in **3** (IR $\nu_{C=O}$ = 1682 cm^{-1}, ^{13}C NMR δ = 186.9 ppm), suggesting that even minor changes around a twisted amide bond can have an influence on its properties.

Scheme 49



Scheme 50

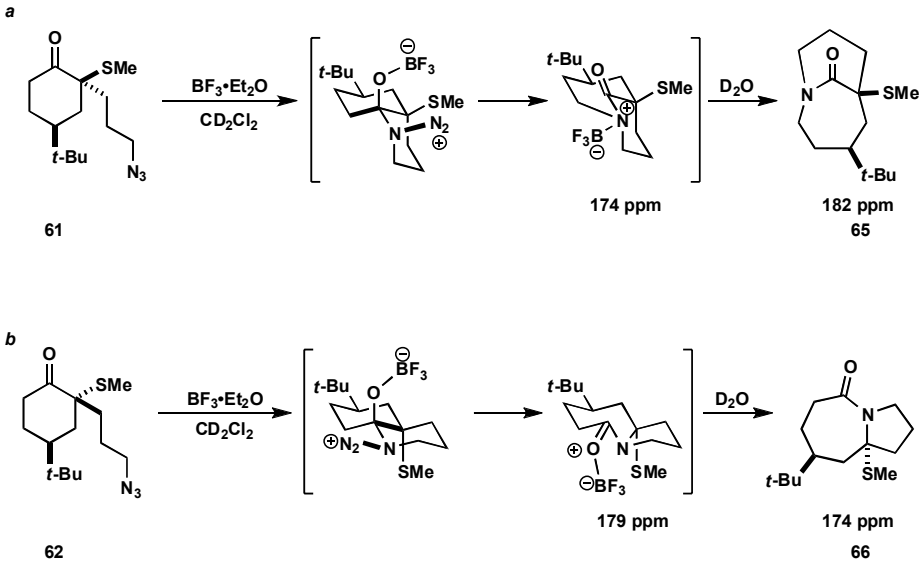


In an effort to gain more insight into the cation–n directed Schmidt reactions, we studied the rearrangement of azides **57**, **61** and **62** by NMR. Thus, the reaction of azide **61** with BF_3•Et_2O ($t_{1/2}$ = 45 min) proceeded about three times more slowly than the analogous reactions of azides **62** and **57** ($t_{1/2}$ = 15 and $t_{1/2}$ = 13 min, respectively). However, at this point we cannot conclude whether the differences in the reaction rate result from the cation–n stabilization or rather from other factors affecting the

Schmidt reaction (for example, axial vs. equatorial azide attack, rearrangement of *cis*- vs. *trans*-azadecalin-type system or ring inversions).

Monitoring the above reactions by ^{13}C NMR permitted the detection of some unusual properties of one-carbon bridged amides contained in a [4.3.1] ring system (Scheme 51). After rearrangement, the carbonyl peak of the isomer **61** appeared at 174 ppm in ^{13}C NMR. Addition of D_2O gave amide **65**, in which the carbonyl peak shifted downfield to 182 ppm. In contrast, values corresponding to the isomer **62** appeared at 179 and 174 ppm, respectively. We ascribe this difference to a change of coordination site between nitrogen (Scheme 51a, bridged lactam) and oxygen (Scheme 51b, fused lactam). The 174 ppm shift is in good agreement with previously reported carbonyl shifts of N-protonated lactams.[26, 189] The switch of the protonation site from O to N is expected for partially rotated lactams (see Scheme 27).[23, 24, 198]

Scheme 51



Transannular cyclization strategy. Although the studies on cation–π and cation–n control of the Schmidt reaction have significantly expanded the utility of the Schmidt reaction in synthesis of one-carbon bridged amides, we remained aware of limitations of the Schmidt reaction for this purpose. While only two different ring systems of one-carbon bridged amides could be prepared by the Schmidt reaction,[228] we wished to test the properties of a wider range of ring systems containing bridged amides. In particular we wished to determine whether more strained analogues of [4.3.1] or [5.3.1] ring systems are isolable and synthetically useful.

Due to their inherent strain, the synthesis of distorted amides is challenging.[41] Although a relatively large number of amides in which C=O bond is placed on two-carbon or longer bridges are known (Figure 12a),[39-41] there are a very few known-examples of amides in which the C=O group is situated on one-carbon bridge (Figure 12b).[31, 114, 117] However, as will be seen in more detail in Chapter 3, due to the increased hydrolytic stability, one-carbon-bridge-containing amides are superior to 2-quinuclidone derivatives insofar as they can be used as an effective platform for studying biological and chemical properties of distorted amide bonds (Figure 12b).[54]

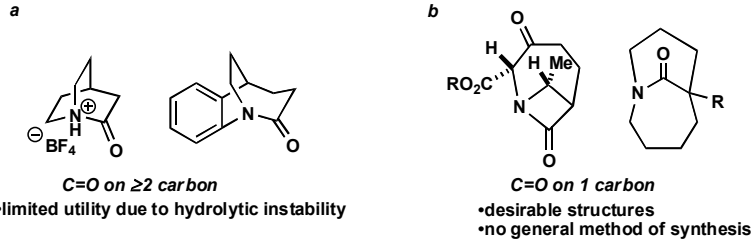
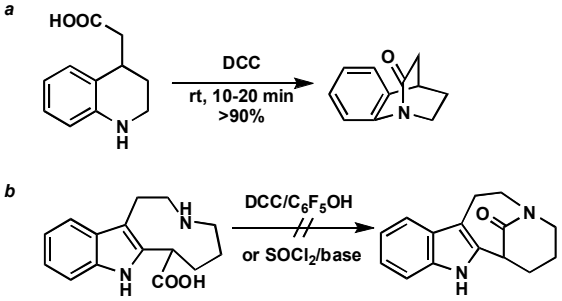


Figure 12. Types of bridged amides.

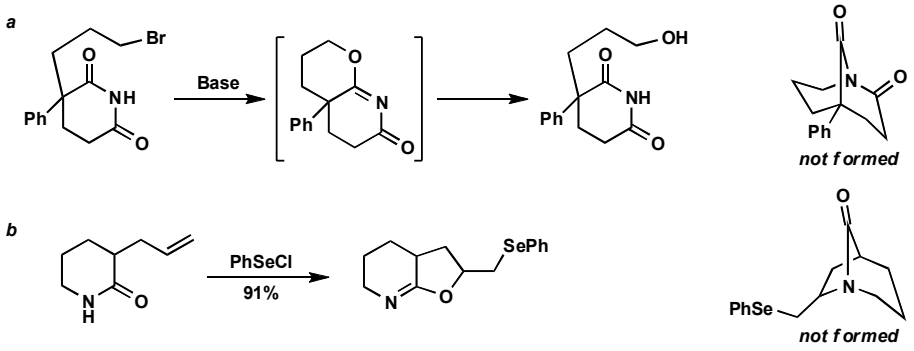
Traditional condensation approaches are commonly utilized for preparation of amides with C=O bond placed on 2 or longer bridge.[41] However, when these reactions were attempted in the context of one-carbon bridged amide synthesis they were reported to be unsuccessful (Scheme 52).[30]

Other failed approaches to one-carbon bridged amides include intramolecular nucleophilic displacement reactions,[127, 130, 131] electrophilic cyclization[231-233] and condensation reactions,[132] all of which are compromised by the inherent nucleophilicity of the amide bond oxygen, resulting in the formation of oxygen–carbon instead of nitrogen–carbon bonds (Scheme 53).

Scheme 52

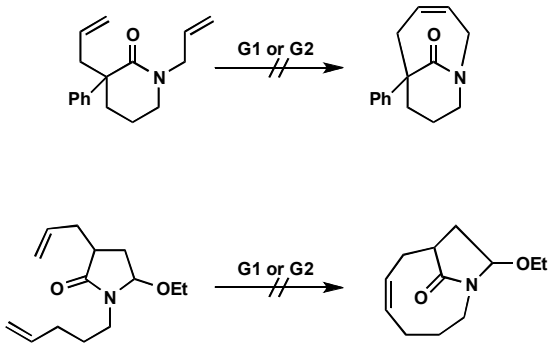


Scheme 53

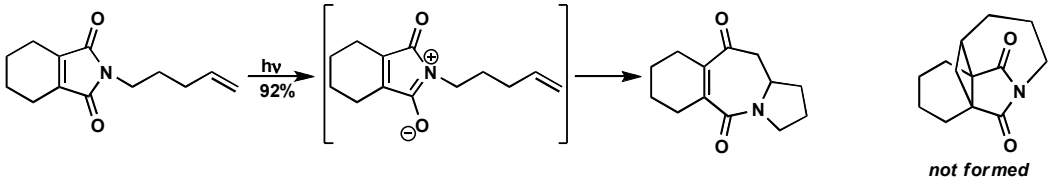


Direct ring-closing metathesis results in isomerization of double bonds and polymerized material but not in closure to the strained twisted amides (Scheme 54).[189, 234] In addition, direct ring-closing metathesis fails in synthesis of bicyclic sultams, which are significantly easier to prepare than bridged amides.[106] Furthermore, [2+2] cycloaddition also does not lead to the expected products (Scheme 55).[142]

Scheme 54



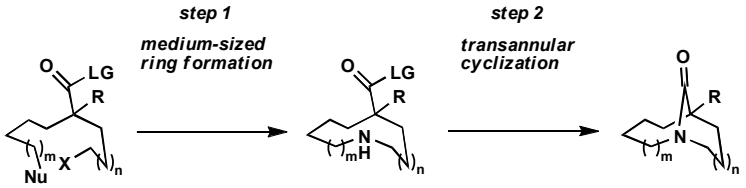
Scheme 55



The only reported examples of one-carbon bridged amides were in the context of single scaffold preparation[114, 117, 144] and were limited to specific examples.[30, 121-123] When the present work was undertaken, Schmidt reaction was the most general method of the synthesis of one-carbon bridged twisted amides.

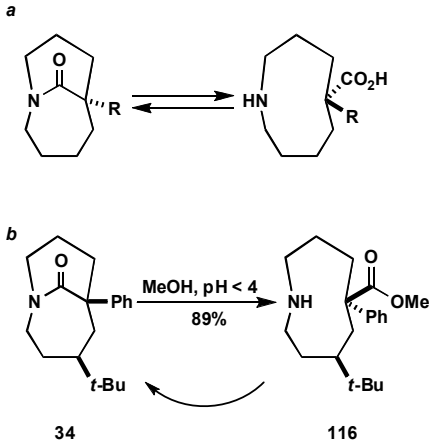
Aware of these difficulties, we envisioned a strategy based on two sequential reactions: 1) efficient formation of medium-sized ring, followed by 2) transannular cyclization reaction (Scheme 56).

Scheme 56



Although the synthesis of medium-ring nitrogen-containing heterocycles with appropriately placed amine and carboxylic acid derivative functionalities was expected to be a major challenge (Scheme 56, step 1),[235-240] we anticipated that transannular lactamization (Scheme 56, step 2) could be capable of overcoming the inherent strain associated with the formation of twisted amide bonds. Evidence supporting the feasibility of this reaction was provided by our studies of hydrolytic stability of bridged amides[54] (see Chapter 3 for details) in which it was determined that some of the open-form amino acids exist in equilibrium with the corresponding bridged amides, even in water (Scheme 57a). Furthermore, we found that the open-form 9-membered amino-methyl ester closes spontaneously to the corresponding bridged amide (Scheme 57b). A limited precedent from previously reported twisted amide chemistry also supported the viability of this strategy.[30, 144]

Scheme 57

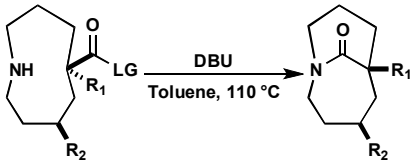


The spontaneous cyclization of **116** to **34** deserves a comment. The methanolysis of **34** was performed as a control reaction to study along with the reduction of **34** under Borch conditions. As expected, the distorted amide bond undergoes facile opening under acidic conditions. Intriguingly, the standard purification by chromatography followed by removal of the residual solvent under vacuum afforded the product **116** contaminated with ca. 6% of the parent amide **34**.

Optimization of the spontaneous amidation revealed that prolonged storage of **116** under vacuum (24 h, rt) led to 11% conversion to amide, while higher temperature (120 °C, 5 h, vacuum) gave ca. 50% conversion along with significant decomposition. In addition, when **116** was kept in a flask open to air, ca. 80% conversion to **34** was observed after two weeks, confirming that the transannular cyclization is a thermodynamically favored reaction pathway. Finally, we determined that a short exposure of **116** to DBU results in a convenient lactamization. Next, the

transannular cyclization of various open-form aminoesters (obtained by alcoholysis of the corresponding amides) back to the bridged lactams was evaluated (Table 13).

Table 13. Transannular Closure to Bridged Amides.



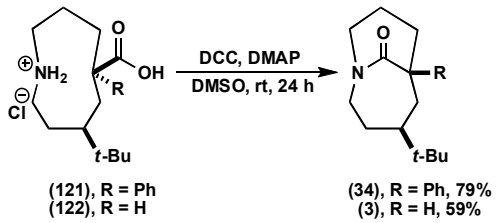
entry	amino ester	R_1	R_2	LG	amide	time	yield [%]
1	**116**	Ph	*t*-Bu	OMe	**34**	1 h	91
2	**117**	H	*t*-Bu	OMe	**3**	1 h	48
3	**118**	SPh	H	OMe	**73**	1 h	84
4	**119**	Ph	*t*-Bu	OEt	**34**	18 h	85
5	**120**	Ph	*t*-Bu	O*i*-Pr	**34**	7 days	49

Gem-dimethyl substitution is not required for the reaction (entry 2). The lower yield obtained in this case is most likely caused by instability of amide **3** (see Chapter 3). It is noteworthy that even this compound could be obtained by the transannular route. The good correlation between the pK_a of the leaving group and the relative rate of the reaction (entries 1, 4 and 5, pK_a MeOH = 15.5, pK_a EtOH = 15.9, pK_a *i*-PrOH = 16.5) suggests that the amino ester exists in equilibrium with the tetrahedral intermediate, and that the expulsion of the alkoxide is the rate-determining step of the

reaction. Importantly, cleavage of the C−C bond (see Chapter 3) was not observed under relatively forcing reaction conditions.

As an alternative, we found that traditional peptide coupling conditions can also be applied for synthesis of [4.3.1] ring system of bridged amides (Scheme 58).

Scheme 58



(121), R = Ph
(122), R = H

(34), R = Ph, 79%
(3), R = H, 59%

Having performed these initial studies, we were prepared for *de novo* synthesis of bridged amides. The first ring system that we wished to prepare was the [3.3.1] scaffold, not accessible by the Schmidt reaction. The comparison of ring strain energies in systems containing bridgehead olefins suggested that the targeted structure might be very strained (Figure 13).[241-243]

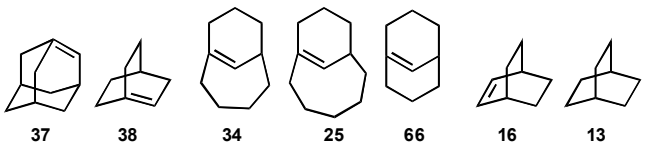
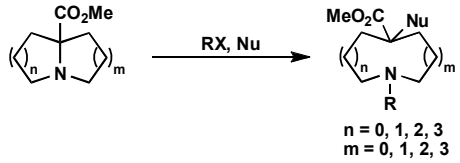


Figure 13. Ring strain energy (kcal/mol) in bridgehead olefins analogous to 1-aza-2-adamantanone, 2-qunuclidone, [4.3.1], [5.3.1] and [3.3.1] one-carbon bridged amides. Planar olefin and saturated hydrocarbon are shown for comparison.[241-243]

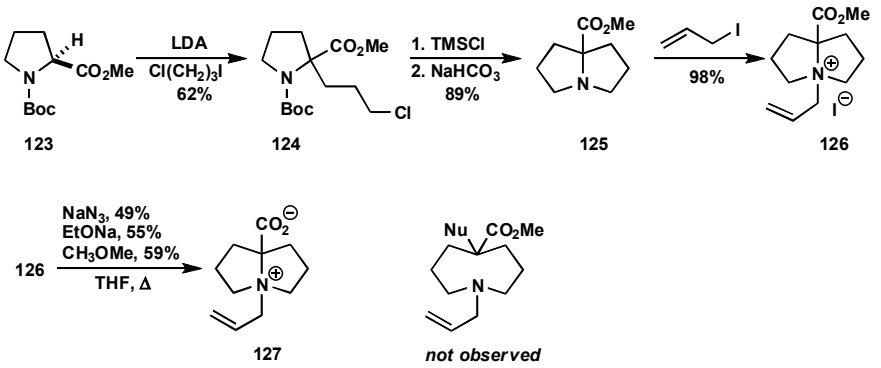
Bicycle opening. The initial approach to a medium-sized nitrogen-containing heterocycle, a precursor to test the key cyclization reaction, relied on the cleavage of the zero-bridged single bond in a bicyclic pyrrolizidine (Scheme 59, m = n = 1).

Scheme 59



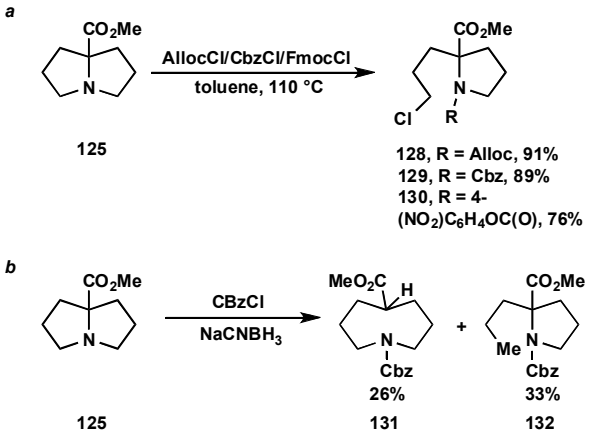
We originally envisioned that opening of analogous bicycles (Scheme 59, m, n ≠ 1) would afford access to a range of additional precursors for the transannular cyclization, especially since the cleavage of zero-bridged bond in fused bicyclic ring systems is a common procedure in the synthesis of indole alkaloids.[244] We found, however, that the cleavage of the internal bond in **125** is problematic (Scheme 60). After alkylation of **125** and exposure to nucleophiles, demethylation was the only reaction pathway observed (Scheme 60, see Experimental Section for further details).

Scheme 60



Conversion of **125** to a series of corresponding carbamates resulted in the cleavage of the external C−N bond by the chloride released from the activating agent (Scheme 61a). Performing the reaction in the presence of other nucleophiles also resulted in the cleavage of the same C−N bond by the chloride, while exposure of **125** to a less reactive benzyl methyl carbonate (toluene, 110 °C, 24 h) led to the recovery of the starting material. We found, however, that activation of **125** with benzyl chloroformate followed by addition of sodium cyanoborohydride[245] afforded ca. 1:1 mixture of reduction products resulting from the cleavage of the desired internal C−N bond and the undesired external C−N bond (Scheme 61b).

Scheme 61

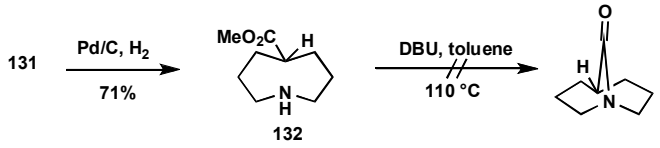


The steric hindrance around the quaternary carbon prevents the efficient cleavage of the zero-bridged bond in the unactivated pyrrolizidine. It is likely that this problem could be circumvented by attaching an aromatic ring (for example, indole or benzene)[244] to the bicycle or by removing the ester group. However, since we wished

to test the properties of unsubstituted bridged amides rather than their heavily modified versions and sought an efficient method for the synthesis of precursors for the transannular cyclization, we did not pursue these pathways.

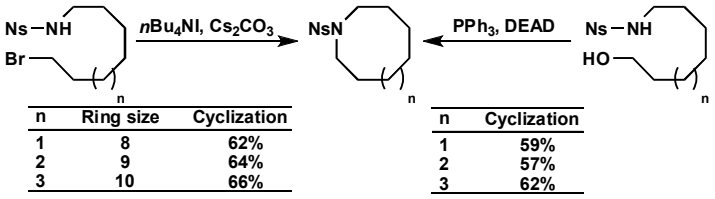
With **131** in hand, after hydrogenative Cbz removal, the stage was set to perform the key transannular cyclization (Scheme 62). Disappointingly, exposure of **132** to our previously developed conditions afforded no conversion to the desired lactam after 1 h and complete decomposition of the starting material after 24 h. The difference of reactivity between **132** and amino ester **117** (Table 13) may suggest that the desired lactam was formed in the present case, but decomposed under the reaction conditions.

Scheme 62



Aware of the lability of α-unsubstituted one-carbon bridged amides (see Chapter 3), we reasoned that substitution α to the ester might enhance the stability of the putative [3.3.1] amide. Being unsuccessful in alkylation of the hindered **131** and because of the previously described problems with the cleavage of the internal C–N bond in the pyrrolizidine precursor, we decided to change our approach to the medium-sized heterocycle.

Fukuyama amine synthesis. Fukuyama has developed a practical synthesis of secondary amines utilizing 2,4-dinitrobenzenosulfonyl and 2-nitrobenzenesulfonyl groups as activating substituents for selective alkylation and Mitsunobu reactions of amines.[240] Fukuyama's group applied this methodology to the synthesis of a number of unsubstituted nitrogen-containing medium-sized rings (Figure 14).



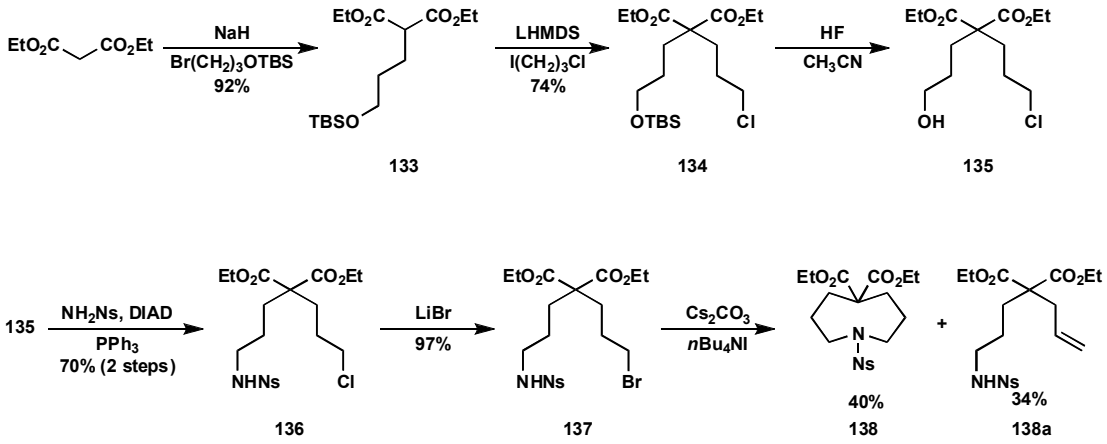
n	Ring size	Cyclization
1	8	62%
2	9	64%
3	10	66%

n	Cyclization
1	59%
2	57%
3	62%

Figure 14. Synthesis of medium-sized heterocycles containing nitrogen by Fukuyama.[240]

Our second generation approach towards synthesis of precursors for the transannular cyclization relied on Fukuyama's amine synthesis. Following the lesson learned with aminoester **132** we envisioned that the α-substituent would be installed in the early stages of the synthesis. To favor the transannular amidation reaction, malonate was chosen as a suitable precursor for the cyclization. The synthesis is summarized in Scheme 63.

Scheme 63

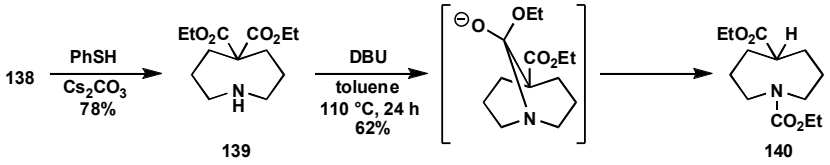


The desired eight-membered ring **138** was prepared in six steps from diethyl malonate. The chloride to bromide exchange (**136**→**137**) was necessary to form **138**; when **136** was subjected to the cyclization conditions the reaction did not occur. The lower yield for the formation of **138** and the significant amount of the elimination product **138a** as compared to model systems (Figure 14) suggested that the reaction is sensitive to steric hindrance created by malonate groups.

After the nosyl group removal, we attempted the transannular cyclization to the twisted amide (Scheme 64). In contrast to aminoester **132** (Scheme 62), the reaction proceeded smoothly. However, instead of the [3.3.1] bridged amide, carbamate **140** was formed. Clearly, the transannular attack of the amine on the ester functionality was followed by the breaking of the C−C bond, which was more favored than the expulsion of the ethoxy leaving group to form the strained [3.3.1] bridged amide. This transformation resembled the cleavage of the unactivated C−C bond

observed earlier in the course of reduction of one-carbon bridged amides (see Chapter 3 for details).

Scheme 64



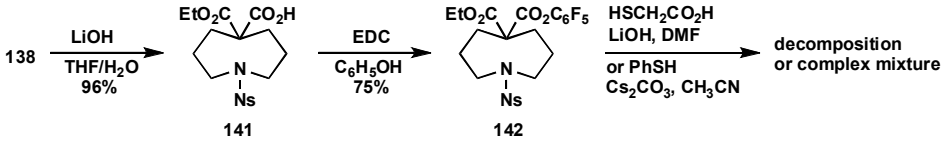
We envisioned three methods to divert the transannular reaction into the desired course: 1) modification of the reaction conditions; 2) replacement of the ethoxy group with a better leaving group; 3) use of an α-substituted acetate instead of the malonate.

It is well-known that an increase in solvent polarity can favor S_N2 reactions.[246] However, when deprotection of **138** was carried out with thioglycolic acid and LiOH in DMF at rt for 1 h, **140** was formed directly from **138**, indicating that the transannular migration proceeds faster in polar solvents. It suggested that other reaction conditions would not change the course of this transannular reaction.

As a second method to favor the transannular cyclization, **138** was converted into **142** (Scheme 65). The subsequent deprotection with thioglycolic acid and LiOH in DMF led to decomposition, while the use of thiophenol and Cs_2CO_3 afforded a complex mixture of products. Interestingly, the HRMS analysis indicated the presence of the desired product (calcd for $C_{11}H_{18}NO_3$ (M^+ + H) 212.1287, found

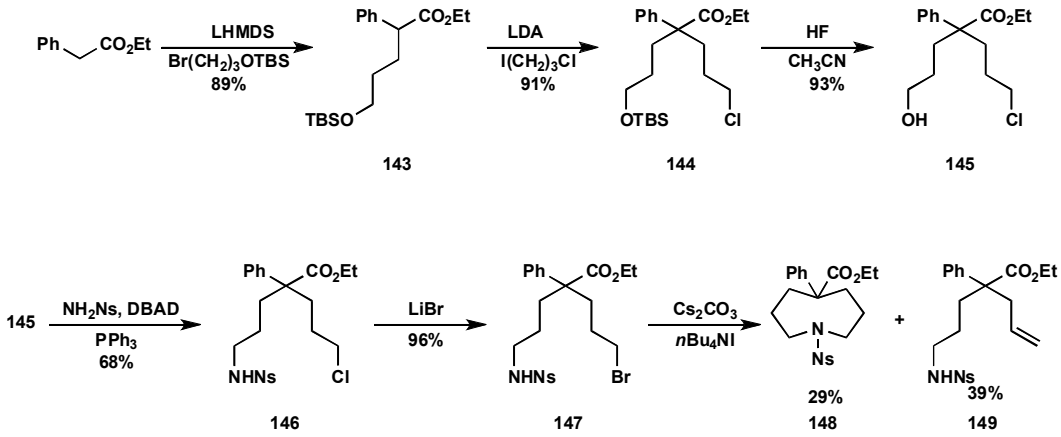
212.1287). As we would learn later, the desired [3.3.1] lactam was indeed formed in this reaction, however due to its instability, this fact was not noticed at that time.

Scheme 65



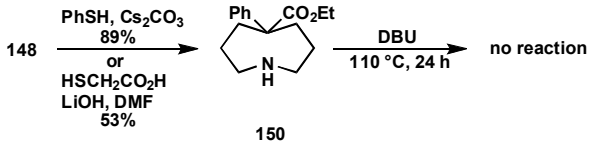
Being unable to convert the aminoester **139** into the desired [3.3.1] amide, we synthesized the eight-membered precursor containing phenyl group in the α position to the ester (**148**, Scheme 66). The choice of the phenyl group was dictated by the fact that the α-phenyl substituted amide **34** afforded a stable hemiaminal after treatment with $NaBH_4$. In contrast, the hemiaminal resulting from the reduction of α-(4-nitrophenyl) substituted amide **36** collapsed with the C–C bond cleavage (see Chapter 3, Table 24 for details). The synthesis of **148** (Scheme 66) mirrored the synthesis of **138** (Scheme 64). The only noteworthy difference is a slightly lower yield of the Fukuyama reaction (**147→148**), reflecting the increase of the steric hindrance around the quaternary carbon.

Scheme 66



In contrast to **138** (Scheme 64), deprotection of **148** with both PhSH and thioglycolic acid afforded the aminoester **150** (Scheme 67). Furthermore, vigorous treatment with DBU did not lead to any productive reaction, clearly indicating the difference in reactivity between these two systems. Thus, ester to phenyl exchange prevented the transannular migration, however this modification did not provide the desired twisted amide.

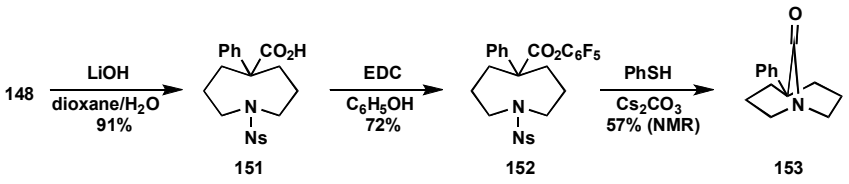
Scheme 67



As a next resort, **148** was converted to **152** (Scheme 68). Similar to the malonate **142**, the exposure of acetate **152** to thioglycolic acid led to complete decomposition (Scheme 65). To our delight, treatment with the alternative

deprotection conditions afforded bridged amide **153** containing the [3.3.1] ring system.

Scheme 68



Compared to the bridged lactam **34** with [4.3.1] ring system, **153** bearing [3.3.1] scaffold is very unstable. The compound decomposed in $CDCl_3$ within 48 h (presumably by polymerization and/or hydrolysis). Attempted purification by chromatography also led to its complete degradation. Although all of the one-carbon bridged amides exhibit similar characteristic polarity on TLC (R_f = 0.2–0.5 in 1/4 EtOAc/hexanes), **153** could not be observed by this method, which is further consistent with its rapid decomposition.

The structure of **153** was secured through detailed NMR analysis (^{1}H NMR, ^{13}C NMR, COSY, NOESY, HMBC and HSQC) of the unpurified reaction mixture (only peaks in the aromatic region were not resolved), and confirmed by HRMS measurements. Particularly noteworthy is the dramatic shift of the carbonyl group in the ^{13}C NMR spectrum at 199.5 ppm. This value matches the N–C=O resonance of the Kirby's amide,[166] strongly suggesting that both compounds exhibit similar distortion of the amide bond. In other words, **153** is one of the most distorted amides

prepared to date. However, in contrast to 1-aza-2-adamantanone, which is embedded in a rigid adamantane structure and stabilized by three additional methyl groups, **153** readily decomposes, which prohibits its use for synthesis and limits its suitability for study.

The instability of **153** was supported by MS measurements. Thus, peaks corresponding to **153** could only be observed when acetone, CH_2Cl_2, or acetonitrile was used as a solvent for ionization in ESI MS experiments. The amide **153** was not detected when H_2O, MeOH or MeOH/water/formic acid were used as diluents (Table 14; note that tricyclic and bicyclic amides containing [4.3.1] ring system are detected in ESI MS when the above solvents are used for ionization). In addition, the carbonyl IR stretching frequency at 1730.5 cm^{-1} is also consistent with a significant degree of twist of the amide bond in **153**.

Table 14. ESI MS Experiments with Lactam **153**.[a]

entry	solvent used for ionization	exact mass observed	assignment
1	CH_3CN	216.1391	**153**
2	CH_2Cl_2	216.1407	**153**
3	CH_3COCH_3	216.1405	**153**
4	THF	-	-
5	H_2O	234.1498	amino acid
6	MeOH	234.1484; 248.1661	amino acid and the methyl ester
7	MeOH/H_2O/ HCO_2H	234.1484; 248.1635	amino acid and the methyl ester

[a] Relevant HRMS calculations: HRMS calcd for $C_{14}H_{18}NO$ (M^+ + H) 216.1388 (**153**); HRMS calcd for $C_{14}H_{20}NO_2$ (M^+ + H) 234.1494 (amino acid of **153**); HRMS calcd for $C_{15}H_{22}NO_2$ (M^+ + H) 248.1651 (methyl ester of amino acid of **153**).

It is possible that **153** or a related [3.3.1] bridged amide could be isolated by crystallization (most likely after its N-protonation, in a manner similar to 2-quinuclidone),[26] however due to the limited synthetic value of **153** and the relatively lengthy synthetic route to **153**, we did not attempt this.

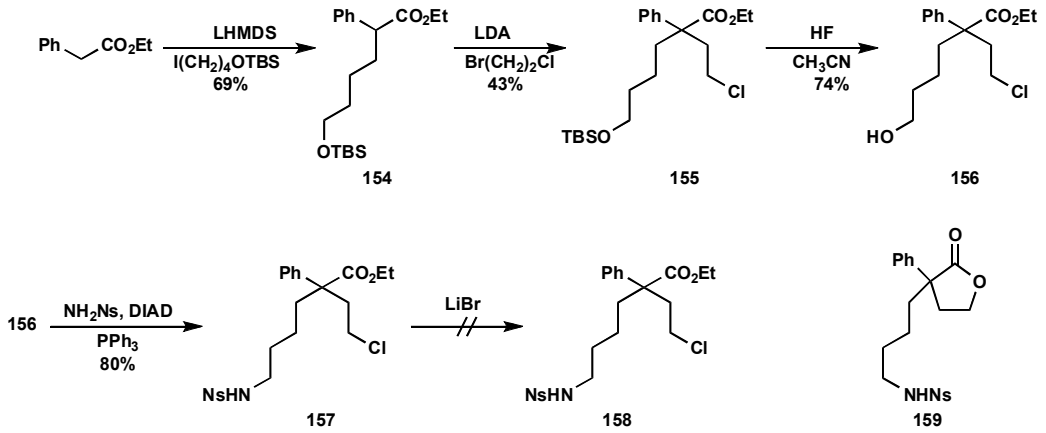
The significant change of stability in transition from [4.3.1] to [3.3.1] ring system of bridged amides is surprising, and suggests that the seven-membered ring secures the stability of one-carbon bridged amides. It is worthwhile to point out that all of the [4.3.1] amides described above could be easily purified by standard chromatography, are bench stable over long periods of time, and do not decompose in $CDCl_3$[189, 225] or in THF/D_2O mixtures.[54] Even the α-unsubstituted amide with a [4.3.1] scaffold, which is considerably less stable than α-substituted bridged amides, could be easily observed in THF/D_2O mixtures (see Chapter 3). Based on the above, it seems likely that one-carbon bridged amides with bridges shorter than in [3.3.1] ring system (for example, [3.2.1] and [3.1.1] scaffolds) are too unstable to be isolated.

Having discovered the instability of the [3.3.1] bridged amide, the focus of our study turned towards testing the stability of the isomeric [4.2.1] ring system. Williams reported that a number of substituted [4.1.1] bridged amides have a reasonable stability.[114] We also hypothesized that the presence of a seven-membered ring in the unsubstituted [4.2.1] bridged system would enhance its stability (as compared to [3.3.1] system), allowing for its isolation and further manipulations.

As before (Scheme 66), ethyl phenylacetate was advanced to the appropriate amino chloride **157** (Scheme 69). However, in contrast to the regioisomeric **146**, the

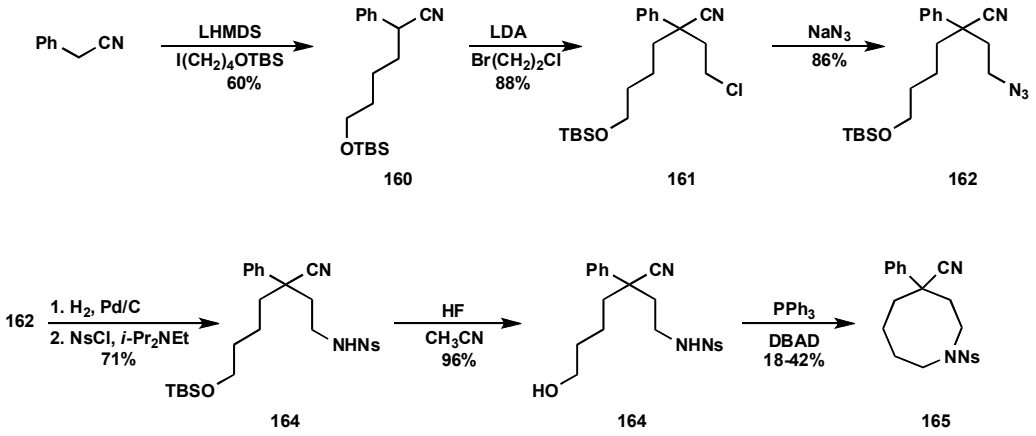
S_N2 displacement with bromide did not afford the desired product **158**. Under standard reaction conditions the reaction did not proceed, while more forcing conditions led to the formation of lactone **159** as the major product. These results suggested that even if the bromide could be installed in this system, the subsequent cyclization to the eight-membered ring is unlikely to succeed. Molecular models showed that the backside attack at the chloride in **158** is prohibited by the steric arrangement of the phenyl and ester moieties. This result also explains low yields in the cyclization to **138** and **148** (Schemes 63 and 66).

Scheme 69



To circumvent the above problem, we envisioned that a much smaller cyano group, serving as a latent carbonyl equivalent, would replace the ester (A value of CN = 0.17 kcal/mol, A value of CO_2Me = 1.27 kcal/mol). To avoid halide elimination during the S_N2 closing, Mitsunobu reaction would be used to cyclize the medium-sized ring (Figure 14). This synthesis is summarized in Scheme 70.

Scheme 70

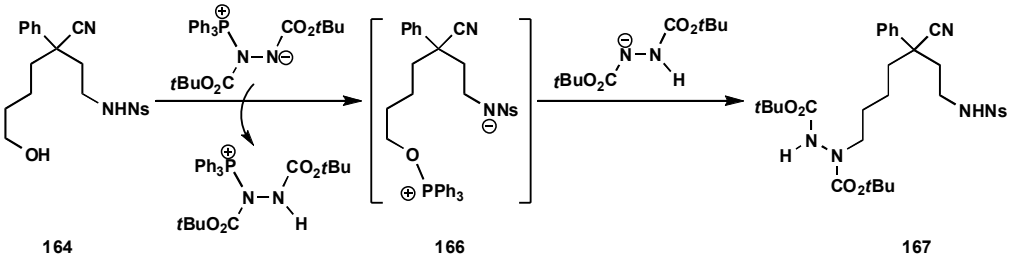


In agreement with our design, nitrile permitted the S_N2 displacement (**161→162**). However, the harsh conditions required for this reaction (NaN_3, 10 equiv, DMF, 90 °C, 6 h) emphasize the steric hindrance around the homoneopentyl carbon. Hydrogenation of **162** provided the primary amine, which was directly protected with the nosyl group. Interestingly, Staudinger reduction of **162** afforded the 5-membered lactam resulting from the cyclization of the amine into the nitrile. This potential for lactamization or lactonization during substrate preparation is a major shortcoming of the Fukuyama's amine synthesis in this context. Overall, this approach requires careful choice of precursors and lengthy manipulations involving numerous changes of protective groups.

Under the Mitsunobu conditions, the amino alcohol **164** was cyclized to the desired **165**. However, we encountered two significant problems with this reaction. First, despite considerable optimization, the yield of the cyclization did not improve as compared to the direct S_N2 displacement (Schemes 63 and 66). Secondly, the

separation of **165** from the hydrazine by-products was problematic. While the use of di-*tert*-butyl azodicarboxylate allowed for removal of di-alkyl hydrazine-1,2-dicarboxylate by-product, the eight-membered **165** was always contaminated with varying amounts of **167** arising from the intermolecular attack of the hydrazine anion on **166** (Scheme 71). The formation of **167** emphasizes the difficulty in cyclization to the 8-membered ring system.

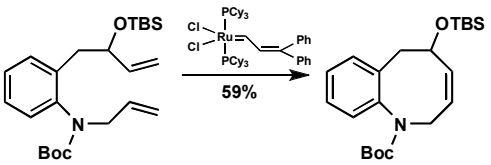
Scheme 71



Despite a low purity of **165**, we attempted a number of further elaborations towards the precursor for the cyclization to the [4.2.1] bridged amide. However, the hydrolysis of the nitrile in the presence of nosyl group was unsuccessful. The DIBAL-H reduction afforded the aldehyde, but again it was inseparable from the aldehyde resulting from the reduction of **167**. The above difficulties, combined with low yields of the cyclization reaction and chemoselectivity problems in the substrate preparation, led us to reconsider the synthetic approach to nitrogen-containing medium-sized rings as precursors to bridged amides.

RCM cyclization. In the last fifteen years ring-closing metathesis has emerged as a reliable method for synthesis of nitrogen-containing heterocycles.[247-251] However, one of the areas that has been relatively underdeveloped is the synthesis of medium-sized nitrogen-containing heterocycles without conformational control. This is exemplified by the early work by Grubbs and coworkers, who demonstrated that cyclization to an eight-membered nitrogen-containing ring was possible only in the presence of the benzene functionality which rigidifies the system (Scheme 72).[252] It is worth noting that for both enthalpic and entropic reasons eight-membered rings are the easiest to prepare in the family of medium-sized rings (Scheme 72).[253]

Scheme 72

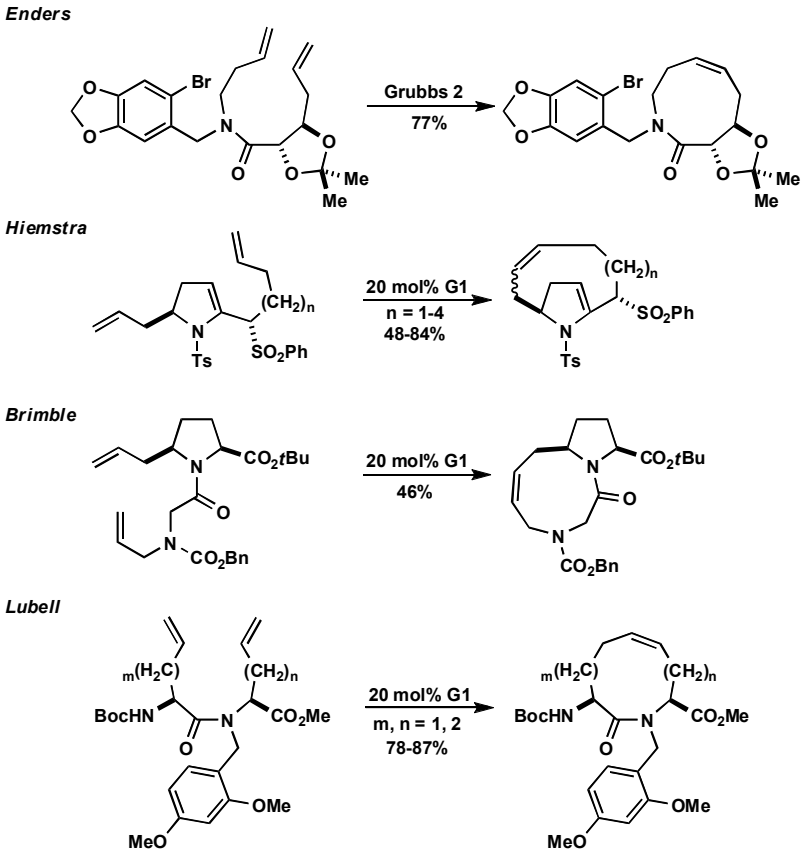


Total strain	
Ring size	[kcal/mol]
8	9.7
9	12.6
10	12.4
11	11.3
12	4.1

Despite a tremendous interest of organic chemists in RCM methodologies, manifesting in thousands of examples and applications, there are very few reported instances of efficient synthesis of nine and ten-membered ring systems containing nitrogen.[247-251] Most of these are limited to rigidified scaffolds and specific cases. For example, cyclization to the nine-membered heterocycle in the Enders synthesis of the cripowellins aglycon[150, 151] is permitted by the rigidifying nature of the amide and the dioxolane groups (Scheme 73). Dihydropyrrole performs a similar function in the

Hiemstra's example.[254] Amino acid mimics prepared by Brimble[255] and Lubell[256] also benefit from the planar arrangement of atoms facilitating the RCM cyclization.

Scheme 73



A careful literature search revealed the examples in Scheme 73 to be the closest systems to those that we would target in the synthesis of precursors for the transannular cyclization. This limited precedence was the major reason why we did not pursue earlier the RCM avenue for the synthesis of medium-sized heterocycles. Although it seemed plausible that RCM could be used for preparation of rigidified

and stabilized systems, it was this modification that we wanted to avoid from the beginning of our approach. Having explored two other and better-precedented methods for the synthesis of medium-sized nitrogen-containing heterocycles with limited success, we turned our attention to the ring-closing metathesis. Gratifyingly, the cyclization to the model 9-membered ring system proceeded in excellent yields. Table 15 summarizes results of extensive optimization of the RCM reaction.[257]

Grubbs 1 catalyst promoted the cyclization, however one equivalent was necessary to achieve full conversion (entry 1). Fürstner indenylidene catalyst[258] had earlier proved to be efficient in cyclization to unsubstituted medium-sized nitrogen-containing rings,[204] however in our system it was not superior to other ruthenium catalysts (entries 2 and 3). Grubbs 2 and Hoveyda–Grubbs 2 catalysts performed efficiently in the reaction (entries 6 and 10). The ideal results were obtained in the presence of HG2 catalyst when argon was bubbled through the reaction mixture to facilitate ethylene removal or when the reaction mixture was simply opened to air (entries 13 and 14).[259-261] It is of note that HG2 catalyst was superior to phosphine-based catalysts.

Typically, the RCM reaction was carried out in degassed, refluxing dichloroethane, however toluene could also be used as a solvent with no decreases in yield (entry 8, G2 catalyst). The catalysis was not inhibited by the close presence of carbamate groups (entry 7).[262-264] In addition, the cyclization could be performed at rt, however much catalyst higher loadings were necessary to promote the reaction (entry 9, G2 catalyst).

Interestingly, a direct comparison of the cyclization of amines **169** and **172** substituted with tosyl and nosyl groups respectively, revealed that **169** undergoes cyclization more efficiently than **172** (entries 11 vs. 1, and 12 vs. 10). As expected, the low concentration was crucial to obtain a high yield of the 9-membered heterocycle (entry 18). The RCM was extended to a number of orthogonally protected ring systems, including easily removable carbamate functionalities (entries 15-17).

Curiously, the DEPT spectrum of heterocycle **173** indicated the presence of four CH_2 carbons instead of five. The structure of **173** was confirmed after hydrogenation of the double bond to afford **177**, which displayed the expected spectroscopic characteristics (Scheme 75). In addition, **176** bearing nosyl instead of tosyl group exhibited the usual spectroscopic properties.

Scheme 74

Preparation of substrates for RCM reaction

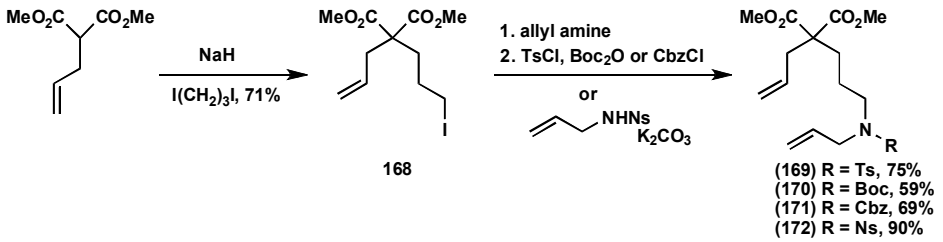
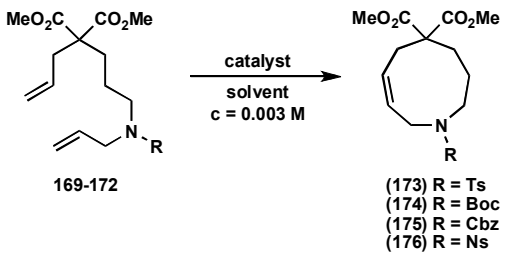


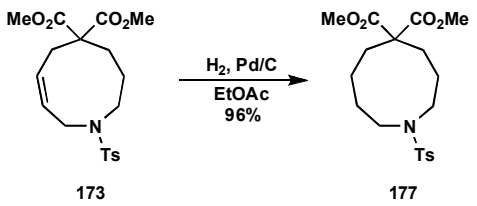
Table 15. Optimization of RCM for the Formation of 9-Membered Ring.



entry	diene	catalyst	mol %	solvent	T [°C]	t [h]	conversion[a] [%]	yield[a] [%]
1	**169**	G1	100	DCM	40	26	>95	87
2	**169**	F	50	DCM	24	25	60	54
3	**169**	F	20	DCM	40	22	43	41
4	**169**	G2	50	DCM	40	21	79	43
5	**169**	G2	20	DCE	80	21	89	76
6	**169**	G2	5	DCE	80	21	75	72
7	**169**	G2[c]	5	DCE	80	21	75	69
8	**169**	G2	5	toluene	90	21	80	72
9	**169**	G2	40	DCM	24	48	>95	77
10	**169**	HG2	5	DCE	80	21	85	81
11	**172**	G1	100	DCM	40	21	66	58
12	**172**	HG2	5	DCE	80	20	74	57
13	**169**	HG2[d]	5	DCE	80	8	>95	87[b]
14	**169**	HG2[e]	5	DCE	80	8	>95	95[b]
15	**172**	HG2[d]	5	DCE	80	16	>95	93[b]
16	**170**	HG2[d]	5	DCE	80	17	>95	85[b]
17	**171**	HG2[e]	5	DCE	80	8	>95	89[b]
18	**172**	HG2[d,f]	5	DCE	80	17	>95	66

[a] Determined by ^{1}H NMR. [b] Isolated yields. [c] With Ti(O*i*Pr)$_4$. [d] Argon bubbled through the reaction. [e] Open to air. [f] Run at 0.01 M. G1 = Grubbs catalyst 1, G2 = Grubbs catalyst 2, F = Fürstner catalyst, HG2 = Hoveyda−Grubbs catalyst.

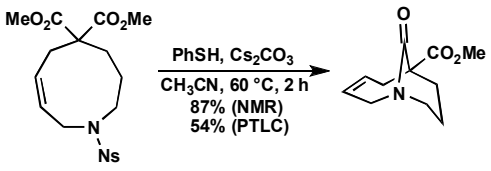
Scheme 75



173 177

With a number of differently N-substituted 9-membered heterocycles available, we were ready to test the key transannular cyclization to twisted amides. We were delighted to discover that deprotection and cyclization of the nosyl containing precursor **176** could be performed in a single operation to provide access to the model [4.3.1] bridged amide ring system (Scheme 76). *In contrast to **139** (Scheme 64), the cleavage of C–C bond was not observed*, indicating a significant difference in stability between [3.3.1] and [4.3.1] ring systems. Lactam **178** displayed modest sensitivity to chromatography but could be isolated in ca. 50% yield after PTLC.

Scheme 76

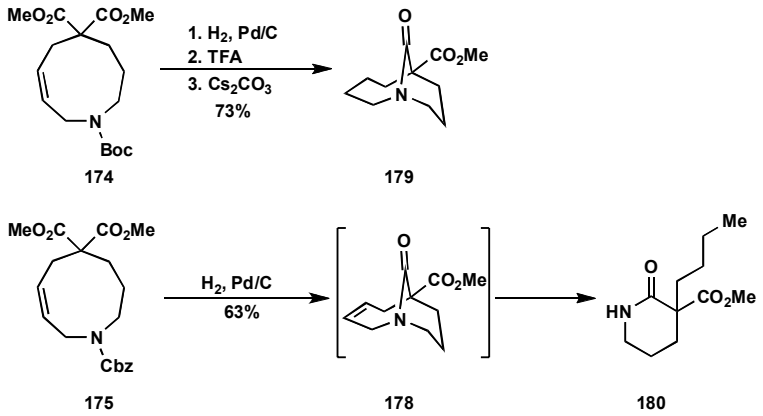


176 178

We have also determined that the Boc-containing precursor **174** could be used for synthesis of bridged amides although the use of Cbz carbamates could be

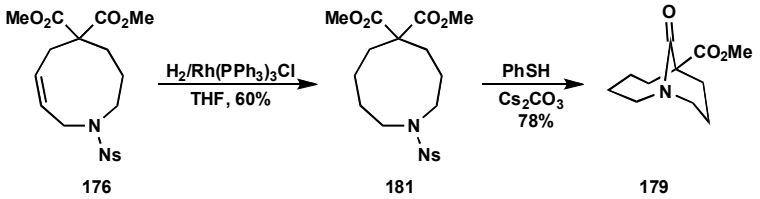
problematic. In the case of **175**, deprotection and cyclization occurred easily but the amide proved to be too unstable to the hydrogenation conditions, giving the piperidone **178** by the C−N ring cleavage reaction (Scheme 77).[31]

Scheme 77



Fully saturated **179** showed lower sensitivity to chromatography than **178** and could easily be obtained after standard purification on silica gel. This suggests that the internal double bond enhances reactivity of bridged amides with a [4.3.1] scaffold. Importantly, the three-step sequence (**174→179**) could be carried out without purification of intermediates, facilitating the synthesis of the saturated amide. As an alternative, **179** could be prepared from the nosyl precursor **176** by chemoselective hydrogenation of the double bond (Willkinson's catalyst),[265] followed by transannular cyclization (Scheme 78).

Scheme 78

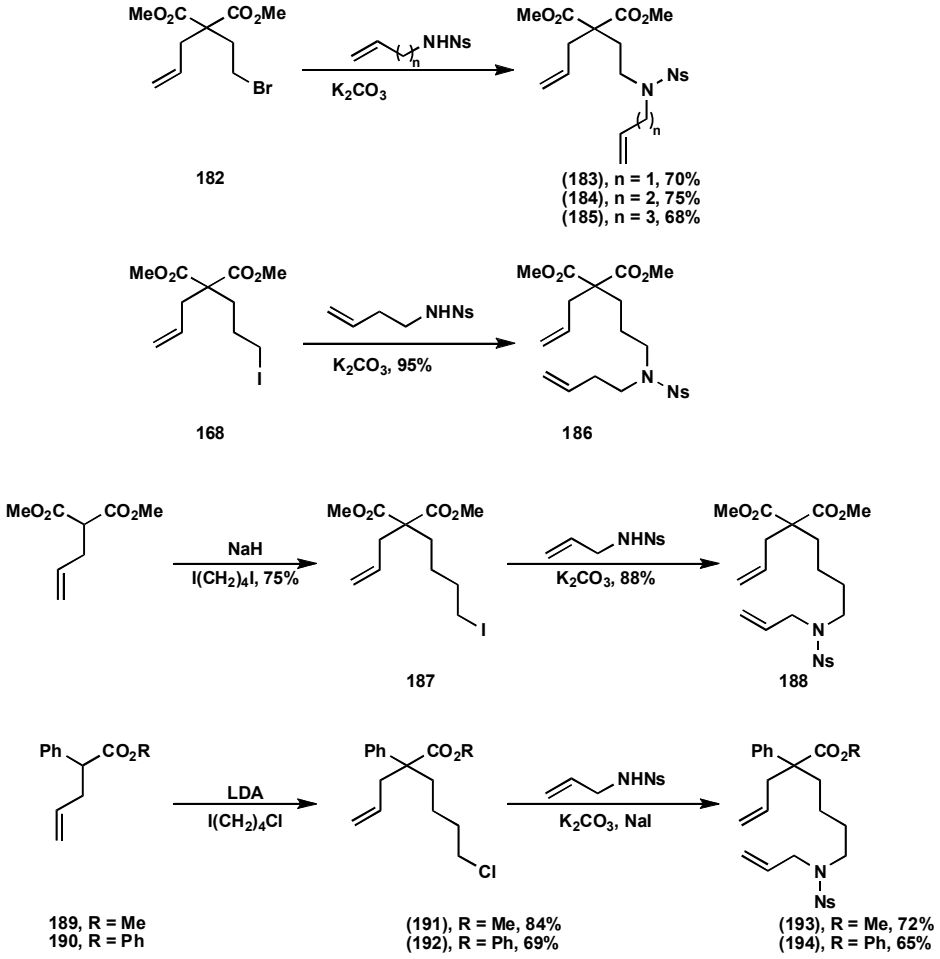


To extend the sequential RCM/transannular cyclization strategy a number of dienes were subjected to the catalytic RCM reaction conditions to provide a family of medium-sized rings with varying distances between the amine and the ester groups (Scheme 79 and Table 16, step 1). In all cases RCM proceeded in very good yields; only one ring was obtained as a mixture of cis/trans double bond isomers (Table 16, entry 3). This study provides very rare examples of the successful formation of 9- and 10-membered nitrogen containing ring systems with minimal conformational constraints by catalytic RCM.[247-251]

Next, we determined the generality of the transannular cyclization reaction, and demonstrated that this transformation can be utilized for preparation of a number of twisted amide scaffolds (Table 16, step 2). When **195** was subjected to the previously developed conditions [4.2.1] twisted amide was formed in excellent 75% yield. *Remarkably, the amide with [4.2.1] scaffold could be easily purified by PTLC showing much superior stability to the regioisomeric [3.3.1] ring system.* Thus, a seven-membered ring appears to be crucial for the stability of one-carbon bridged amides.

Scheme 79

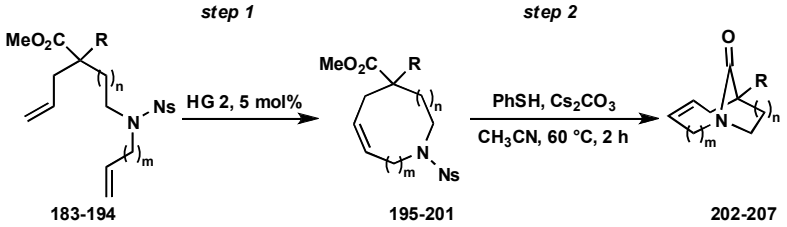
Synthesis of dienes for RCM reactions



Extending the larger ring by one carbon had a minor effect on the cyclization rate. Thus the [5.2.1] lactam was obtained in 85% yield (Table 16, entry 2). Although, the cyclization of compound **197** was found to be sluggish under initially developed conditions, the [5.3.1] bridged amide could be generated by treatment with DBU after deprotection (Table 16, entry 3). Although, malonate could not be used for preparation of the [4.4.1] ring system, replacement with phenyl acetate to prevent

decarboxylation pathways allowed for preparation of the desired compound. The experiment in entry 7 was performed to explore the effect of the leaving group on cyclization reaction. Replacing methoxide (pK_a = 15) with phenoxide (pK_a = 10) dramatically increased the yield of the transannular cyclization, delivering the twisted amide in excellent 86% yield.

Table 16. Synthesis of Bridged Lactams via RCM/Transannular Cyclization Sequence.

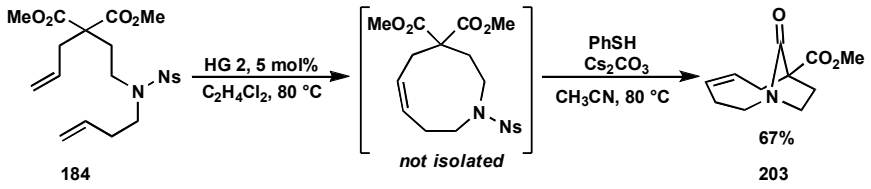


entry	diene (n, m)	heterocycle step 1	amide step 2	R	ring system	yields [%] steps 1/2	notes
1	**183** (1, 1)	**195**	**202**	CO_2Me	[4.2.1]	90/75	
2	**184** (1, 2)	**196**	**203**	CO_2Me	[5.2.1]	94/85	a
3	**186** (2, 2)	**197**	**204**	CO_2Me	[5.3.1]	90/64	b, c
4	**185** (1, 3)	**198**	**205**	CO_2Me	[6.2.1]	92/41	d
5	**188** (3, 1)	**199**	**206**	CO_2Me	[4.4.1]	79/0	
6	**193** (3, 1)	**200**	**207**	Ph	[4.4.1]	76/33	e
7	**194** (3, 1)	**201**	**207**	Ph[f]	[4.4.1]	60/86	g

[a] Step 2 run for 13 h. [b] Compound **197** obtained as 5:1 mixture of Z/E isomers. [c] Step 2: (i) PhSH, Cs_2CO_3; (ii) DBU, PhMe, 200 °C, 3 h. [d] Step 2: (i) PhSH, Cs_2CO_3; (ii) DBU, PhMe, 180 °C, 12 h. [e] Step 2: (i) PhSH, Cs_2CO_3; (ii) DBU, PhMe, 220 °C, 10 h. [f] PhO_2C instead of MeO_2C. [g] Step 2 run at 110 °C for 16 h.

As a testament to the efficiency of this methodology, we demonstrated that the RCM/deprotection/cyclization reactions could be combined in a one-pot process to deliver a previously inaccessible [5.2.1] ring system from a very simple acyclic precursor in a single-pot operation (Scheme 80).

Scheme 80

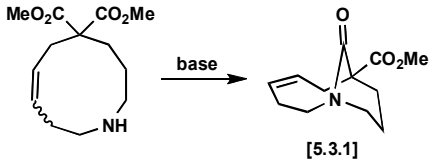


Another advantage of the sequential RCM/transannular strategy is the ease of preparation of the diene precursors for the RCM reaction. In most cases the required dienes are synthesized in 2-3 steps from commercially available materials (Scheme 79). In contrast to the Fukuyama's amine synthesis, often plagued by undesired side-reactions during the preparation of precursors, the dienes are chemically inert until the RCM step. This property bodes well for the use of this methodology for synthesis of bridged amides with diverse substitution patterns. The overall synthesis of the lactam **178** featuring a [4.3.1] scaffold proceeds in four steps from dimethyl allyl malonate, matching the efficiency of the Schmidt reaction in the synthesis of the same type of bridged amides.

The examination of different ring systems allowed us to determine the relative rates of the transannular amidation reactions. Tables 17 and 18 show the conditions

utilized for cyclization of the most difficult to close ring systems. The closure to [5.3.1] system was sluggish in refluxing toluene (Table 17, entry 5). The optimum results were obtained upon short exposure to high temperatures (entry 9). However, the reaction time had to be carefully controlled to prevent decomposition (entry 7). The cyclization to the isomeric [4.4.1] system was even more difficult. With dimethyl malonate, conversion was not observed in refluxing toluene, and decomposition occurred at higher temperatures (Table 18, entry 3). With methyl phenyl acetate, the cyclization proceeded between 200 and 220 °C (entries 4 and 5). The facility of the closure could be dramatically improved by using a better leaving group (entry 7). The above results suggest that the relative rates for the transannular cyclization reaction are in following order: [4.2.1] > [4.3.1] > [5.2.1] > [5.3.1] > [6.2.1] > [4.4.1].

Table 17. Transannular Cyclization to a [5.3.1] Ring System.

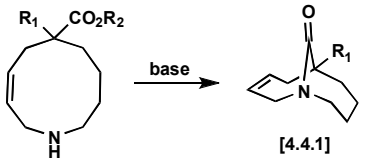


[5.3.1]

entry	base	solvent	T [°C]	t [h]	conversion [%]
1	Cs_2CO_3	CH_3CN	60	3	<5
2	Cs_2CO_3	Toluene	110	1	<5
3	Cs_2CO_3	CH_3CN	150	1	<5
4	NaH	THF	60	14	<5
5	DBU	Toluene	110	17	6
6	DBU	Toluene	110	48	24
7	DBU	Toluene	140	24	>95[b]
8	DBU	Toluene	180	3	46
9	DBU	Toluene	200	3	>95[c]
10	DBU	THF	180	3	23

[a] Determined by ^{1}H NMR. [b] Isolated in 20%. [c] Isolated in 65%.

Table 18. Transannular Cyclization to a [4.4.1] Ring System.

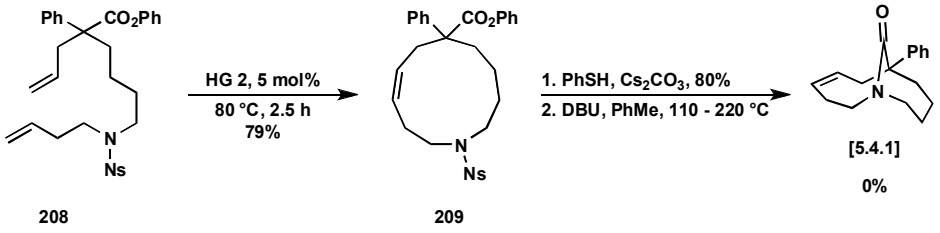


entry	R_1	R_2	base	solvent	T [°C]	t [h]	conversion [%]
1	CO_2Me	Me	DBU	Toluene	110	2	<5
2	CO_2Me	Me	DBU	Toluene	180	12	<5
3	CO_2Me	Me	DBU	Toluene	220	5	decomp.
4	Ph	Me	DBU	Toluene	200	20	<5
5	Ph	Me	DBU	Toluene	220	10	60[b]
6	Ph	Ph	Cs_2CO_3	Cs_2CO_3	60	2	5
7	Ph	Ph	DBU	Toluene	110	16	>95[c]

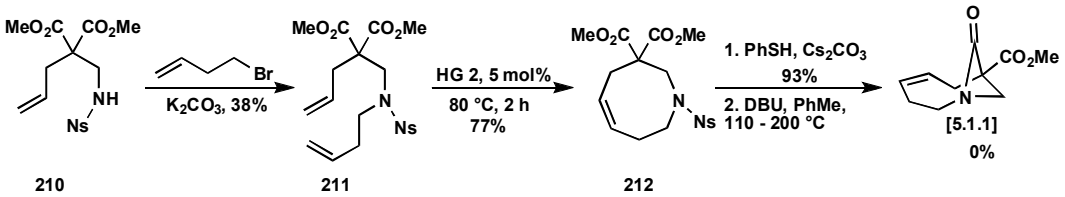
[a] Determined by ^{1}H NMR. [b] Isolated in 34%. [c] Isolated in 86%.

Using RCM/transannular cyclization strategy we attempted to prepare two additional scaffolds of bridged amides, the relaxed [5.4.1] system (Scheme 81) and strained [5.1.1] system (Scheme 82). In both cases RCM reactions proceeded uneventfully. However, transannular lactamization to [5.4.1] system did not occur (only the starting material was observed by NMR), while the [5.1.1] system behaved similarly to the α-unsubstituted [3.3.1] scaffold (Scheme 62, decomposition depending on temperature). Both of these systems should be accessible when a better leaving group is installed, as was the case with [3.3.1] ring system.

Scheme 81



Scheme 82

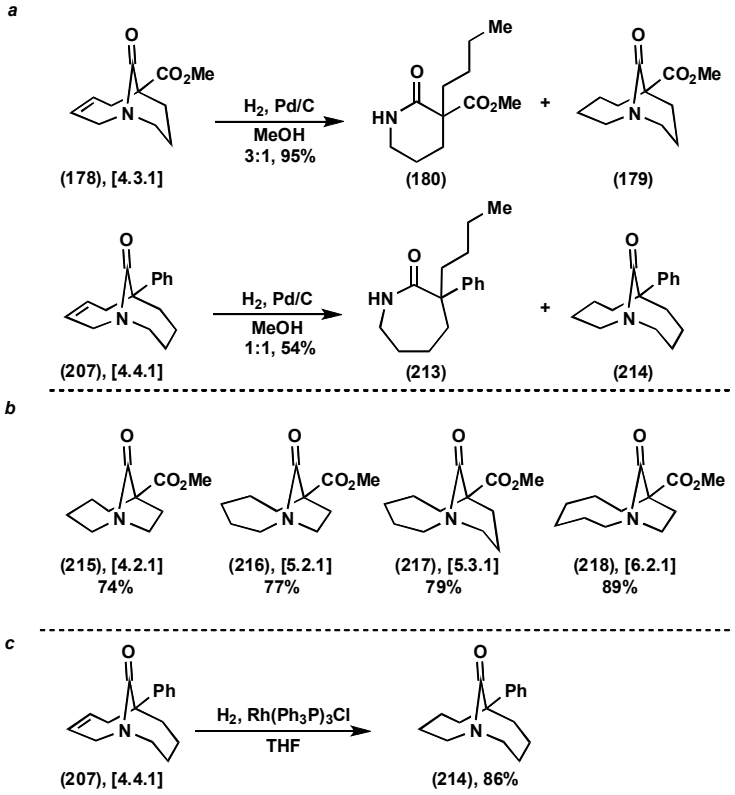


Having prepared six different ring systems of bridged amides, we briefly explored the influence of strain on the properties of these compounds. We chose hydrogenation reaction as a test reaction. Previously we reported that some twisted amides undergo an unprecedented C–N cleavage reaction under mild hydrogenolysis conditions.[31] When twisted amides prepared in the current study were subjected to standard hydrogenation conditions, [4.3.1] and [4.4.1] systems showed the highest reactivity, participating in C–N cleavage to afford the corresponding monocyclic amides (Scheme 83a). In contrast, [4.2.1], [5.2.1], [5.3.1] and [6.2.1] scaffolds were less reactive, undergoing only the traditional reduction to the saturated analogues (Scheme 83b, only products shown). As expected, allylic olefins are more susceptible to hydrogenolysis than isolated π bonds; the control reactions with saturated amides

179 and **37** bearing [4.3.1] ring system resulted only in the recovery of starting materials. It should be noted, however, that the only other bicyclic amide that had been previously noted to participate in the C−N cleavage reaction so far also contains an internal double bond (**53**, hydrogenation under high pressure). Possibly, the presence of internal olefin increases the strain and hence the reactivity of bicyclic bridged amides (see also Schemes 77 and 78). Interestingly, when hydrogenation of [4.4.1] ring system was carried out in the presence of Willkinson's catalyst, the amide bond remained intact (Scheme 83c).

Intriguingly, the reactivity of twisted amides in the hydrogenation reaction does not follow the trend predicted from the cyclization rates to twisted amides and from the comparison of spectroscopic properties of these compounds (see Table 19). These results suggest that the N–C cleavage reaction of distorted lactams depends more on the alignment of the bond that is being cleaved relative to the amide C=O system than on the inherent strain of the amide bond.[31]

Scheme 83



One of the goals of our study was to obtain a family of bridged amides with varying ring systems to allow systematic investigation of the twist influence on spectroscopic properties of bridged lactams.[38] Although most of the amides prepared so far do not contain perfectly orthogonal amide bonds, these compounds exhibit more downfield shifts in ^{13}C NMR spectrum and higher stretching frequencies in infrared spectrum corresponding to the amide bonds (Table 19). This is consistent with a considerable degree of twist and ketone-like character of these amides. As expected, some of the relaxed ring systems have spectral properties close to those of the fused amides.

Interestingly, the infrared stretching frequencies of one-carbon bridged lactams cover a spectrum that starts in the range for planar amides (entry 6), and ends close to that of a traditional ketone (entry 1). This suggests that the family of one-carbon bridged amides is well-suited for the systematic evaluation of the effect of geometry on properties of amide bonds.

Table 19. Comparison of Spectroscopic Properties of Saturated Lactams.

entry	lactam	α-substituent	ring system	C=O ^{13}C NMR [ppm]	IR $\nu_{C=O}$ [cm^{-1}]
1	**215**	CO_2Me	[4.2.1]	183.4	1716
2	**216**	CO_2Me	[5.2.1]	180.1	1693
3	**218**	CO_2Me	[6.2.1]	173.4	1685
4	**179**	CO_2Me	[4.3.1]	181.0	1679
5	**217**	CO_2Me	[5.3.1]	176.6	1647
6	**214**	Ph	[4.4.1]	186.3	1643
7	**37**	Ph	[4.3.1]	184.4	1668
8	**153**	Ph	[3.3.1]	199.5	1730
9	**27**	Ph[a]	[5.3.0]	172.4	1635
10	**219**	CO_2Et[b]	[5.3.0]	173.2	1630

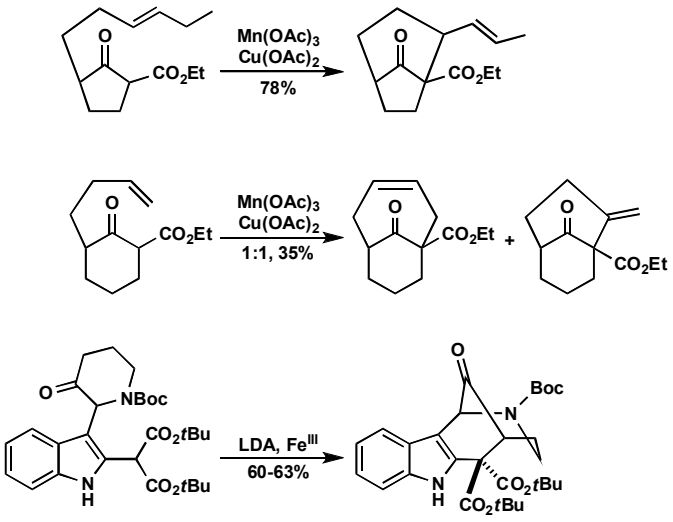
[a] Reference 188. [b] Reference 173.

It is likely that the RCM/transannular strategy could also be applied for the preparation of a set of distorted amides with varying distortion parameters. This in turn, will allow for the systematic investigation of the strain influence on the chemical and biological properties of amide bonds.

Oxidative cyclization approach. In an effort to improve synthesis of distorted lactams, we briefly examined the possibility of using radical cyclizations as a method for preparation of one-carbon bridged amides.

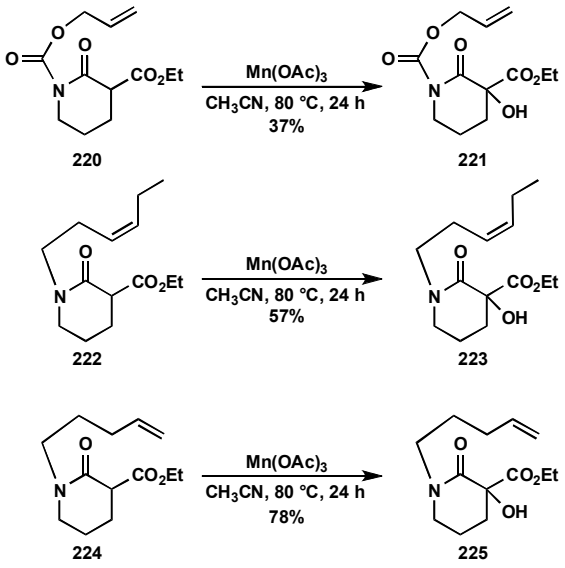
Although only bridged lactams with relatively relaxed ring systems could be prepared by direct S_N2 displacement (e.g., the [6.3.1] ring system),[27] we expected that a radical cyclization might overcome the inherent strain associated with the formation of bridged amide bonds. It is well precedented that manganese (III) acetate-mediated radical cyclizations[266] and oxidative enolate couplings[267-269] can be used for synthesis of strained bridged systems (Scheme 84).

Scheme 84



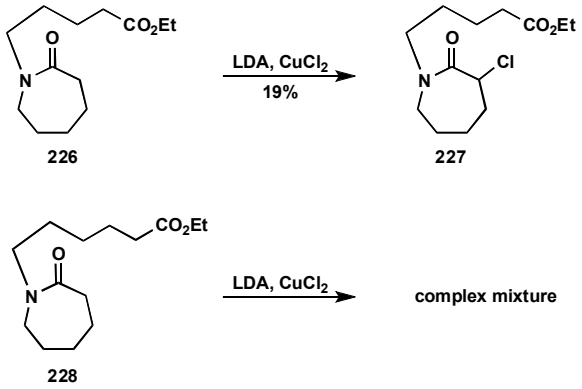
However, when we subjected β-amidoesters with pendant olefins to the manganese acetate-mediated radical cyclization, only α-hydroxylated products were obtained. Clearly, the radical was unable to react with the olefin and was instead eventually trapped by acetate or oxygen. This suggests that the cyclization to bridged amides cannot occur due to a large distance between the radical and the olefin (Scheme 85).

Scheme 85



Similarly, attempts to prepare bridged amides by oxidative enolate coupling resulted in complex mixtures, arising from side reactions of the radicals (Scheme 86). Again, the desired products were not detected in the crude reaction mixtures.

Scheme 86



Having in sight more viable routes to bridged amides, we did not further pursue the oxidative cyclization approach. However, these results emphasize the difficulty in synthesis of bridged lactams as compared to other strained systems which do not contain bridged amide moieties.

Summary. Synthesis of one-carbon bridged amides using different approaches has been investigated. Electrostatic cation–π control between aromatic ring systems and the leaving diazonium cation in the intramolecular Schmidt reaction provides efficient access to amides with [4.3.1] ring systems. This reaction occurs by the uncommon migration of the distal C–C bond relative to the reactive ketone. The selectivity of the rearrangement depends on the electron density on the aromatic ring system. The reactive conformation of the azidohydrin intermediate must be locked to prevent the exclusive migration of the C–C bond proximal to the ketone.

Electrostatic cation–n control between the lone pair of electrons on the heteroatom and the diazonium cation in the Schmidt reaction also provides access to bridged amides with [4.3.1] and [5.3.1] ring systems. This method does not require a locked conformation of the azidohydrin intermediate, significantly expanding the scope of the Schmidt reaction in the synthesis of bridged lactams. In addition, a thiomethyl substituent, which is used as a directing group, can be readily modified to furnish additional examples of twisted amides, following initial ring expansion.

In addition to providing access to one-carbon bridged amides, which are very difficult to synthesize using alternative routes, another highlight of the Schmidt methodology is the application of electrostatic cation–π and cation–n interactions to control the regiochemistry of this reaction. The synthesis of bridged amides from conformationally flexible ring systems constitutes one of the first examples of utilizing cation–n effect in organic chemistry.

Transannular cyclization strategy has been found to allow synthesis of bridged amide scaffolds not available by the Schmidt reaction. The major difficulty in this approach is the synthesis of appropriately functionalized medium-sized heterocycles to serve as precursors to bridged amides. The initial route relied on Fukuyama's amine synthesis and permitted the synthesis of a bridged amide with [3.3.1] scaffold. This amide contains one of the most distorted amide bonds prepared to date.

The application of ring-closing metathesis allowed for significant improvements in the synthesis of nitrogen-containing heterocycles set up for the cyclization step to bridged lactams. The following transannular condensation has been successfully applied to the preparation of six different ring systems of one-carbon bridged amides. These compounds, as evidenced by their spectroscopic properties, span a wide range of amide bond distortion. Depending of the geometry of the amide bond, the hydrogenation of bridged amides provides fully saturated analogues or results in hydrogenative cleavage of C−N bond.

Overall, both the Schmidt reaction and the transannular cyclization approaches have been shown to provide general routes to one-carbon bridged amides. As a result of this work a variety of bridged amide systems is now accessible, some of them by alternative methods. This will allow for a systematic study of the twist influence on chemical and biological properties of amide bonds. In addition, the lower limits for the scaffold-dependent stability of one-carbon bridged amides have been set.

Chapter 3

Reactivity of Medium-Bridged Twisted Amides

As described in the introductory chapter, due to the limited conjugation of amide bonds, distorted amides exhibit reactivity dissimilar to traditional amides. In general, C=O group is more electrophilic than in planar amides, while nitrogen, depending on the twist of the amide bond, might behave as a basic amine. Despite the considerable synthetic potential of these amides, there are very few reports addressing the reactivity of bridged amides. Indeed, the reader may note that *all* known examples are presented in the introductory chapter. Furthermore, the fundamental question of just how much distortion is necessary for the shift from the amide-like to the keto amine-like reactivity of amide bonds has remained largely unanswered.

The discovery that the intramolecular Schmidt reaction affords tricyclic and bicyclic bridged amides with [4.3.1] scaffold provided us with the opportunity to explore the properties of bridged amides in which the amide bond is almost exactly half-way rotated. The initial studies of Aubé's group focused on a novel C–N bond cleavage reaction, clearly demonstrating that synthetic potential of bridged amides extends far beyond the enhanced reactivity towards hydrolysis (Scheme 30).[31] Furthermore, Lei and Aubé[189] discovered a number of intriguing reactions of bridged lactams, including the isolation and the first crystallographic characterization of N-protonated amides, synthesis of isolable hemiaminals upon reduction of tricyclic

amides with mild $NaBH_4$, and the collapse of hemiaminal corresponding to amide **53** with the cleavage of an unactivated C–C bond (Schemes 31 and 32).

Accordingly, we were interested in further expanding the scope of reactivity of bridged amides. First, we wished to investigate whether the unique placement of nitrogen next to a heteroatom in a bridged twisted amide could deliver compounds that cannot be prepared from unstrained lactams. Secondly, we wished to further examine nucleophilic addition reactions to the carbonyl group and electrophilic activation of the nitrogen, with the major goal of identifying the border of the keto amine-like reactivity of bridged amides. However, the study that would lay the foundations for investigation of reactivity of bridged amides was the examination of hydrolytic stability of one-carbon bridged amides.[54]

Hydrolytic stability of one-carbon bridged amides. Due to the limited $n_N \rightarrow \pi^*_{C=O}$ donation (with resulting enhanced electrophilicity of the amide carbonyl group), the vast majority of bridged amides is unstable to aqueous conditions. This hydrolytic instability is the major factor complicating the synthesis and isolation of some of the more distorted bridged amides and has prevented a thorough investigation of the properties of bridged lactams.[11] Comparison of the rate constants for hydrolysis of 2-quinuclidone derivatives with the notoriously unstable β-lactam antibiotics underscores the difficulty of synthetic manipulations with bridged amides (Table 1).

While very few bridged amides are both reactive electrophiles and stable in protic nucleophilic solvents,[81, 167] the hydrogenolysis study of *one-carbon bridged amides* (Scheme 30, typically performed in MeOH or EtOH) suggested that one-carbon bridged lactams do not readily decompose upon exposure to alcohols. In a preliminary investigation, Lei and Aubé demonstrated that incubation of tricyclic amides at different pH conditions resulted in the recovery of the parent amides, suggesting unprecedented levels of hydrolytic stability.[189] Now, we wished to examine the stability of one-carbon bridged amides in greater detail, aware that elucidation of limits of the hydrolytic stability would also facilitate the study of other chemical properties of one-carbon bridged amides.

Our investigation started with a set of simple extraction experiments of the tricyclic amide **229**, readily available from the Diels-Alder/Schmidt reaction sequence and characterized by twist angle (τ) of 50° (Figure 15 and Table 20).[31]

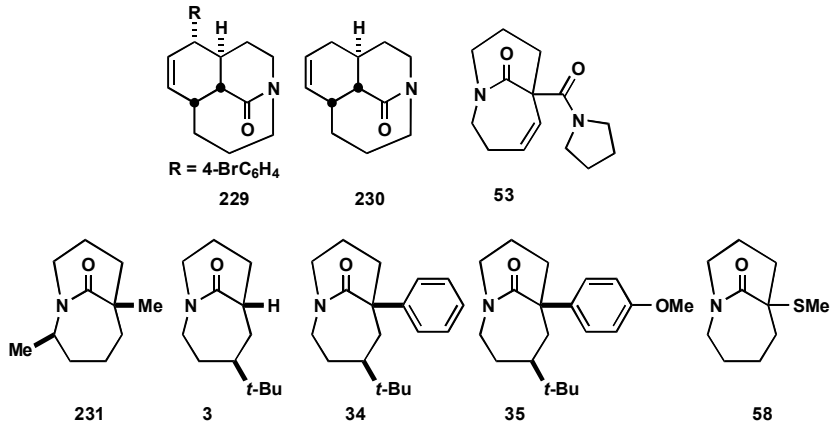


Figure 15. Amides used in the study of hydrolytic stability of one-carbon bridged lactams.

Initial studies were carried out using acetonitrile as a solvent due to a good solubility of **229** in this solvent. Thus, samples of **229** were dissolved in acetonitrile and either water or an aqueous solution of NaOH or HCl was added to afford ca. 4:1-24:1 CH_3CN:aqueous solution ratio (Table 20 entries 1-3). This was vigorously stirred for ca. 20 h and extracted with ethyl acetate. A typical twisted amide (including bridged amides with a twist angle much lower than that corresponding to **229**; see Table 1) would be expected to exclusively afford amino acid following treatment with such conditions. However, unchanged **229** could be recovered in high yield from the above experiments. In addition, samples of **229** could be directly recovered from strongly acidic solutions without prior neutralization of the reaction mixtures.

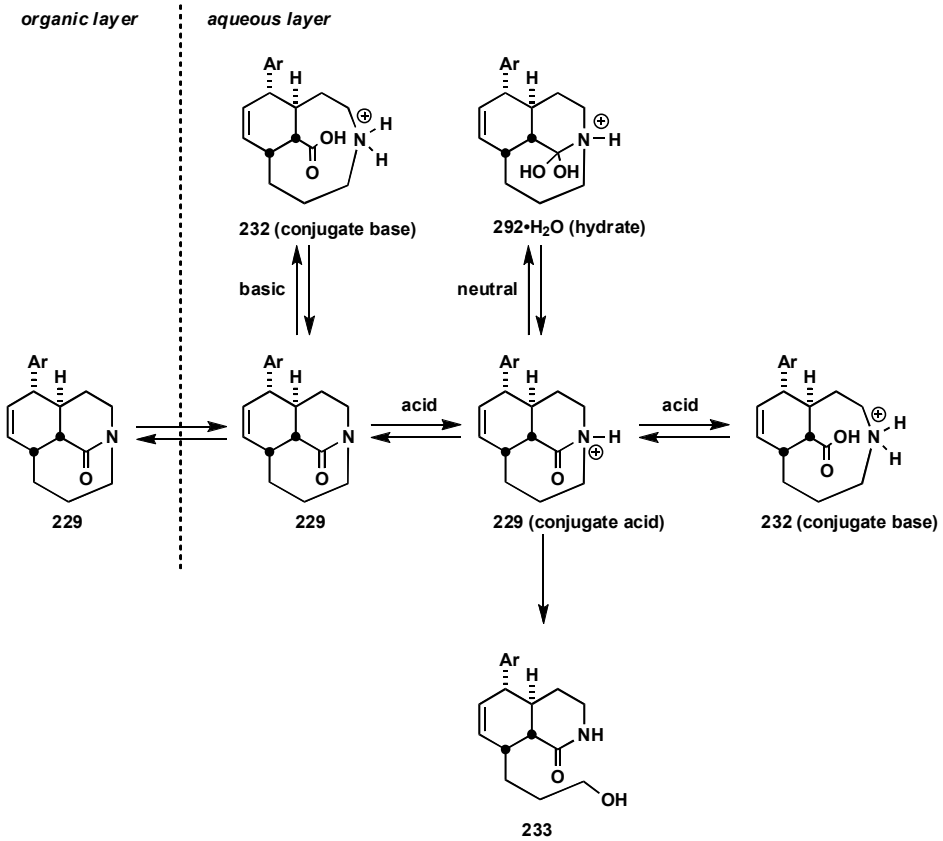
We found that the reaction time could be extended to one week under acidic conditions (entry 4), and the temperature increased to 80 °C under basic conditions (entry 5) with no changes in recovery levels of **229**. The only irreversible chemical reaction occurred when **229** was heated to reflux in HCl/acetonitrile mixture (entry 6). However in this case, the cleavage of the C−N bond adjacent to the amide bond occurred, while the amide bond remained intact. This reaction resembles the cleavage of the C−N bond upon hydrogenation of tricyclic amides and highlights the unusual reactivity of a twisted amide bond constrained in a bridged system.[31]

Table 20. Extraction Studies of Lactam **229**.

entry	conditions[a]	time, temp	result
1	1:4 H_2O/CH_3CN	20 h, rt	>85% recovery of **229**
2	1:8 aq $NaOH/CH_3CN$ (pH ca. 14)	20 h, rt	>85% recovery of **229**
3	1:24 aq $NaOH/CH_3CN$ (pH ca. 14)	22 h, 80 °C	>80% recovery of **229**
4	1:8 aq HCl/CH_3CN (pH ca. 1)	20 h, rt	>80% recovery of **229**
5	1:8 aq HCl/CH_3CN (pH ca. 1)	8 days, rt	>85% recovery of **229**
6	1:24 aq HCl/CH_3CN (pH ca. 1)	23 h, 80 °C	conversion to **232**[b]

[a] The pH values refer to the aqueous layers. [b] 95% yield.

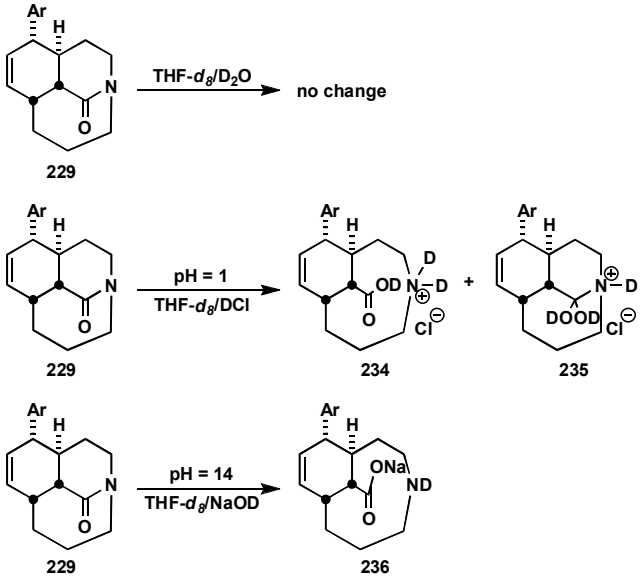
Scheme 87



The recovery of **229** is consistent with two scenarios. The one-carbon bridged amide linkage could be thermodynamically stabilized in the medium-sized heterocycle. Thus, the dissolution of **229** in an aqueous environment would result in reversible hydrolysis, with re-closure to the parent amide occurring during the extraction with organic solvents. Alternatively, the amide bond in **229** could be kinetically stabilized towards hydrolysis. Some of the species that could be present upon treatment of **229** with acidic or basic conditions are presented in Scheme 87.

To address the question of thermodynamic or kinetic stability of **229** we performed a set of NMR experiments. Thus, **229** was dissolved in THF-d_8, treated with D_2O, DCl or NaOD, respectively, and the solutions were examined by NMR (Scheme 88). The resonance of the carbonyl group in ^{13}C NMR provided the most useful information about the species present in the solution (Figure 16 and Table 21). The chemical shift of the signal corresponding to the carbonyl group in $CDCl_3$ appears at 187 ppm and at 185 ppm in THF-d_8 (Figure 16a and Table 21). Upon dissolution in 1:1 D_2O/THF-d_8 this signal moves slightly downfield to 189 ppm (Figure 16b), while the rest of spectrum bears a close similarity to the spectrum of **229** in $CDCl_3$. The broadening of the carbonyl signal observed in Figure 16b most likely results from hydrogen bonding to water and is typically observed for aqueous solutions of amides. These results indicate that **229** is kinetically stable under neutral conditions.

Scheme 88



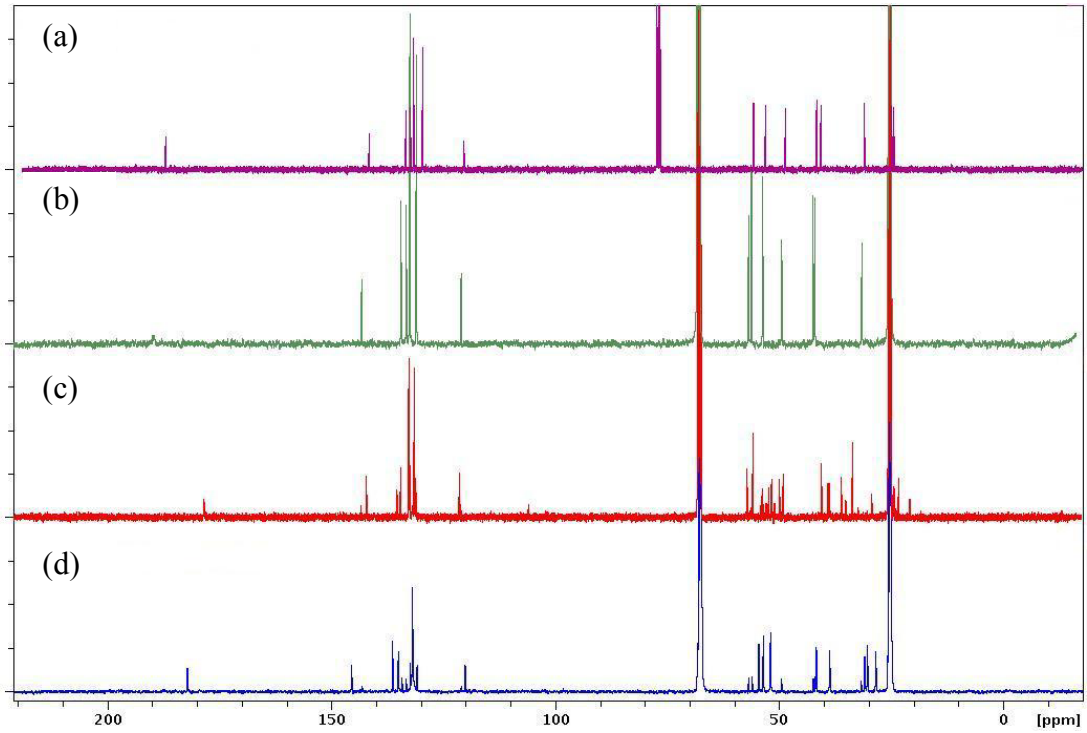


Figure 16. ^{13}C NMR spectra of compound **229** in (a) $CDCl_3$, (b) 1:1 D_2O:THF-d_8, (c) 1:6 DCl (1 *N* in D_2O)/THF-d_8 and (d) 1:6 NaOD (1 *N* in D_2O)/THF-d_8.

Table 21. ^{13}C NMR Carbonyl Shifts of Lactam **229** and Its Derivatives.

entry	conditions	assignment	shift [ppm]
1	$CDCl_3$	**229**	187.1
2	THF-d_8	**229**	185.0
3	DMSO-d_6	**229**	186.2
4	1:1 D_2O/THF-d_8	**229**	189.6
5	1:6 DCl (1 *N* in D_2O)/THF-d_8	**232** (conjugate acid)	178.5
		229•H_2O (hydrate)	106.1
6	1:6 DCl (1 *N* in D_2O)/DMSO-d_6	**232** (conjugate acid)	178.5
		229 (conjugate acid)	176.9
		229•H_2O (hydrate)	104.9
7	1:6 NaOD (1 *N* in D_2O)/THF-d_8	**232** (conjugate base)	182.3
8	1:6 NaOD (1 *N* in D_2O)/DMSO-d_6	**232** (conjugate base)	179.0
9	$CDCl_3$	**229**	176.9

In contrast, at pH ca. 1, several species were observed by ^{13}C NMR. We assigned the predominant peak in the THF-d_8 solution at 178 ppm to the N-protonated form of **232** (Scheme 87 and Figure 16c), and the minor peak observed at 106 ppm to the hydrate **229**•H_2O, also protonated at nitrogen (Table 21, entry 5). Interestingly, when **229** was dissolved in DMSO-d_6 at pH ca. 1, in addition to the same two species observed in THF-d_8, the N-protonated form of **229** was present (Table 21, entry 6). The shift of 176.9 ppm is in very good agreement with fully characterized N-protonated salts of tricyclic lactams.[189]

At pH ca. 14, the carbonyl signal of **229** was replaced by an upfield resonance at 182 ppm. In this case, the most reasonable assignment is the conjugate base of the amino acid **232** (Scheme 87). This assignment is consistent with values observed for simple carboxylic acids (for example, the carbonyl of acetic acid in $CDCl_3$ appears at 178.1 ppm and the corresponding signal for the conjugate base is at 181.5 ppm in aqueous solution).[270]

The presence of various species arising from **229** under highly acidic and basic conditions was supported by mass spectrometry measurements taken from samples prepared as described above (Table 22). Aliquots from each experiment were diluted by the solvents indicated in Table 22 to prepare them for ionization. Thus, only the starting lactam **229** was observed in samples dissolved in D_2O/THF (entries 1 and 2). *Note a remarkable difference in stability between **229** and the lactam **153** with [3.3.1] ring system (Table 14).* Under basic conditions (entries 3-6) the parent lactam **229** or the corresponding amino acid **232** is observed, depending on the solvent used for ionization. Samples of **229** dissolved under acidic conditions (entries 7-10) indicated the presence of both **229** and **232**. The ratio **229**/**232** was also dependent on the solvent used for ionization, with higher contribution of **229** observed when water was used as a diluent vs. either THF or acetonitrile. In addition, the methyl ester of **232** was observed when samples for MS experiments were prepared by dissolution with MeOH/water/aqueous formic acid mixtures (entry 9).

Table 22. ESI MS Experiments with Lactam **229**.[a]

entry	conditions	solvent[b]	exact mass	assignments
1	1:1 D_2O/THF	THF	346.0818	**229**
2	1:1 D_2O/THF	H_2O	346.0797	**229**
3	1:6 NaOD (1 *N* in D_2O)/THF	THF	346.0856	**229**
4	1:6 NaOD (1 *N* in D_2O)/THF	CH_3CN	346.0792	**229**
5	1:6 NaOD (1 *N* in D_2O)/THF	H_2O	364.0918	**232**
6	1:6 NaOD (1 *N* in D_2O)/THF	DMSO	364.0920	**232**
7	1:6 DCl (1 *N* in D_2O)/THF	THF	346.0752; 364.0903 (ratio ca. 1:1)	**229** and **232**
8	1:6 DCl (1 *N* in D_2O)/THF	H_2O	346.0722; 364.0913	**229** and **232**
9	1:6 DCl (1 *N* in D_2O)/THF	MeOH/H_2O /HCO_2H	346.0761; 378.1022 (ratio ca. 3:1)	**229** and the methyl ester of **232**
10	1:6 DCl (1 *N* in D_2O)/THF	CH_3CN	346.0776; 364.0916 (ratio ca. 1:1)	**229** and **232**

[a] Relevant HRMS calculations: HRMS calcd for $C_{18}H_{21}BrNO$ (M^+ + H) 346.0806 (compound **229**); HRMS calcd for $C_{18}H_{23}BrNO_2$ (M^+ + H) 364.0912 (compound **232**); HRMS calcd for $C_{19}H_{25}BrNO_2$ (M^+ + H) 378.1069 (methyl ester of compound **232**). [b] Solvent used for ionization.

Overall, NMR and MS data obtained with lactam **229** are consistent with both kinetic and thermodynamic stability of **229** at neutral pH. When **229** is subjected to strong acid or base the hydrolysis occurs, but remarkably *the bridged amide bond is able to spontaneously reform even in a medium saturated with water*.

We made considerable efforts to retrieve the samples of zwitterions **232** by concentrating the aqueous solutions (prepared under acidic and basic conditions) and

examining the residues by NMR and IR. However, only the starting lactam **229** was observed in these experiments, strongly suggesting that simple removal of water is sufficient to move the equilibrium back to the lactam **229**.

Interestingly, although the species arising from **229** are present in solution for a considerable period of time (see Experimental Section for details), the parent lactam **229** crystallized spontaneously from the NMR sample at pH = 14 (structure confirmed by X-ray crystallography),[54] suggesting that the bridged amide is the thermodynamically favored compound in the equilibrium. Selected recovery and NMR experiments were repeated with tricyclic amide **230**, which behaved identically to the lactam **229**, confirming that the properties of tricyclic amides are general.

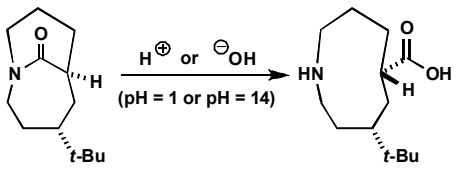
Having investigated the stability of tricyclic amides, we investigated hydrolytic properties of some bicyclic analogues. Of particular interest was the role of conformation in constraining the nine-membered amino acid. Open-form species arising from tricyclic amides (for example **232**) exhibit in/out isomerism[271] around the six-membered ring, which likely contributes to holding the carboxylic acid in a close proximity to the amino group, facilitating the closure to the parent lactam.

Thus, a bicyclic lactam **53** was treated with D_2O/THF-d_8 solutions at neutral, acidic and basic conditions. A direct observation of the samples by ^{13}C NMR spectroscopy indicated a behavior identical to the tricyclic **229** (no reaction under neutral conditions, hydrolysis to the amino acid at pH ca. 1 and 14). However, when we attempted recovery studies of the bicyclic **53**, the parent lactam could be re-isolated only after treatment with 1:4 H_2O/acetonitrile mixtures. The lactam **53** could

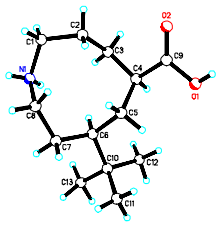
not be recovered after exposure to aqueous solutions (pH ca. 1 and 14), in a manner analogous to the described for tricyclic **229**. Similarly, recovery of other bicyclic amides (**233**, **3**, **34** and **35)** was also attempted but these compounds could not be re-isolated from strongly acidic or basic conditions. These results suggested that the additional six-membered ring in the tricyclic lactams enhances the thermodynamic stability of one-carbon bridged amides.

Although the exposure of lactam **3** to strongly acidic and basic conditions did not permit its recovery, the removal of solvent afforded a quantitative yield of the amino acid **237** (Scheme 89). The X-ray crystallography[54] established that this compound was able to undergo conformational change, in which the carboxylic acid has flipped outside of the nine-membered heterocycle and is unable to reach the amide group. Thus, conformation is crucial in the reversibility of the amide bond formation in this series of one-carbon bridged amides.

Scheme 89



3 237



Next, we investigated the limits of the kinetic stability of these bicyclic bridged lactams (Table 23). Although the α-unsubstituted amide **3** exhibited good stability in neutral solutions (entry 1), it underwent irreversible conversion to amino acid under moderately acidic (pH ca. 4) or basic (pH ca. 10) conditions. However, α-aryl-substituted amides **34** and **35** could be completely recovered after the exposure to aqueous solutions where pH = 4, 7 or 10 (entries 4-6). Importantly, the lactam **58** substituted with α-methylthio group and lacking the *tert*-butyl substituent was fully water-soluble, which allowed its study in aqueous solutions at pH = 4, 7 and 10 (entries 7-9). Under all of these conditions **58** was kinetically stable. Additionally, the stability of **58** was demonstrated by comparison of its ^{13}C NMR spectra recorded in $CDCl_3$ and D_2O (Figure 17), which are very similar to each other. To the best of our knowledge *lactam **58** represents the first example of a significantly distorted bridged amide that is both stable and soluble in water.*[11]

Table 23. Extraction Studies of Bicyclic Lactams.

entry	lactam	solvent	time, conditions	result
1	**3**	1: 1 D_2O/THF-d_8	13 d, rt	ca. 50% recovery of **3**
2	**3**	aq HCl (1.0 *N*)	0.25 h, rt	conversion to **237**
3	**3**	aq NaOH (1.0 *N*)	3 h, rt	conversion to **237**
4	**35**	1: 1 D_2O/THF-d_8	7 d, rt	>95% recovery of **35**
5	**34**	buffer (pH 4)/CH_3CN	2 h, rt	>90% recovery of **34**
6	**34**	buffer (pH 10)/CH_3CN	2 h, rt	>90% recovery of **34**
7	**58**	D_2O	6 d, rt	>95% recovery of **58**
8	**58**	buffer (pH 4)	2 h, rt	>90% recovery of **58**
9	**58**	buffer (pH 10)	2 h, rt	>90% recovery of **58**

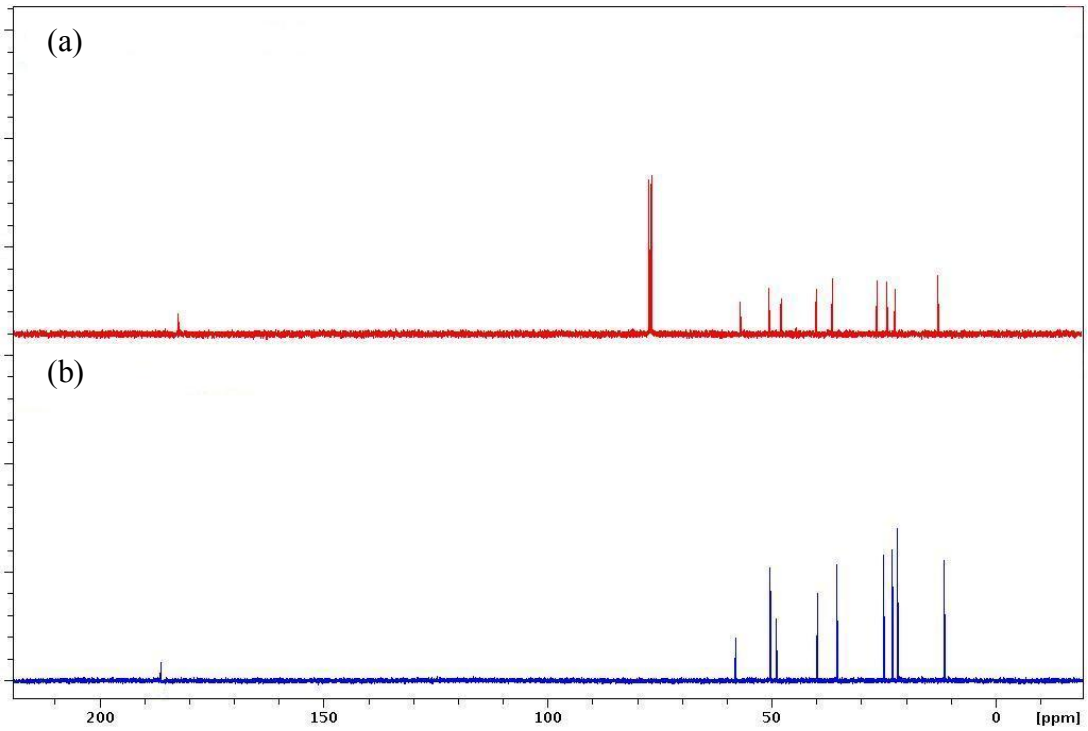


Figure 17. ^{13}C NMR spectra of lactam **58** in (a) $CDCl_3$ and (b) D_2O.

Overall, these results indicate that incorporation of the amide carbonyl into a one-carbon bridge situated across a medium-sized heterocycle results in an enhanced hydrolytic stability of twisted amides. Inherent distortion parameters of amide bonds (for example, [3.3.1] bridged amide **153**) and scaffolding effects of particular ring systems (for example, tricyclic lactam **229**) are additional factors that need to be considered in predicting hydrolytic stability of one-carbon bridged amides. Furthermore, α-substituted lactams are more hydrolytically stable than the α-unsubstituted analogues.

We believe that the hydrolytic stability of one-carbon bridged amides, combined with the fact that these compounds are readily amenable to synthesis and

structural diversification, will increase the range of biological and chemical studies available with lactams containing distorted amide bonds.

Although it has been suggested that twisted amides could provide an attractive platform for the study of enzymatic processes,[11] the previously available bridged amides were too unstable in water and/or insufficiently diversifiable to allow for their exploration in biological settings. One of the more intriguing potential biological applications of bridged amides would be as inhibitors of cis/trans isomerases (see Introductory Chapter).[17, 18] Furthermore, with the knowledge that one-carbon bridged amides are stable under biologically relevant pH conditions, these compounds can serve as templates for enzymatic hydrolysis of amide bonds[26, 41] and be used as scaffolds[272-275] or conformationally constrained analogues[128] in medicinal chemistry.

Similarly, the investigation of chemical properties of twisted amides has been severely limited by their hydrolytic instability. However, the first examples of novel reactivity of amide bonds contained in distorted and hydrolytically robust one-carbon bridged amides have already emerged (see Scheme 30).[31] Additional examples are presented in the next parts of the Chapter 3, and we expect that distorted amide bonds will find more widespread application in target- and diversity-oriented synthesis.

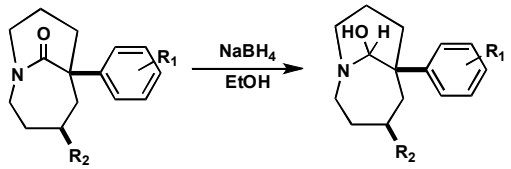
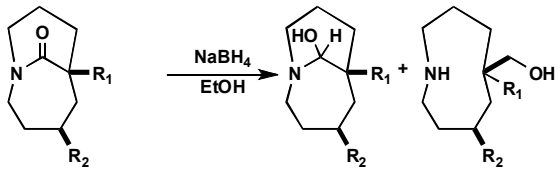
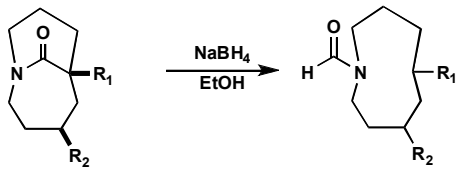
Proximity Effects in Nucleophilic Addition Reactions. The study of hydrolytic stability of one-carbon bridged amides clearly demonstrated that despite having significant twist values of their amide bonds, one-carbon bridged lactams are not hydrolyzed by nucleophilic solvents. This unusual (to twisted amides) property was ascribed to destabilization of the potentially formed carboxylic acid and amine functionalities by their placement on the opposite sides of the medium-sized ring, where they would be subjected to strong proximity effects.[54]

The presence of transannular amine-carbonyl interactions in tetrahedral intermediates resulting from addition of nucleophiles to carboxylic acid derivatives was discussed in the introductory chapter. We wondered if the enhanced carbonyl reactivity of one-carbon bridged lactams unified with transannular proximity effects could be combined to allow for the isolation of stable tetrahedral intermediates. Preliminary results regarding the stability of hemiaminals derived from tricyclic amides reported by Lei and Aubé (Scheme 32)[189] further suggested that one-carbon bridged amides would provide a useful platform for investigating tetrahedral intermediates.

We began our study by examining the behavior of one-carbon bridged amides in addition reactions of hydride, the smallest available nucleophile (Table 24). In agreement with our hypothesis, treatment of the bridged bicyclic amide **34** with $NaBH_4$ in EtOH led to the formation of stable hemiaminal **238** in excellent yield (entry 1). Since planar amides are typically not reduced by $NaBH_4$,[276] this transformation occurs due to the increased reactivity of the bridged amide bond. The

stability of **238** indicates that lone pairs of electrons at oxygen do not overlap with σ^*_{C-N} bond in the bicyclic hemiaminal system. Furthermore, since the reduction stops at the tetrahedral intermediate stage, the bridged nitrogen is incapable of donation of its n electrons into the σ^*_{C-O}, which would ordinarily led to the formation of the corresponding iminium ion.

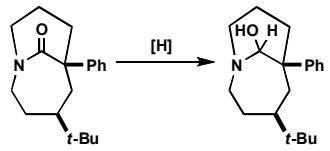
Table 24. Hydride Addition to One-Carbon Bridged Amides.

entry	amide	product (yield, %)
		
1	(**34**), R_1 = Ph, R_2 = *t*-Bu	**238** (90)
2	(**35**), R_1 = 4-$MeOC_6H_4$, R_2 = *t*-Bu	**239** (91)
3	(**40**), R_1 = 3,5-$(MeO)_2C_6H_4$, R_2 = *t*-Bu	**240** (94)
4	(**39**), R_1 = 3,4-$(OCH_2O)C_6H_4$, R_2 = *t*-Bu	**241** (95)
		
5	(**3**), R_1 = H, R_2 = *t*-Bu	**242** (24) and **243** (52)
6	(**58**), R_1 = SMe, R_2 = H	**244** (40) and **245** (48)
7	(**73**), R_1 = SPh, R_2 = H	**246** (62) and **247** (34)
		
8	(**84**), R_1 = SO_2Me, R_2 = H	**248** (98)
9	(**36**), R_1 = 4-$NO_2C_6H_4$, R_2 = *t*-Bu	**249** (82)

To examine the effect of structure on the stability of hemiaminals, the reduction was carried out on a number of related bridged amides (Table 24, entries 2-9). Thus, bicyclic amides with electron-rich aromatic rings in the α-position smoothly underwent the reduction, providing isolable hemiaminals in all cases (Table 24, entries 2-4). Note that two tricyclic lactams previously reported by Lei and Aubé also provided stable hemiaminals (Scheme 32).[189] However, analogous reactions of the α-unsubstituted bridged amide and amides possessing heteroatoms α to the carbonyl led to mixtures of hemiaminals and primary alcohols (entries 5-7). The net result is the traditional cleavage of the C−N bond. Remarkably, reduction of bridged amides decorated with α-electron-withdrawing substituents afforded formamides (entries 8 and 9). Note that these examples are analogous to the C–C cleavage with the bicyclic amide **53** (Scheme 32),[189] however in the latter case it was unclear whether the anion was stabilized by the α-carbonyl group or by the internal double bond in **53**. In all three cases the driving force in the collapse of hemiaminals is the formation of a stabilized anion. This transformation is unique in that it results in the cleavage of unactivated C−C bond. Overall, these results demonstrate that the identity of the α-substituent strongly affects the stability of tetrahedral intermediates constrained in bicyclic systems.

Using amide **34** as a model substrate, we also briefly investigated the role of the hydride source and reaction conditions on the formation of stable hemiaminals.[277] These results are summarized in Table 25.

Table 25. Reduction of Lactam **34**.



34 238

entry	reagent	solvent	temp. [°C]	time [h]	yield [%]	dr[a]
1	$NaBH_4$	EtOH	24	20	96	80:20
2	$NaBH_4$[b]	MeOH	24	20	32[c]	86:14
3	$NaBH_4/CeCl_3$	EtOH	24	20	31[c]	81:19
4	$LiBH_4$	EtOH	24	20	94	82:18
5	$LiAl(OtBu)_3H$	THF	24	24	<5[d]	nd
6	L-Selectride	THF	24	24	<5[d]	nd
7	$LiAlH_4$	Et_2O	24	5	99	82:18
8	Red-Al	PhMe	110	2	96	80:20
9	DIBAL-H	PhMe	110	2	97	81:19
10	BH_3	THF	66	24	47	74:26
11	$LiEt_3BH$	THF	24	3	92[e]	84:16

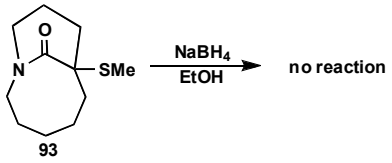
[a] Determined by ^{1}H NMR; [b] 4-$MeOC_6H_4$ derivative was used; [c] Conversion; [d] Only starting material was observed by ^{1}H NMR; [e] Combined yield of aminal and primary alcohol **250** (isolated in 38% and 54% yield, respectively); nd = not determined.

Reaction of **34** with a number of different hydride sources afforded stable hemiaminal **238**. Interestingly, the reduction with $NaBH_4$ was found to be slower when methanol was used as a solvent (entry 2); typically, the reduction of carbonyl groups by $NaBH_4$ proceeds more readily in MeOH than EtOH.[278] Similarly, the reaction was suppressed when a combination of $NaBH_4$ and $CeCl_3$ was used (entry

3).[279] Hydrogen bonding and coordination to the amide bond oxygen might be responsible for lower reaction rates in entries 2 and 3. Tributoxyaluminum hydride[280] and L-Selectride[281] (entries 5 and 6) did not reduce **34**, while $LiAlH_4$,[282] Red-Al and DIBAL-H[283] smoothly provided hemiaminal **238** (entries 7-9). In contrast, $LiEt_3BH$[284] promoted the collapse of **238** to the aldehyde (entry 11), indicating that the outcome of the reduction of one-carbon bridged amides could also be modified by changes in reaction conditions.

Importantly, when a higher homologue of **34** was reacted with $NaBH_4$, no reduction was observed, indicating that this [5.3.1] scaffold is more similar in properties to traditional rather than twisted amides (Scheme 90).

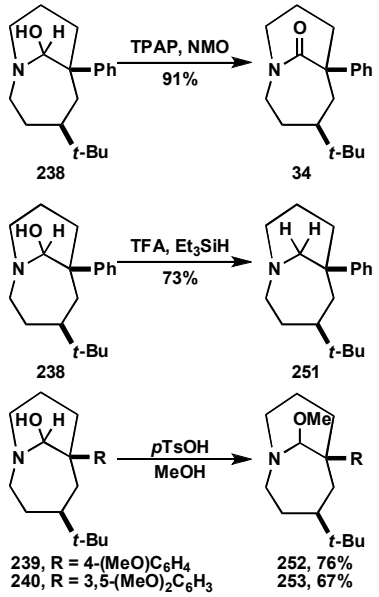
Scheme 90



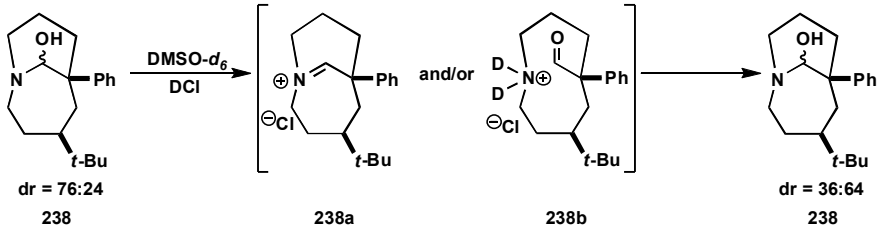
Reactions of bridged hemiaminals. Bridged hemiaminals are valuable synthetic intermediates and we explored their potential utility by performing a set of transformations. Noteworthy is the oxidation of **238** to the parent amide **34**, full reduction to the amide **251** (proceeding via the intermediacy of rarely encountered bridgehead iminium ion)[285-287] and preparation of protected hemiaminals **252** and **253** as single diastereoisomers (stereochemistry not determined) (Scheme 91). We also determined that hemiaminal **238** readily epimerizes upon treatment with acids

(Scheme 92). This reaction could occur either via the intermediate bridged iminium ion **238a** or through the acid-promoted opening to the aldehyde **238b** with re-closure to the more thermodynamically favored isomer. Overall, the success of these reactions bodes well for synthetic applications of bridged hemiaminals derived from one-carbon bridged amides.

Scheme 91

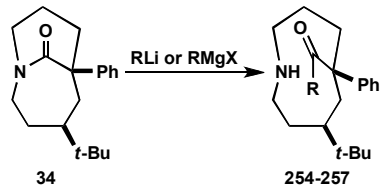


Scheme 92



Having determined the stability of hemiaminals derived from hydride addition to one-carbon bridged amides, next we evaluated the stability of hemiaminals formed in the addition of more sterically demanding organometallic reagents (Table 26).

Table 26. Organometallic Addition to Bicyclic Amides.



34 254-257

entry	reagent	conditions[a]	product (yield, %)
1	MeLi	Et_2O, -78 °C → rt, 3 h	**254** (89)
2	MeLi•LiBr	Et_2O, -78 °C → rt, 3 h	**254** (85)
3	*n*-BuLi	Et_2O, -78 °C → rt, 3 h	**255** (83)
4	*sec*-BuLi	Et_2O, -78 °C → rt, 3 h	**256** (93)
5	*t*-BuLi	Et_2O, -78 °C → rt, 3 h	**257** (80)
6	MeMgI	Et_2O, -78 °C → rt, 24 h	**254** (73)
7	$TMSCH_2Li$	Et_2O, -78 °C → rt, 3 h	b
8	PhLi	Et_2O, -78 °C → rt, 24 h	c
9	PhCCLi	THF, -78 °C → reflux, 24 h	b
10	$CH_2CHMgBr$	THF, -78 °C → reflux, 20 h	d
11	MeMgCl	THF, rt → reflux, 24 h	e
12	HCCMgBr	THF, rt → reflux, 24 h	b

[a] The reactions were typically carried out with 3 equiv of the organometallic reagent. [b] Only starting material was observed by NMR. [c] <10% yield of the desired phenyl ketone, obtained as 1:2.5 mixture with aminal **238**, 44% conversion. [d] Formation of the desired product not observed. Occasionally **238** was formed (presumably via radical reduction). [e] Complex mixture of products.

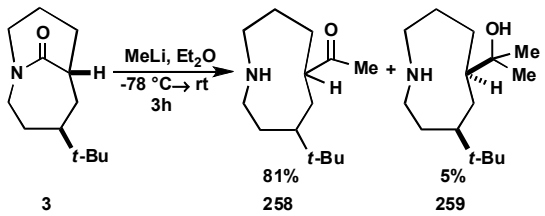
Treatment of bicyclic amide **34** with MeLi afforded keto amine **254** (entry 1). Thus, an increase of the steric hindrance at the hemiaminal carbon results in the collapse of the tetrahedral intermediate. Similarly, the reaction of **34** with other reagents, including secondary and tertiary organolithiums furnished the

corresponding amino ketones (entries 3-5). While it was previously known that tertiary amides react with organolithiums,[288-290] the addition of organometallic reagents to sterically congested bridged amide bonds is without precedent and results from the increased electrophilicity of distorted lactams.

We also determined that MeMgI could be utilized for transfer the alkyl group (entry 6), however $TMSCH_2Li$ (which is only slightly less nucleophilic than MeLi) was unreactive with **34** (entry 7). A number of other organometallic reagents were also tested, however the addition product was formed in low yield or was not observed (Table 26, entries 8-12). These results exemplify the difficulty of addition of organometallic reagents to the sterically hindered amide bonds.

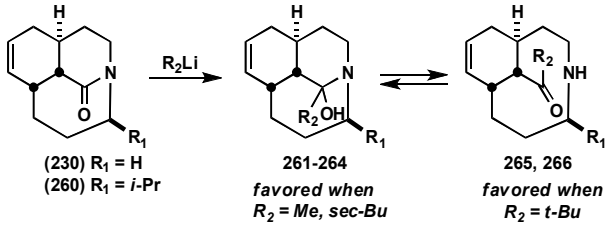
Interestingly, in the case of amide **34** the addition stopped at the ketone stage. Re-subjection of the aminoketone **254** to the reaction conditions did not result in the formation of the tertiary alcohol, suggesting that the steric hindrance around the quaternary carbon prohibits further addition of the organometallic reagent. However, it is also possible that the initially formed addition product persists in the reaction mixture prior to workup. In contrast, α-unsubstituted amide **3** undergoes partial reaction to afford the tertiary alcohol **259** (Scheme 93).

Scheme 93



The instability of the bicyclic hemiaminals corresponding to amino ketones **254**–**257**, prompted us to examine the behavior of their tricyclic analogues. We reasoned that the six-membered ring attached to the bridged system could stabilize the closed hemiaminal, in a manner similar to the results observed in the hydrolytic stability studies (Scheme 87).[54] Indeed, exposure of **230** to MeLi afforded hemiaminal **261** (Table 27, entry 1). Increased bulk close to the reactive amide bond did not influence the reaction and **260** led to the corresponding tetrahedral intermediate (entry 2). Remarkably, addition of a secondary organolithium also provided stable hemiaminals (entries 3 and 4). However, the tricyclic scaffolds were incapable of supporting hemiaminals substituted with tertiary carbon and instead ketones **265** and **266** were formed (Table 27, entries 5 and 6).

Table 27. Organometallic Addition to Tricyclic Amides.



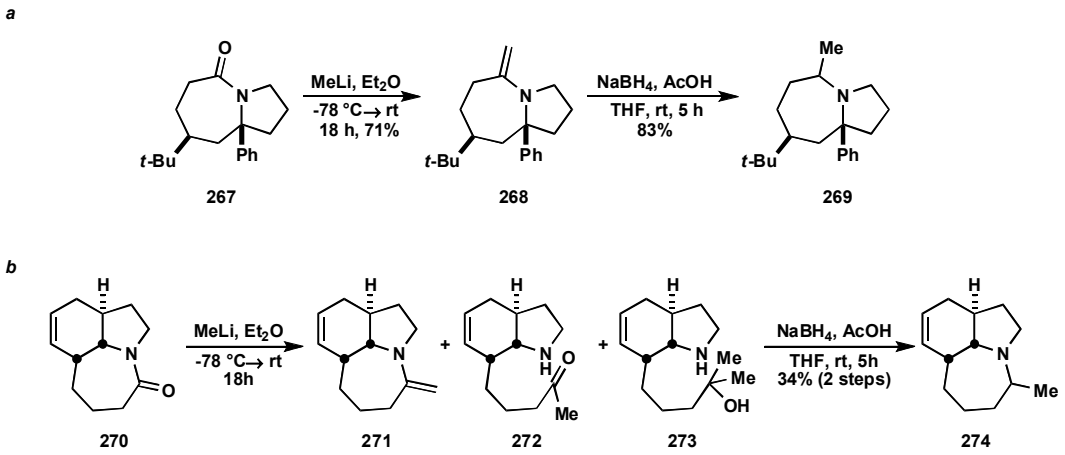
entry	amide	hemiaminal/ amino ketone	R_2	reagent	yield [%]
1	**230**	**261**	Me	MeLi	95
2	**260**	**262**	Me	MeLi	92
3	**230**	**263**	*sec*-Bu	*sec*-BuLi	80
4	**260**	**264**	*sec*-Bu	*sec*-BuLi	88
5	**230**	**265**	*tert*-Bu	*tert*-BuLi	90
6	**260**	**266**	*tert*-Bu	*tert*-BuLi	90

The hemiaminals **261-264** exemplify some of the most sterically hindered tetrahedral intermediates isolated to date. Although, it is possible that these structures exist in equilibrium with the corresponding amino ketones the presence of the hemiaminal form is supported by NMR and IR spectra. The major species observed by NMR was characterized by the presence of a typical to hemiaminal ^{13}C NMR resonance about 86-88 ppm. In addition, the ketone peak was not detected in ^{13}C NMR. In only two instances were marginal peaks corresponding to the CO group visible in IR spectra (the presence of these peaks could also suggest that the hemiaminal and the amino ketone exist in a dynamic equilibrium).[291] Although, in theory, equilibrium between hemiaminal and amino ketone was also possible in the transannular amino-*tert*-butylketones **265** and **266**, in these cases only carbonyl peaks were observed. Overall, these results indicate that the steric contribution can override the inherent stability of tetrahedral intermediates provided by the scaffolding effects. We also determined that the tricyclic amide **260** affords a clean addition product in reaction with $TMSCH_2Li$, indicating that nucleophilic addition reactions to bridged amides depend on the degrees of twist of the amide bond (see Table 36 for details).

To compare the reactivity of distorted and planar amides we subjected selected fused amides (obtained as complementary products to the bridged amides in the Schmidt reactions) to analogous reactions with organometallic reagents (Scheme 94). The reaction of planar bicyclic amide **267** with MeLi (3.0 equiv) afforded enamine **268** (Scheme 94a, the structure confirmed after reduction to **269**, stereochemistry not determined). The dehydration[292] was not general; for example,

addition of *n*-BuLi to **267** resulted in a complex mixture of products including starting material, ketone, enamine, and alcohol. Similarly, the reaction of a tricyclic fused amide **270** with MeLi afforded inseparable 3:1:1 mixture of enamine **271**, ketone **272**, and alcohol **273** (Scheme 94b). Subsequent reduction furnished amine **274** (stereochemistry not determined). Furthermore, we determined that in the case of planar amides, the reaction time was longer than with the bridged lactams (for example, after 3 h of the reaction with MeLi, bridged **34** >95% conversion vs. fused **267** ~70% conversion). Overall, these results exemplify the effect of the amide bond distortion on the outcome of the nuclophilic addition reactions to amide bonds.

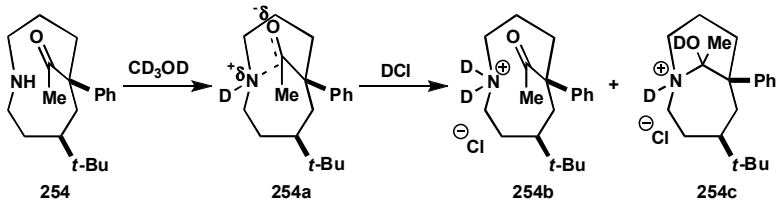
Scheme 94



Although, the hemiaminal corresponding to **254** (Table 26) was in equilibrium favoring the corresponding amino ketone, we hypothesized that the conformation of the 9-membered ring should favor the placement of the reactive nitrogen and ketone groupings on the same side of the ring. This hypothesis was confirmed when we

found that upon treatment of **254** with MeOD-d_4, a transannular N···C=O interaction took place (Scheme 95). Thus, the ^{13}C NMR spectrum of **254** in chloroform exhibited one set of sharp signals, with a peak at 211 ppm corresponding to the methyl ketone carbonyl. Upon dissolution in methanol this signal was no longer present and other peaks were significantly broadened. We ascribed this phenomenon to the N···C=O interaction affording a pseudo-tetrahedral hemiaminal-type carbon, adopting a hybridization state between sp^2 and sp^3 (**254a**). Addition of DCl terminated the equilibrium, affording 9:1 mixture of protonated amino ketone **254b** and hemiaminal **254c**. We determined that a similar interaction does not occur upon dissolution of **254** in C_6D_6 and CD_3CN. However in DMSO-d_6 minor quantities of aminal **254c** are formed. In addition, when more sterically hindered ketones **256** and **257** were treated with MeOD-d_4 the transannular effect was not observed, indicating the role of steric influence on the proposed N···C=O interaction.

Scheme 95



The observation that N···C=O interaction is favored in polar media is in agreement with previous findings.[209] This is, however, the first illustration of a continuum of change in a single system: from hemiaminal **238** (stable tetrahedral

intermediate) to amino ketone **254** (collapsing tetrahedral intermediate) through N···C=O interaction (**254a**, MeOD-d_4). This picture also includes a progressive change from hemiaminals **261-264** (stable tetrahedral intermediates) to amino ketones **265** and **266** (unstable tetrahedral intermediates).

The difference in stability between the hemiaminal collapsing to amino ketone **254** (Table 26) and the stable hemiaminal **261** (Table 27) could reflect the increased scaffolding effect gained by the presence of the additional cyclohexene ring in **261**. However, it could also arise from a difference in distortion parameters of the two parent amides. We previously found that the tricyclic lactam **229** is characterized by twist angle $\tau = 51.5°$,[54] while a representative bicyclic lactam **35** is slightly less distorted, and characterized by $\tau = 43.2°$.[226] The influence of distortion parameters on the reactivity of bicyclic and tricyclic amides and comparison of their reactivity will be discussed in the final part of Chapter 3.

Overall, these results demonstrate that tetrahedral intermediates formed in the addition of nucleophiles to one-carbon medium-bridged twisted amides exhibit remarkable proximity-induced stability. One-carbon bridged amides can serve as models to delineate the transition from stable tetrahedral intermediates, through N···C=O interactions, to unstable tetrahedral intermediates. The comparison of reactivity of bridged and planar lactams highlights the role of amide bond geometry on the reactivity in nucleophilic addition reactions.

Corey-Chaykovsky Reaction of Bridged Amides. The epoxide is one of the most useful functional groups in organic chemistry.[293] Epoxides are essential structural motifs in many biologically active natural products. Due to the ease of opening, often with high regio- and enantiocontrol, epoxides have been utilized as versatile precursors in the synthesis of complex targets.[294-298] Given the importance of this functional group, numerous researchers have been engaged in the application of novel heteroatom substituted variants of traditional epoxides. For example, alkoxy-substituted epoxides developed by Danishefsky are especially useful as intermediates in carbohydrate synthesis.[299-301] However, the analogous aminoepoxides have received much less attention, primarily since their stability is compromised by the nitrogen-assisted ring opening and polymerization.[302-307] Very few examples of stable epoxyamines are known (Figure 18).

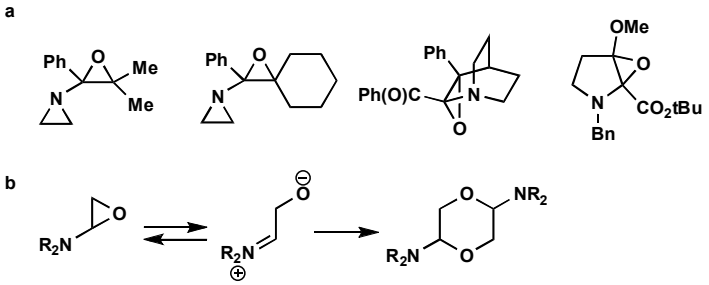


Figure 18. (a) Examples of isolable aminoepoxides. (b) Common decomposition pathway of unmodified aminoepoxides.

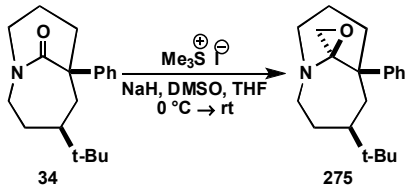
One attractive strategy to improve the stability of aminoepoxides is to limit the delocalization of nitrogen n electrons into a $\sigma^*_{C\text{-}O}$ orbital. This can be achieved by incorporating the aminoepoxide into a rigid ring system. Such an approach was utilized by Stevens in a seminal examination of aminoepoxides,[302-304] in which inherent strain of aziridines was exploited to inhibit the epoxide opening (Figure 18a, first two examples). However, this method was limited to aminoepoxides containing aziridine rings. A different approach would utilize basic scaffolds of bridgehead enamines and bridged amides, compounds that feature diminished conjugation between the nitrogen and C=C or C=O π systems. However, the oxidation of enamines can be complicated by competing N-oxide formation and elimination reactions.[307] In addition, a very limited number of bridged enamines are known.

In this context, epoxidation of much more easily-accessible bridged amides seemed to be a particularly attractive method, especially since we had already demonstrated that one-carbon bridged amides differ markedly in properties from planar amides and can undergo reactions more commonly associated with ketones rather than amides.[308]

Our investigations began with amide **34**, readily available from the intramolecular Schmidt reaction (Table 28). We found that when **34** was exposed to dimethylsulfonium methylide under Corey-Chaykovsky conditions,[309-311] the spiro-epoxyamine **275** was formed in excellent yield (Table 28, entry 2). Very importantly, the resulting aminoepoxide was stable to the reaction and chromatographic isolation conditions, and could be stored over long periods of time without detectable

decomposition. To the best of our knowledge, such a direct amide epoxidation reaction is without precedent. This transformation provided further evidence for the increased reactivity of the twisted amide carbonyl group, and a consequence of a limited overlap of the lone pair of electrons of the amide nitrogen and the carbonyl systems. In a similar vein, the decreased $n_N \rightarrow \sigma^*_{C\text{-}O}$ delocalization is responsible for the stability of the aminoepoxide **275**.

Table 28. Corey-Chaykovsky Reaction with Amide **34**.



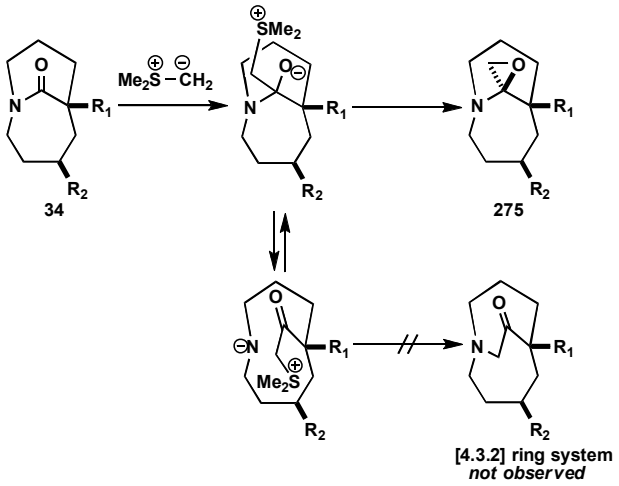
entry	equiv		time	conc.	conversion	yield
	NaH	Me_3SI	[h]	[M][a]	[%][b]	[%][c]
1	5.0	2.0	15	0.005	81	nd
2	7.0	2.5	17	0.005	>95	75
3	20.0	5.0	24	0.005	>95	80
4	7.0	2.5	18	0.007	>95	0
5	7.0	2.5	18	0.005	>95	53
6	7.0	2.5	18	0.004	>95	73
7	7.0	2.5	19	0.005	>95	78
8	7.0	2.5	18	0.003	>95	88

[a] See experimental section for details. [b] Determined by ^{1}H NMR.
[c] Isolated yield. nd = not determined.

Interestingly, the epoxidation proved to be very dependent on the concentration of the reaction (Table 1, entries 4 and 5). Even slight increases in the concentration led to the complete decomposition of the reaction components. In

addition, monitoring of the reaction by NMR revealed a reaction $t_{1/2}$ of ~ 5 h.[312] This is consistent with the initial fast addition of the methylide to the amide bond. We think that the resulting zwitterion exists in the equilibrium with the ring-opened 9-membered heterocycle, which is destabilized due to a transannular interaction between the amine and ketone groups (Scheme 96).[54]

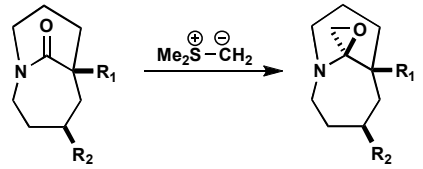
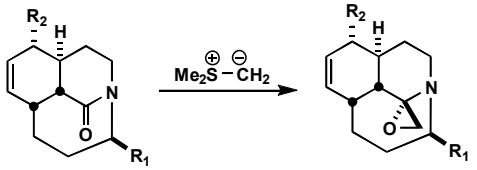
Scheme 96



We next examined the scope of this Corey-Chaykovsky reaction by varying the substituents and the ring systems of bridged amides (Table 29). Both substitution with a heteroatom in the α position and removal of the bulky *tert*-butyl group also permit isolation of spiro-epoxyamines in very good yield (entry 2). Remarkably, even the hydrolysis-sensitive α-unsubstitued bridged amide **3** could be used to deliver isolable aminoepoxide (entry 3). Although the thiomethyl analogue was incompatible with the polar solvent system, resulting in the polymerization of the aminoepoxide

product, we found that the use of modified conditions allowed for isolation of the sensitive epoxide **241** (entry 4). However, a carbon-higher homologue of **241** ([5.3.1] ring system) did not undergo the epoxidation reaction. Tricyclic amides can also be employed to access spiro-epoxyamines. Substitution with aromatic rings and protected alcohols is tolerated (entry 5 and 6). The double bond is not required for the reaction (entry 7). Finally, increased steric hindrance close to the reactive amide bond did not have any influence on the facility of aminoepoxide formation (entry 8).

Table 29. Scope of the Corey-Chaykovsky Reaction.

entry	amide	product (yield, %)
		
1	(**34**), R_1 = Ph, R_2 = *t*-Bu	**275** (88)
2	(**73**), R_1 = SPh, R_2 = H	**276** (81)
3	(**3**), R_1 = H, R_2 = *t*-Bu	**277** (41)
4	(**58**), R_1 = SMe, R_2 = *t*-Bu	**278** (89)
		
5	(**229**), R_1 = H, R_2 = 4-BrC_6H_4	**281** (70)
6	(**279**), R_1 = H, R_2 = $(CH_2)_2OBn$	**282** (73)
7	(**280**), R_1 = H, R_2 = H[a]	**283** (77)
8	(**260**), R_1 = *i*-Pr, R_2 = H	**284** (70)

[a] Compounds **280** and **283** lack the olefin.

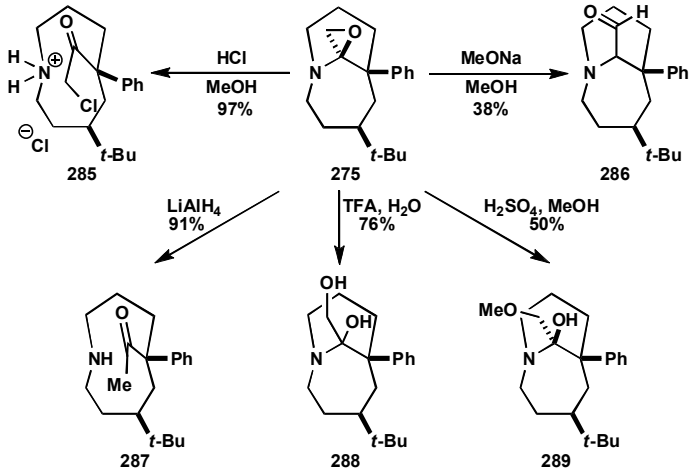
We have also attempted Corey-Chaykovsky epoxidations using a number of other sulfur ylides, including dimethylsulfoxonium methylide,[309] diphenylsulfonium ethylide,[313] diphenylsulfonium cyclopropylide,[314] tetrahydrothiophenium 1-carbomethoxylide[315] and benzylide[316, 317] under variety of conditions. However, the formation of the corresponding epoxyamines were not observed. In most cases, analysis of the reaction mixtures indicated only the presence of starting materials, although decomposition was also noticed in several instances. In these reactions, the addition of ylides to amide carbonyls is complicated by (1) lower nucleophilicity of the ylides relative to dimethylsulfonium methylide and (2) their decreased stability.[312] In such cases, the resulting zwitterions may sometimes be formed, however the zwitterions revert to the starting materials instead of undergoing the rearrangement to spiro-epoxyamines. Alternative routes to aminoepoxides, including addition of chloromethyl TMS[318] and bromomethyl anions[319] to bridged amides were unsuccessful. Given the stability of bridged aminoepoxides, epoxidation of now easily accessible bridged enamines (see Table 34) could provide an attractive alternative.

As expected, the twist of amide bonds is important for the Corey-Chaykovsky reaction. As evidenced by spectroscopic properties, bridged amides having [5.3.1] ring are less distorted than amides having [4.3.1] ring system. The behavior of the latter scaffolds is consistent with less “amide-like” and greater “ketone-like” nature of the carbonyl group (see also Scheme 90).

A vital factor allowing for the epoxidation of one-carbon bridged amides is their superior hydrolytic stability as compared to other twisted amides, for example 2-quinuclidone derivatives. Under Corey-Chaykovsky reaction conditions, quinuclidone-based twisted amides would be expected to undergo hydrolysis to amino acids or collapse after ylide addition. Transannular interactions between amine and ketone groups in these systems are much weaker than in 9-membered heterocycles, in which the ketone is placed at the carbon adjacent directly to the ring.

Having established a general route to bridged spiro-epoxyamines, we probed the reactivity of this new class of compounds, using epoxide **275** as a test substrate. In particular, we were curious whether the reactivity of bridged aminoepoxides would correlate with traditional epoxides. Initial experiments are shown in Scheme 97.

Scheme 97

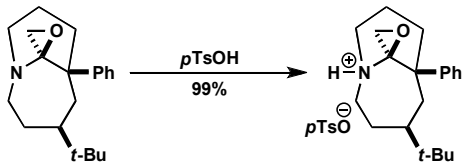


Among the most synthetically useful reactions of epoxides are ring opening under acidic, basic and reductive conditions.[294] Thus, exposure of **275** to hydrochloric acid resulted in the selective epoxide opening at the less substituted carbon, however the following collapse of the bicyclic ring system is highly unusual (Scheme 97, **286**). Treatment with bases led to a 1,2-hydride shift to provide unstable aldehyde **287**. We think that in this case the epoxide opening is reversible due to a close proximity of the alkoxide and the methoxy leaving group, affording the thermodynamically favored product. The reduction of **275** resembled the opening under acidic conditions, involving the final collapse of the bicyclic aminal **287**.

The bicyclic structure can be retained, for example upon exposure to trifluoroacetic acid to give the aminodiol **288** or upon treatment with methanol/aqueous acid to furnish the aminohydroxy ether **289**. Especially interesting is the stability of the latter (characterized by the resonance of the hemiaminal carbon at 96.5 ppm in ^{13}C NMR). It suggests that when the XCH_2 group (where X is an electronegative atom) is added to the bicyclic bridged amides instead of an alkyl group (see for example **287** or **255**), the resulting hemiaminals do not collapse as readily to the corresponding open-form analogues.

Furthermore, we determined that aminoepoxides undergo reactions at nitrogen with preservation of the epoxide structure as exemplified by N-protonation with *p*TsOH (Scheme 98).

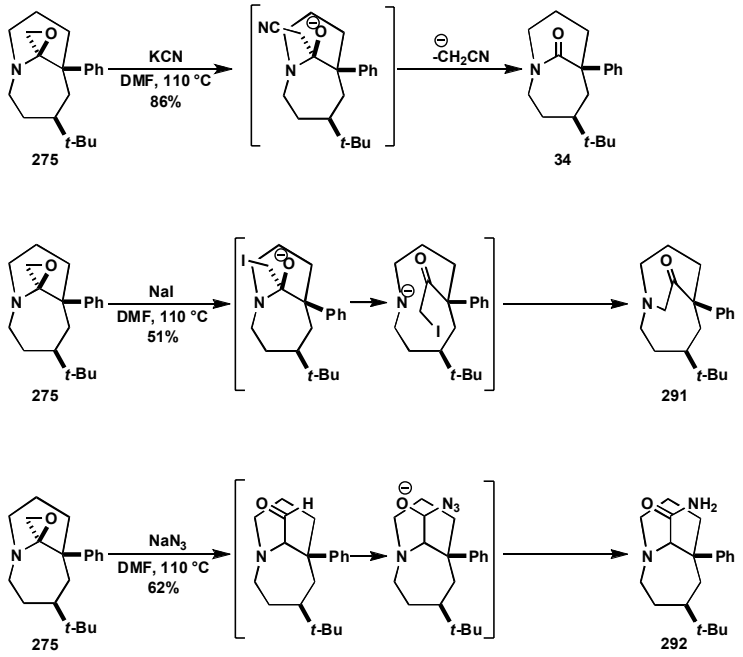
Scheme 98



275 290

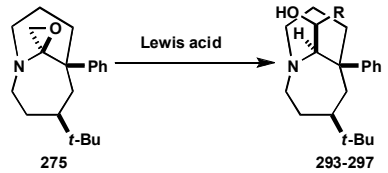
The stability of bridged aminoepoxides allowed for a number of thermal manipulations to confirm their unusual reactivity profile (Scheme 99). When **275** was subjected to KCN, the bridged amide **34** was obtained; the use of NaI under similar conditions afforded the bicyclic **291**. In addition, when heated to higher temperatures, **275** underwent a 1,2-hydride shift to provide aldehyde **286** (not shown, $PhCH_3$, 200 °C, 81%), while exposure to NaN_3 resulted in the rearrangement to the primary amide **292**. This reaction proceeds most likely via rearrangement to aldehyde, azide addition and Schmidt reaction. The proposed intermediates involved in each of these transformations are shown in Scheme 99.

Scheme 99



Next, we established that bridged spiro-epoxyamines participate in a number of Lewis acid-catalyzed reactions not typical to traditional epoxides (Table 30). For example, upon exposure of **275** to Et_2AlCl or Me_2AlCl conversion to aldehyde and subsequent alkyl transfer was observed (Table 30, entries 1 and 2). When additives such as TMSCN and Et_3SiH were utilized, closely-related derivatives were formed after the rearrangement to the aldehyde (entries 4 and 5), while acid change to $MeAlCl_2$ resulted in the formation of a Friedel-Crafts product (entry 7, Scheme 100). In contrast, it is well-precedented that when traditional epoxides are exposed to alkylaluminum compounds, they undergo a direct alkyl transfer.[320-326]

Table 30. Reactions of **275** under Lewis Acidic Conditions.

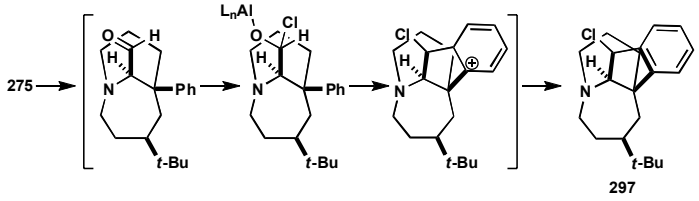


275 293-297

entry	acid/additive	R	yield [%]
1	Et_2AlCl	Et (**293**)	92
2	Me_2AlCl	Me (**294**)	58
3	Me_3Al	Me (**294**)	45
4	Et_2AlCl/TMSCN	CN (**295**)	70
5	Et_2AlCl/Et_3SiH	H (**296**)	56
6	Et_2AlCl/allylTMS	Et (**293**)	87
7	$MeAlCl_2$	Ar[a] (**297**)	68
8	$BF_3•Et_2O$	H, (CHO)[b] (**286**)	0

[a] Friedel-Crafts product, see below. [b] Aldehyde is the expected product of this transformation, see SI for details.

Scheme 100

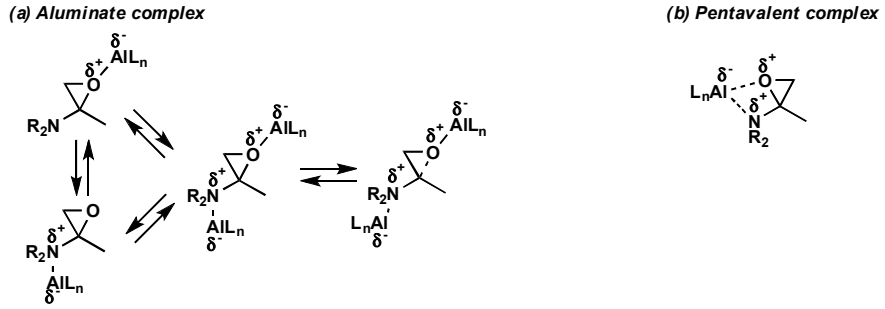


Interestingly, although $BF_3•Et_2O$ is the most common Lewis acid used for the transformation of epoxides into carbonyl groups,[327-332] and it has even been suggested that "no epoxide is insensitive" to this reagent,[333] we have determined that bridged spiro-epoxyamines are inert to $BF_3•Et_2O$ (Table 30, entry 8).

Although the detailed mechanism of the aluminum-promoted rearrangement of bridged aminoepoxides is unknown at present, it is tempting to suggest a dual

activation mode of aminoepoxides by aluminum[334-336] being responsible for their unusual reactivity (Scheme 101b). It is also possible that the aluminate complex with the acid coordinating to the oxygen and/or nitrogen is formed, and that one of these intermediates is prone to the rearrangement (Scheme 101a). Further studies will be necessary to elucidate the role of Lewis acids in reactions with spiro-epoxyamines.

Scheme 101



In addition, to the above examples we attempted a number of other reactions, however the epoxyamine **275** was either unreactive or decomposed under the reaction conditions. Selected results are summarized in Table 31.

Table 31. Additional Reactions of Amino-epoxide **275**.

entry	reagent	conditions	result/notes
1	NaN_3	NH_4Cl, EtOH/H_2O, 6 h, Δ	a
2	H_2O	90 °C, 5 h	decomposition
3	KOH	DMSO, 90 °C, 20 h	decomposition
4	MeONa	DMF, 110 °C, 16 h	b
5	thiourea	$NaHCO_3$, MeOH, rt, 18 h	no reaction
6	allylamine	EtOH, 50 °C, 17 h	no reaction
7	allylamine	$LiClO_4$, 120 °C, 21 h	decomposition
8	MeI	CH_2Cl_2, 60 °C, 22 h	c
9	MeLi	-78 °C → rt, 16 h	no reaction
10	*t*-BuLi	-78 °C → rt, 16 h	no reaction
11	LDA	-78 °C → rt, 16 h	no reaction
12	*sec*-BuLi, sparteine, TMSCl	-90 °C, 3 h	no reaction
13	*n*-BuLi, BF_3.Et_2O	-78 °C → rt, 5 h	no reaction
14	*n*-BuLi, CuCN	-20 °C → rt, 5 h	no reaction
15	$LiCH_2CO_2Li$	THF, 60 °C, 15 h	no reaction[d]
16	dimethylmalonate/NaH	MeOH, 60 °C, 15 h	e
17	EtMgBr	THF, 60 °C, 15 h	f
18	CH_3CO_2tBu, LDA, Et_2AlCl	-20 °C → rt, 5 h	no reaction
19	Cp_2TiCl_2Zn	THF, rt, 0.5 h	no reaction
20	$AlCl_3$	rt, 15 h	g
21	$TiCl_4$	rt, 15 h	h

[a] Traces of the desired azidohydrin. [b] <10% conversion to the aldehyde. [c] Methylation, followed by ring opening, similar to **285**, see the experimental section for details. [d] Partial decomposition was observed. [e] 50% conversion to aldehyde. [f] 70% conversion to aldehyde. [g] The chlorohydrin was formed. [h] Complex mixture of products, including the aldehyde.

In conclusion, we have discovered an unprecedented Corey-Chaykovsky reaction that permits the direct epoxidation of twisted amides. This method allows for

preparation and isolation of bridged aminoepoxides, compounds which, as correctly suggested (and pioneered in reactions with aziridine-derived aminoepoxides) by Stevens 40 years ago,[302-304] display reactivity divergent from traditional epoxides. The generality of this approach was demonstrated by the application to a range of bicyclic and tricyclic bridged amide substrates. We expect that spiro-aminoepoxides will find their application in target- and diversity-oriented synthesis.

Synthesis and Rearrangement of a Bridged Thioamide. Thioamides often appear in biologically active molecules[337-342] (Figure 19) and are useful synthetic intermediates.[187, 343-351] In particular, thioamides as close isosteres of amide bonds, have found widespread application in peptidomimetics, drug design and synthesis of metal complexes where they often have beneficial effects compared to typical amide linkages. Thioamides as more reactive analogues of amide bonds, have been utilized extensively in natural product synthesis, conformational control, and preparation of nitrogen-containing heterocycles.

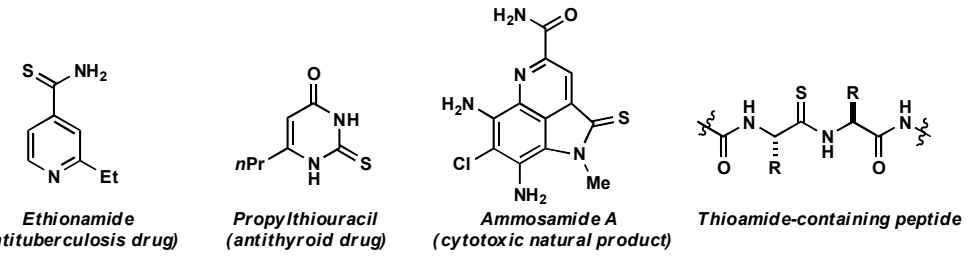


Figure 19. Biologically relevant thioamides.

Thioamides are also of fundamental theoretical interest. Experimental and theoretical studies have shown that in addition to the larger van der Waals radius of sulfur, the C=S bond in thioamides is longer than the corresponding C=O bond in amides.[352] The sulfur atom is a weaker hydrogen-bond acceptor and the N–H bond in thioamides is a stronger hydrogen-bond donor than those atoms in the corresponding amides.[353] Also, the barrier of rotation around the C(S)–N bond in thioamides is higher than the barrier of rotation around C(O)–N bond in amides.

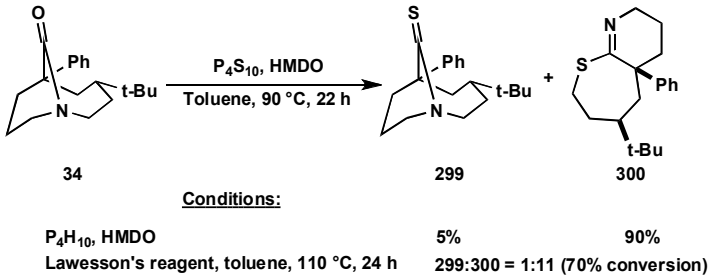
This difference results from the increased contribution of the dipolar canonical structure in thioamides.[354-356] Consequently, thioamides exhibit higher preference for a planar geometry than amides.

Although non-planar lactams, as discussed above, have attracted considerable attention, no examples of bridged thioamides have been reported. Note, however that due to a large van der Waals radius of sulfur, thioamides have been used to increse twist angles of amide bonds by steric repulsion approach.[49, 357, 358] Bridged thioamides would be expected to extend the already unusual reactivity profile of bridged lactams. Synthesis of bridged thiolactams is also important from theoretical perspective and offers a potential to test bridged thioamides in medicinal chemistry as amide bond isosteres. Given our successful efforts in exploring the synthesis and reactivity of non-planar bridged lactams, we wished to prepare a bridged thiolactam analogue, and investigate its reactivity in comparison with bridged amides as well as planar thioamides.

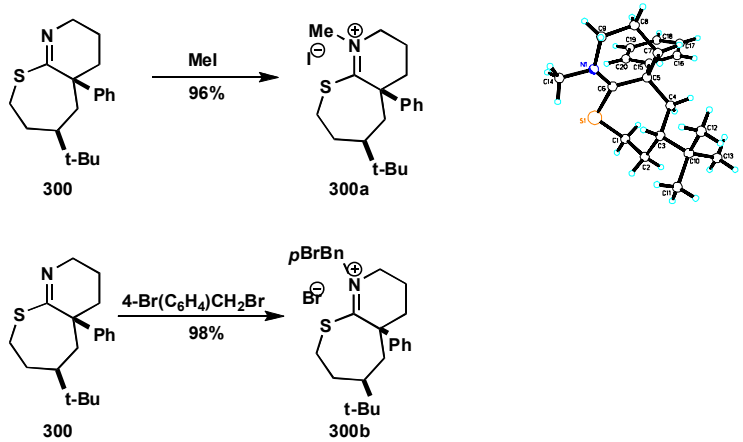
Most commonly, the preparation of thioamides involves the thionation of amides with two reagents: phosphorus pentasulfide[359] and Lawesson's reagent.[360] Accordingly, our study started with the thionation of the readily available lactam **34** (Scheme 102). We found that upon exposure of lactam **34** to 0.25 equiv of P_4S_{10} and 1.7 equiv of HMDO (Curphey reagent), two compounds were formed in very good overall yield. The minor product was identifed as the desired thiolactam **299**, exhibiting lower polarity than the oxygen analogue and characterized by the expected spectroscopic properties (more downfield shift in ^{13}C NMR, 225 ppm for

thiolactam C=S vs. 184 ppm for lactam C=O, and very similar ^{1}H NMR spectrum to the bridged lactam). The major product, however, showed puzzling spectroscopic characteristics, and could be identified as the rearranged product **300** only after conversion to the methylated analogue **300a** and X-ray crystallographic analysis of this derivative (Scheme 103).[361] Contrary to expectations, *p*-bromobenzyl salt **300b** was not crystalline.

Scheme 102



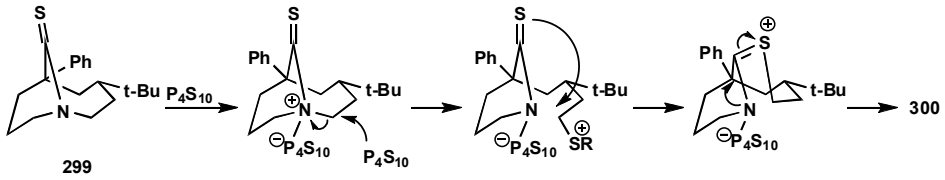
Scheme 103



The proposed mechanism for the rearrangement of **34** to **300** is presented in Scheme 104. We think that **299** is an intermediate in the formation of **300**. Thus, electrophilic activation of the nitrogen of the bridged thioamide with phosphorus pentasulfide can allow for intermolecular attack of sulfur on the C−N adjacent to the bridged amide bond. The following nucleophilic displacement by the thioamide sulfur and tautomerization provides the final product. Although alternative mechanisms can be proposed (for example, the intramolecular attack of the thioamide sulfur on the C−N bond or the cleavage of the C−N bond of the bridged amide, with the following thionation and reclosure), a number of observations supports the pathway in Scheme 104. First, resubjecting thioamide **299** to the reaction conditions results in conversion to the product **300**. Second, when **299** is exposed to thermal conditions in the absence of the thionating reagent, no reaction occurs. From inspection of molecular models, it seems unlikely that the thioamide sulfur can position itself in the backside arrangement for the direct S_N2 attack necessary for the intramolecular reaction.

The observed cleavage of the C−N bond in **299** is closely related to the hydrogenolysis reaction of tricyclic and bicyclic bridged lactams, in which breaking of C−N bond adjacent to the strained amide bond was observed.[31] The rearrangement of the thioamide **299** further confirms novel reactivity profile of bridged lactams.

Scheme 104



We also briefly examined the influence of the reaction conditions on this reaction (Table 32). Thus, the shortening of the reaction time does not significantly improve the yield of the bridged thiolactam. Interstingly, the use of larger excess of thionating agent supresses the formation of the thiolactam. HMDO is not necessary for the reaction, however in its absence the yield of **3** is decreased. As proposed by Curphey,[359] the beneficial effect of the HMDO additive is to supress the electrophilicity of the polythiophosphates. Lawesson's reagent can also be utilized; however, the reaction is much slower.

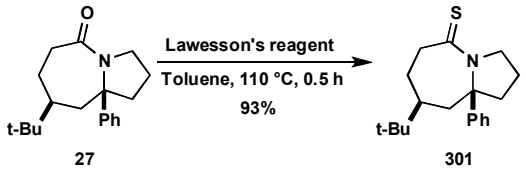
Table 32. Influence of Reaction Conditions on Thionation of **34**.

entry	reagents	conditions	**299**:**300**	yield [%]
1	$P_{10}S_{10}$/HMDO (0.25/1.7 equiv)	toluene, 90 °C, 6 h	<5:95	79[a]
2	$P_{10}S_{10}$/HMDO (0.25/1.7 equiv)	toluene, 90 °C, 3 h	n.a.	13[b]
3	$P_{10}S_{10}$/HMDO (1.3/7.5 equiv)	toluene, 90 °C, 15 h	<5:95	93[a]
4	$P_{10}S_{10}$/HMDO (1.3/7.5 equiv)	toluene, 90 °C, 2 h	1:3	40[c]
5	$P_{10}S_{10}$ (5.0 equiv)	toluene, 90 °C, 15 h	<5:95	76[a]

[a] Isolated yield of **300**; [b] Isolated yield of **299**; [c] Combined yield; n.a. = not available; <5:95 indicates that **299** was not observed by ^{1}H NMR of the crude reaction mixture. Note: no conversion was observed at lower temperatures, or in CH_2Cl_2, THF solvents.

In general, the lactam carbonyl group is the most easily thionated of the common carbonyl derivatives, while the thionation of ketones is often problematic. Thus, it was of interest to compare the reactivity of bridged amides (compounds which display properties on the border between amides and ketones) with traditional planar amides. We determined that, while the thionation of the bridged amide **34** proceeded relatively slowly with Lawesson's reagent, the thionation of the fused analogue **27** was rapid (Scheme 105). In addition, no reaction was observed when less distorted higher homologues of the amide **34** were used (for example, lactam **93** having a [5.3.1] ring system and lactam **203** with a [5.2.1] ring system), suggesting that the N-activativion is required for the thionation of bridged amides. As expected, the twist of the amide bond is important for the thionation, and in cases where N-activation cannot occur, steric hindrance around the bridged structure prevents the reaction. There are very few examples of thionation of sterically hindred planar amides. It is very likely that the direct thionation of bridged amides will be possible with the same ring scaffolds that undergo cleavage of C–N bond under the hydrogenolysis conditions.

Scheme 105



27 301

One of the goals of our study was to explore the effect of amide twist on the spectroscopic properties. For example, we demonstrated that non-planar amides often display spectral features consistent with less "amide-like" and greater "ketone-like" nature of the carbonyl group (Table 19).[257] As outlined in Table 33, the bridged thioamide **299** also follows a similar pattern, with the bridged thiolactam carbonyl deshielded by 25 ppm in ^{13}C NMR as compared to the planar fused thioamide **301** (Table 33, entry 2 and 4). This value is consistent with a decreased conjugation $N_{lone\ pair}$–thiocarbonyl grouping and indicates a consderable degree of twist. The difference of carbonyl shifts between bridged analogues **34** and **299** is practically midway (41.1 ppm) between the values for ketones **302** and **303** (55.6 ppm) and fused amides **27** and **301** (28.1 ppm). Accordingly, we have determined that bridged lactams possessing [4.3.1] scaffold lie almost exactly on the keto-amide reactivity border (see below for details).

Table 33. Spectroscopic Properties of Bridged and Planar Lactams and Thiolactams in Comparison with Structurally-Related Ketones and Thioketones.

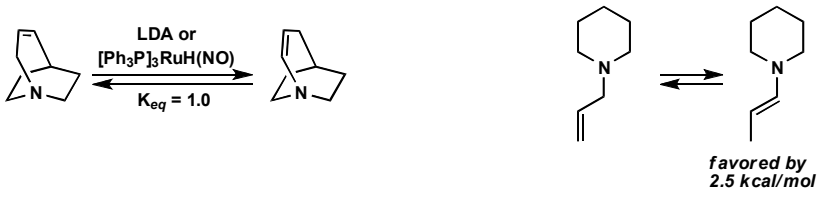
entry	compound	C=O or C=S ^{13}C NMR [ppm]	$\nu_{C=O}$ or $\nu_{C=S}$ IR [cm^{-1}]	Δ [a] [ppm]
1	**34**	184.4	1670	-
2	**299**	225.5	1491	41.1
3	**27**	172.4	1635	-
4	**301**	200.5	1470, 1443	28.1
5	Cycloheptanone (**302**)	205.8	1702	-
6	Cycloheptathione (**303**)	261.4[362]	-	55.6

[a] Δ = (^{13}C NMR δ C=S - δ C=O), entry 2 **299** - **34**, entry 4 **301** - **27**, entry 6 **303** - **302**.

In summary, a synthesis of the first bridged thiolactam and an unusual rearrangement of this compound has been investigated. The rearrangement of the bridged thiolactam confirms that C−N bond adjacent to twisted amides can undergo interesting strain-activated chemistry. Further work aimed at improving the facility of the bridged thioamide formation and at studying its chemical behavior is necessary, however these results are the first step towards the use of bridegd thioamides in chemistry and biology.

Bridged exocyclic enamine. In an attempt to extend the synthetic utility of one-carbon bridged amides we considered olefination of the bridged amide carbonyl. Enamines are recognized as valuable synthetic intermediates,[363, 364] with Stork enamines[365] and enamines in organocatalysis[366] being some prominent examples. In contrast to planar enamines, which due to delocalization of nitrogen lone electrons into the alkene □ system are nucleophilic at carbon, bridged enamines are expected to behave as more or less isolated amino-olefins. For example, Doering[367] demonstrated that the enamine constrained in [2.3.2] ring exits in the equilibrium with the corresponding allylamine (Scheme 106). However, there is very few examples of bridged enamines described in literature and most of them are based on quinuclidone skeleton (Figure 20).[65, 166, 368-373]

Scheme 106



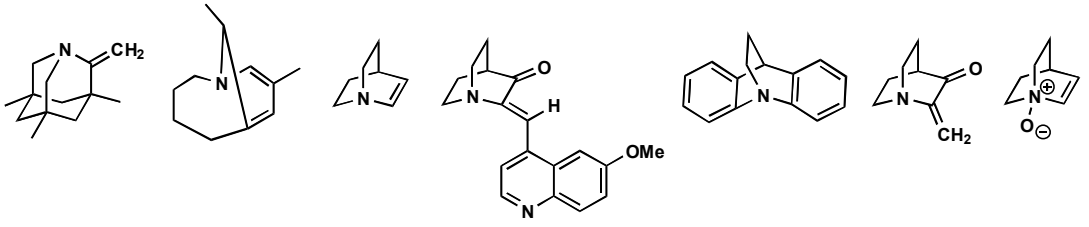
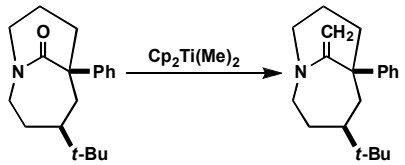


Figure 20. Examples of bridged enamines and their derivatives.

After some experimentation, we determined that exposure of bridged amide **34** to Petasis olefination conditions[374-378] is a convenient method for preparation of the bridged exocyclic enamine **304** (Table 34). Optimization of reaction conditions revealed that the enamine decomposes under the reaction conditions (entries 3 and 4). The use of pyridine as an additive to suppress the decomposition pathways proved beneficial (entry 5). Careful control of the reaction time afforded the desired product in very high yield (entry 7).

Table 34. Optimization of Petasis Olefination of Amide **34**.



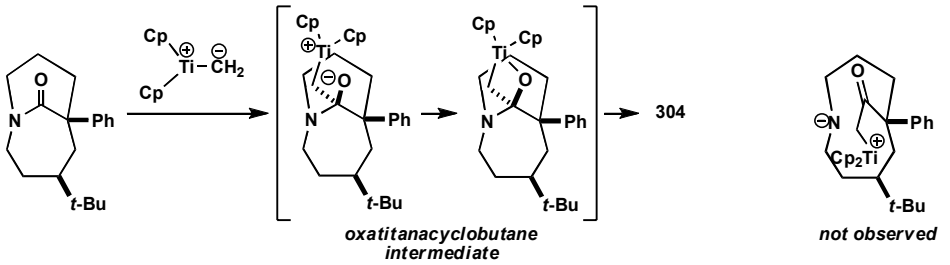
34 **304**

entry	equiv	solvent	temp [°C]	time [h]	conversion[a] [%]	yield[a] [%]
1	5.0	THF	60	12	60	58
2	10.0	THF	66	24	>95	60[b]
3	5.0	$PhCH_3$	80	14	>95	52
4	5.0	$PhCH_3$	80	24	>95	37
5	5.0	$PhCH_3$/pyridine	80	12	85	61
6	5.0	$PhCH_3$/pyridine	105	15	>95	80[b]
7	5.0	$PhCH_3$/pyridine	105	10	>95	95[b]

[a] Determined by ^1H NMR. [b] Isolated. $PhCH_3$/pyridine indicates 100/1 mixture.

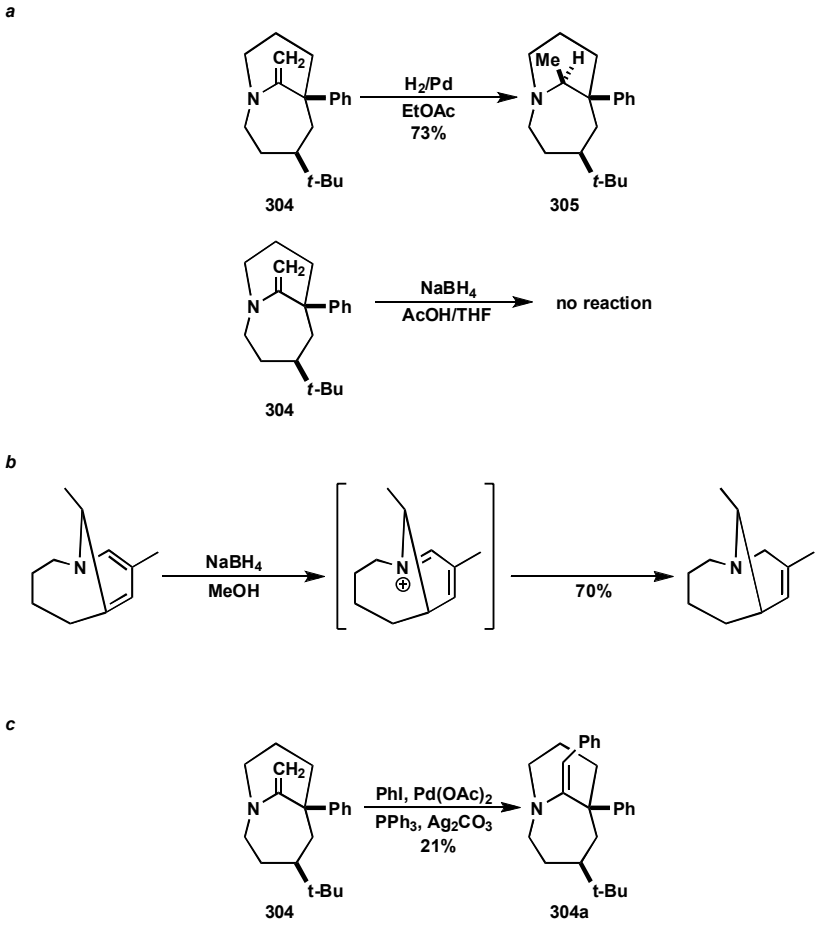
Although planar amides undergo Petasis olefination,[377] to the best of our knowledge this is the first example of a direct olefination of a bridged lactam with a metalloorganic reagent. It is particularly noteworthy that the oxatitanacyclobutane intermediate does not collapse with the opening to the nine-membered ring system (Scheme 107, see also Table 26) and that the bridged enamine was stable to chromatographic purification.

Scheme 107



Initial explorations of the reactivity of enamine **304** confirm that this compound exhibit properties of an isolated amino-olefin. For example, hydrogenation of **304** affords the corresponding methyl analogue **305**, however no reaction was observed upon reduction under acidic conditions (Scheme 108a). This reactivity profile stands in a sharp contrast to the behavior of a bridged endocyclic enamine (Scheme 108b),[368] which was reduced under protic conditions. These results suggest that the electron delocalization in the exocyclic enamine **304** is unlikely.

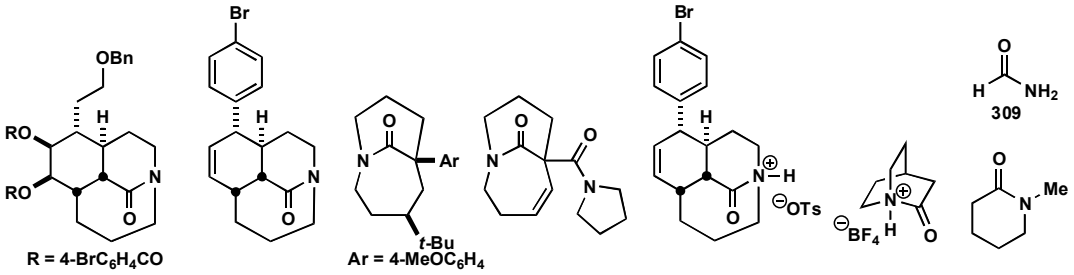
Scheme 108



We expect that the functionalization of the enamine carbon will provide access to bridged compounds that are not easily accessible by other methods. For example, Heck reaction afforded the phenyl derivative in an unoptimized 21% yield (Scheme 108c, olefin geometry not determined).

Miscellaneous Reactions (Comparison of Distortion Parameters). As mentioned in the introductory chapter, the intramolecular Schmidt reaction provides access to tricyclic and bicyclic bridged amides which contain amide bonds from the previously unknown distortion range. Table 35 summarizes distortion parameters of all bridged amides obtained in the Schmidt reaction that have been amenable for X-ray crystallography to date. The table also includes the corresponding values for representative planar and orthogonal amides, and the structural parameters of the N-protonated amide **229**. For additional examples of 2-quinuclidone derivatives, see Table 1.

Table 35. Summary of Structural Parameters of Bridged Amides.



entry	amide	N–C(O) [Å]	C=O [Å]	χ_N [deg]	χ_C [deg]	τ [deg]
1	**306**[b]	1.418	1.212	49.8	7.1	72.4
2a[a]	**229**[c]	1.387	1.217	35.9	13.2	51.7
2b		-	-	35.5	13.0	50.8
3a[a]	**229**[d]	1.387	1.218	36.1	12.8	51.5
3b		1.383	1.221	35.3	13.1	50.8
4	**35**[e]	1.363	1.234	33.8	16.3	43.2
5a[a]	**53**[c]	1.374	1.210	48.0	13.2	34.7
5b		-	-	16.6	13.2	50.4
6	**53**[b]	1.375	1.219	43.7	12.4	35.9
7	**307**[c]	1.503	1.192	52.1	1.5	81.9
8	**308**[f]	1.526	1.192	59.5	0.2	90.9
9	**309**[f,g]	1.349	1.193	0.0	0.0	0.0
10	**309a**[g,h]	1.325	1.233	-	-	2.5

[a]Two independent molecules in the unit cell. [b] Ref. 225; [c] Ref. 189; [d] Ref. 54; [e] Ref. 226; [f] Ref. 26; [g] Calculated; [h] Ref. 166.

Of this series of bridged amides, the most distorted is amide **306** with a twist angle close to the perpendicular amide bond and nitrogen practically pyramidal in character (Table 35, entry 1). At present it is unclear whether the increased distortion of **306** as compared to the amide **229** (entries 2a-3b) is caused by the saturation of the six-membered ring or by the steric repulsion between the amide bond and the *p*-bromobenzoyl moiety. The tricyclic amide **229**, which seems to be representative for the class of tricyclic amides obtained in domino Diels-Alder/Schmidt sequence, is

characterized by τ ca. 50° (entries 2a-3b). This is slightly more than the τ of the bicyclic **35**, which is a good model for the amide bond constrained in a bicyclic [4.3.1] ring system (entry 4). Pyramidalization at nitrogen is similar in **229** and **35**. Interestingly, the distortion parameters of the amide **53** depend on whether its six-membered ring adopts a boat-like (entries 5a and 6) or a chair-like (entry 5b) conformation, and is possibly influenced by crystal packing of **53**.

The N-protonated amide **307** (entry 7) is even more distorted than **306** (entry 1). Note a dramatic increase in the rotation around the C–N bond (τ moves from 51.5° to 81.9°) and the changes in bond lengths upon N-protonation. In **307** the N–C(O) bond experiences significant lengthening (by 0.116 Å), while the C=O bond is moderately shortened (by 0.026 Å).

Comparison of structures in Table 35 indicates that the bond lengths display a good correlation with distortion parameters of amide bonds. Thus, the N–C(O) bond length increases from 1.325Å in planar amide (entry 10) through 1.363 Å and 1.387 Å (entries 4 and 3a) to 1.418 Å (entry 1) and 1.503 Å (entry 7). The last value practically matches the N–C(O) bond length for perfectly perpendicular and protonated 2-quinuclidone. On the other hand, the length of the C=O bond shortens with the increased distortion of amide bonds. The elongated N–C(O) bond and the shortened C=O bond are consistent with the increased twist angle of amide bonds, and result from a lower ability of nitrogen to donate its n electrons into π* orbital of C=O group.

As presented in Table 35 tricyclic bridged amides obtained in the Schmidt reaction are slightly more distorted than their bicyclic analogues; importantly, both classes of compounds contain half-way rotated amide bonds. This provided us with an opportunity to test how the midway rotation of the amide bonds would influence the reactivity of amide bonds. In particular, we wished to estimate the border between an amide-like and keto amine-like reactivity of amide carbonyl groups. Towards this end we performed a number of reactions that are typical to ketones and amines but not to traditional amides. The relevant results are summarized in Table 36.

Table 36. Reactions of Bicyclic and Tricyclic Bridged Amides.

entry	lactam	conditions	result/notes
1	**230**	NaN_3/H_2SO_4	no reaction[a]
2	**230**	*m*-CPBA	no reaction[b]
3	**230**	H_2O_2, Davis oxaziridine	no reaction[c]
4	**34**, **230**	$Ph_3PMeBr/KOtBu$, 110 °C, 24 h	no reaction[d]
5	**34**	n-$C_6H_{13}N_3$, PPh_3, 110 °C, 24 h	no reaction
6	**34**	Dimethylmalonate, NaH, 66 °C, 27 h	no reaction
7	**34**	Ethyl bromoacetate, LHMDS, 66 °C, 24 h	no reaction
8	**34, 230**	TMSCN, KCN, 18-crown-6, 90 °C, 24 h	no reaction[e]
9	**34**	Danishefsky's or Rawal's diene, 170 °C, 24 h[f]	no reaction
10	**34**	$C_3H_5SiMe_3$, $TiCl_4$, 24 h	no reaction
11	**34**	$PhCH_2NH_2$, 110 °C, 20 h	no reaction
12	**229**	$PhCH_2NH_2$, 110 °C, 23 h	imine **310**
13[g]	**53**	$(CH_2OH)_2$, , 80 °C, 48 h	no reaction
14[g]	**230**	$(CH_2OH)_2$, , 80 °C, 48 h	ketal **311**
15	**34**	$TMSCH_2Li$, -78 °C → rt, 3 h	no reaction
16	**260**	$TMSCH_2Li$, -78 °C → rt, 3 h	hemiaminal **312**
17[g]	**229**	MeI, 40 °C	N-methylation
18	**34**	MeI, 160 °C[h]	N-methylation
19	**230**	HCl, *p*-TsOH	N-protonation
20	**3**	HCl, *p*-TsOH	hydrolysis
21	**38**	HCl, *p*-TsOH	hydrolysis[i]

[a] Schmidt reaction was tried under variety of conditions. [b] Baeyer-Villiger reaction was tried under variety of conditions. [c] N-oxide formation was attempted under variety of conditions. [d] Wittig reaction was tried, under various conditions. [e] attempted cyanohydrin formation under variety of conditions. [f] Lewis acid mediated hetero Diels-Alder reactions were also tried. [g] Reference [189]. [h] No reaction at lower temperatures. [i] Starting material was also observed.

As expected, the bridged amides were unreactive under some of the reaction conditions, indicating that 50° distortion of amide bonds is not sufficient for certain carbonyl additions to amide bonds (entries 1-10). However, the half-way rotated lactams also provided examples of some unusual reactivity, indicating that the amide

bond does not need to be perfectly perpendicular to experience reactions typically associated with ketones and amines rather than amides (entries 12, 14, 16-18).

Very importantly, we found a significant difference in reactivity between tricyclic and bicyclic amides, with the tricyclic structures being more reactive than bicyclic analogues. Given that the first class of compounds is more distorted, this provides the first experimental evidence regarding degrees of the amide bond distortion that mark the border between amide-like and ketone-like carbonyl reactivity of lactams. Of particular note are reactions with amines (entries 11 and 12), alcohols (entries 13 and 14), TMS methylide (entries 15 and 16) and MeI (entries 17 and 18). In addition, although Kirby demonstrated that perfectly perpendicular 1-aza-2-adamantanone ($\tau = 90.5°$) undergoes Wittig olefination, twist angle of currently investigated amides did not allow for this reaction; only starting amides were re-isolated (entry 4).

Overall, these results demonstrate that the lactam twist angle of ca. 50° is close to a barrier for carbonyl reactions typically associated with ketones but not amides. A similar amide bond distortion range suffices for efficient N-activation of amide linkages. We expect that these findings will facilitate the understanding of biological and chemical activation of amide bonds.

Summary. The reactivity of one-carbon bridged amides has been investigated. Examination of the hydrolytic stability of bicyclic and tricyclic bridged lactams indicates that one-carbon bridged amides exhibit levels of stability unprecedented to other classes of bridged lactams. This property results from a unique placement of the amide carbonyl at one-carbon bridge located at the center of a medium-sized heterocycle. The stability of one-carbon-bridged amides allows for synthetic manipulations not possible with other distorted lactams.

One-carbon bridged amides undergo facile nucleophilic addition reactions of hydrides and metalloorganic reagents. Remarkably, due to the geometrical constraints imposed by rigid cyclic structures, some of the hemiaminals are isolable. These scaffolds can be used to monitor a transition from stable tetrahedral intermediates to unstable species.

One-carbon bridged amides participate in a direct Corey-Chaykovsky epoxidation; the resulting spiro-epoxyamines are chromatographically stable. Of particular interest is the chemistry of bridged aminoepoxides, which differ significantly from the traditional epoxides.

Other noteworthy compounds prepared from bridged amides include a bridged thioamide and a bridged exocyclic enamine. Furthermore, it has been demonstrated that the lactam twist angle of ca. 50° marks a barrier for certain reactions typically associated with ketones and amines but not amides.

The stability and rich chemistry of one-carbon bridged amides bode well for their use in medicinal chemistry and target and diversity oriented synthesis.

Chapter 4

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 (400 MHz and 100 MHz, respectively) or a Bruker AM-500 (500 MHz and 125 MHz, respectively) instrument. Unless otherwise noted, all samples were dissolved in $CDCl_3$, and the shifts are expressed in parts per million (ppm) relative to residual $CHCl_3$ as an internal standard. Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; br s, broad singlet. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer or a Nicolet Fourier Transform Infrared spectrometer and are expressed in wave numbers (cm^{-1}). Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Low resolution mass spectroscopic data (CI, chemical ionization or FAB^{+}, fast atom bombardment) were obtained with a Ribermag R10-10 quadrupole instrument. High resolution mass spectra were collected using a VG Analytical ZAG double focusing spectrometer. All flash chromatography was performed using Fischer Scientific silica gel (230-400 mesh) with the noted eluent system. Tetrahydrofuran, dichloromethane, and ether were purchased from Fisher Scientific and purified using an Innovative Technologies solvent purification system. All other solvents were used without further purification or drying procedures. Reaction flasks were oven or flame-dried and cooled under vacuum then purged with argon; all reactions were conducted under argon or nitrogen atmosphere unless otherwise noted. Where indicated, microwave heating was

performed in Biotage™ Initiator microwave reactor. All starting material were purchased from Aldrich, Lancaster, Fischer, or Strem chemical companies and used as received. The following compounds are known: azide **1**, fused and bridged lactam **2** and **3**,[188] arylketones **6**[379] and **7**, azides **20** and **21**, bridged and fused lactams **27**, **34**, **28** and **35**,[188] ethyl 5-*tert*-butyl-2-oxocyclo hexanecarboxylate **43**,[380] 4-*tert*-Butyl-2-(methylthio)cyclohexanone **60**,[381] azide **72**,[173] ketone **75**,[382] 2-methylthioketones **86**, **90**, **96** and **103**,[383, 384] N-Allyl-2-nitrobenzenesulfonamide,[385] N-(But-3-enyl)-2-nitrobenzenesulfonamide,[386] 2-Nitro-N-(pent-4-enyl)benzenesulfonamide,[386] Dimethyl 2-allyl-2-(2-bromoethyl)malonate,[387] Methyl allylphenylacetate,[388] Phenyl allylphenylacetate,[389] bridged lactams **229**, **230**, **53**, **231**,[31] bridged lactam **260**,[188] fused lactam **270**,[31] bridged lactams **279** and **280**.[31]

2-aryl-*tert*-butylcyclohexanones were prepared following procedures by Hartwig[390] and Rawal.[391] Ester **43** was prepared following a procedure by Lachia *et al.*[392] using diethyl carbonate in 84% yield. Amide **44** was prepared following a procedure by Hendi *et al.*[393] 2,2-Dimethoxycyclohexanol (precursor to **75**) was prepared following the method by Zacuto *et al.*[394] 2-thiomethylyketones **55**, **86**, **90**, **96** and **103** were prepared following the method of Trost.[395] Dimethyl 2-allylmalonate, Grubbs 1, Grubbs 2 and Hoveyda-Grubbs 2 were purchased from Aldrich and used as received. Fürstner catalyst was purchased from Strem and used as received. All nitrobenzenosulfonamides were prepared by method of Cluzeau *et al*.[385] Phenyl allylphenylacetate was obtained by alkylation of commercially available phenyl phenylacetate following a procedure by Molander.[396]

Cation–π control of regiochemistry in Schmidt reaction.

General procedure for Schmidt Reaction. To a solution of azidoketone (1.0 equiv) in CH_2Cl_2, Lewis or protic acid was added dropwise at 0 °C, the reaction was allowed to slowly warm to rt and was stirred at rt for a specified time. The reaction was cooled to 0 °C, quenched with water (10 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was washed with brine (1 x 20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography afforded the title lactams. Note: typically bridged lactams are less polar and more UV active than fused lactams. These properties are another consequence of the decreased conjugation of the lone pair of electrons at nitrogen with the amide C=O system.

Optimization of Product Distribution in Schmidt Reaction with Azide 1. According to the general procedure azide **1** was reacted with acids specified in Tables 2-4. The reactions were monitored by TLC, and worked-up after consumption of the starting material. Analysis of crude reaction mixtures by ^{1}H NMR indicated ratio of **2** to **3**.

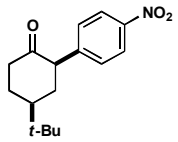
General procedure for arylation.[390] (Synthesis of 2-arylketones **6-12**). To a 100 mL round bottom flask charged with $Pd(OAc)_2$ (0.02 equiv), *t*Bu_3P (0.025 equiv), NaO*t*Bu (1.5 equiv) and THF (20-40 mL), aryl chloride or bromide (1.0 equiv) and *tert*-butylcyclohexanone (1.1 equiv) were added under argon. The flask was sealed and the reaction mixture was heated to 60-65 °C for 18-24 h. The reaction mixture was cooled to rt, diluted with ether (200 mL), washed with water (1 x 50 mL) and

brine (1 x 50 mL). The aqueous layer was re-extracted with ether (2 x 100 mL). Combined organic layers were dried (Na_2SO_4), and concentrated. Flash chromatography afforded the title arylketones. Note: this method did not afford 4-*tert*-butyl-2-(4-nitrophenyl)cyclohexanone (**8**). **8** was prepared following a procedure by Rawal *et al.*[391]

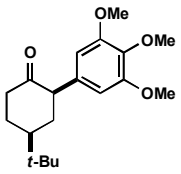
General procedure for alkylation with iodo-chloroalkane. (Synthesis of chlorides **13-19**). To a suspension of NaH (60% dispersion in mineral oil, 1.05-1.10 equiv) in THF (40 mL), HMPA (1.2 equiv) was added and the reaction mixture was stirred at rt for 10 min. After the reaction mixture was cooled to 0 °C, the ketone (1.0 equiv) was added dropwise in THF (5-10 mL). After stirring for 3 h at rt, the chloro-iodoalkane (4.0 equiv) was added at rt, and the reaction was stirred for additional 15 - 18 h. The reaction mixture was diluted with ether (200 mL) and quenched with water (50 mL). The aqueous layer was extracted with ether (2 x 20 mL), and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography afforded the title products.

General procedure for S_N2 displacement with sodium azide. (Synthesis of azides **20-26**). *Caution! Low molecular weight alkylazides are potential explosion hazards and should be used with appropriate caution.* To a solution of chloride (1.0 equiv) in DMF (20-30 mL) NaN_3 (5.0 equiv) was added, and the reaction mixture was heated at 80° C for 2-3 h. Ether (150 mL) was added, and the mixture was washed

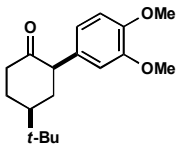
with water (4 x 50 mL) and brine (1 x 50 mL). The organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography afforded the title products.



(2R,4S)-4-*tert*-Butyl-2-(4-nitrophenyl)cyclohexanone (8). P*t*Bu_3 (1.0 M in toluene, 1.20 mL, 0.06 equiv) was added to a mixture of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane (4.5 g, 19.9 mmol, 1.0 equiv), 1-bromo-4-nitrobenzene (2.03 g, 9.9 mmol, 0.5 equiv), $Pd_2(dba)_3$ (0.46 g, 0.51 mmol, 0.025 equiv) and Bu_3SnF (6.15 g, 19.9 mmol, 1.0 equiv) in THF (30 mL) and the resulting mixture was heated to reflux for 13 h. The reaction was cooled to rt, diluted with ether (200 mL), tin residue was removed by decantation, washed with 1.0 *N* NaOH (2 x 50 mL), brine (1 x 50 mL), dried and concentrated. Chromatography (1/15 EtOAc/hexanes) afforded the title compound as solid (Mp = 105-106 °C, R_f = 0.43, 1/10 EtOAc/hexanes). Yield 61% (2.22 g, 8.1 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.59-1.72 (m, 1H), 1.79 (m, 2H), 2.21-2.35 (m, 2H), 2.48-2.64 (m, 2H), 3.72-3.79 (m, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 8.21 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 28.5, 32.6, 36.7, 41.6, 47.3, 56.7, 123.5, 129.8, 146.6, 147.0, 209.1; IR (neat) 2959, 1715, 1518, 1346 cm^{-1}; HRMS calcd for $C_{16}H_{21}NO_3Na$ (M^+ + Na) 298.1419, found 298.1408.

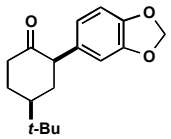


(2R,4S)-4-*tert*-Butyl-2-(3,4,5-trimethoxyphenyl)cyclohexanone (9). Prepared according to the general procedure using $Pd(OAc)_2$ (0.0678 g, 0.30 mmol, 0.02 equiv), tBu$_3$P (0.0762 g, 0.38 mmol, 0.025 equiv), NaOtBu (2.24 g, 22.7 mmol, 1.5 equiv), 4- 5-bromo-1,2,3-trimethoxybenzene (3.83 g, 15.1 mmol, 1.0 equiv) and *tert*-butylcyclohexanone (2.56 g, 16.6 mmol, 1.1 equiv) in THF (40 mL) at 65 °C for 18 h. Chromatography (1/5 EtOAc/hexanes) afforded the title compound as oil. Yield 46% (2.24 g, 7.0 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.58-1.83 (m, 4H), 2.18-2.26 (m, 1H), 2.27-2.35 (m, 1H), 2.46-2.62 (m, 2H), 3.53-3.63 (m, 1H), 3.86 (s, 3H), 3.88 (s, 6H), 6.36 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.5, 32.6, 37.1, 41.7, 47.5, 56.1, 57.4, 60.8, 105.8, 134.8, 136.8, 153.1, 210.5; IR (neat) 2950, 1705, 1585, 1455, 1240, 1120 cm^{-1}; HRMS calcd for $C_{19}H_{28}O_4Na$ (M^+ + Na) 343.1885, found 343.1893.



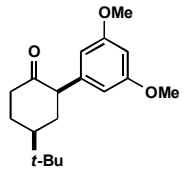
(2R,4S)-4-*tert*-Butyl-2-(3,4-dimethoxyphenyl)cyclohexanone (10). Prepared according to the general procedure using $Pd(OAc)_2$ (0.0420 g, 0.18 mmol, 0.02 equiv), tBu$_3$P (0.0510 g, 0.23 mmol, 0.025 equiv), NaOtBu (1.35 g, 13.7 mmol, 1.5 equiv), 4-bromoveratrole (1.33 mL, 9.1 mmol, 1.0 equiv) and *tert*-

butylcyclohexanone (1.56 g, 10.0 mmol, 1.1 equiv) in THF (40 mL) at 65 °C for 22 h. Chromatography (1/4 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.24, 1/4 EtOAc/hexanes). Yield 52% (1.38 g, 4.8 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.58-1.69 (m, 1H), 1.70-1.83 (m, 2H), 2.17-2.25 (m, 1H), 2.26-2.34 (m, 1H), 2.45-2.61 (m, 2H), 3.58 (q, *J* = 6.9 Hz, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 6.66-6.73 (m, 2H), 6.87 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.6, 32.6, 37.1, 41.7, 47.5, 55.9, 55.9, 56.6, 111.1, 112.1, 120.6, 131.7, 148.0, 148.7, 210.9; IR (neat) 2958, 1715, 1518, 1464, 1259, 1231, 1144, 1028 cm^{-1}; HRMS calcd for $C_{18}H_{27}O_3$ (M^+ + H) 291.1960, found 291.1946.

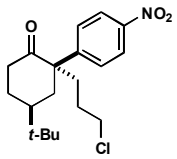


(2R,4S)-2-(Benzo[d][1,3]dioxol-5-yl)-4-*tert*-butylcyclohexanone (Al). Prepared according to the general procedure using $Pd(OAc)_2$ (0.029 g, 0.13 mmol, 0.02 equiv), *t*Bu_3P (0.036 g, 0.16 mmol, 0.025 equiv), NaO*t*Bu (0.95 g, 9.6 mmol, 1.5 equiv), 5-chloro-1,3-benzodioxole (0.76 mL, 6.4 mmol, 1.0 equiv) and *tert*-butylcyclohexanone (1.09 g, 7.0 mmol, 1.1 equiv) in THF (20 mL) at 65 °C for 22 h. Chromatography (1/20 EtOAc/hexanes) afforded the title compound as solid (Mp = 83-84 °C, R_f = 0.29, 1/10 EtOAc/hexanes). Yield 37% (0.65 g, 2.4 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.56-1.79 (m, 3H), 2.17-2.32 (m, 2H), 2.44-2.60 (m, 2H), 3.50-3.58 (m, 1H), 5.97 (s, 2H), 6.60 (dd, *J* = 1.5, 7.9 Hz, 1H), 6.66 (d, *J* = 1.4 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.5,

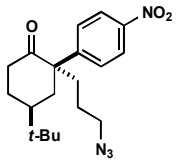
32.6, 37.1, 41.7, 47.4, 56.6, 101.0, 108.2, 109.2, 121.7, 132.9, 146.5, 147.6, 210.7; IR (neat) 2955, 1868, 1715, 1504, 1491, 1443, 1250, 1231, 1040 cm^{-1}; HRMS calcd for $C_{17}H_{22}O_3Na$ (M^+ + Na) 297.1467, found 297.1456.



(2R,4S)-4-tert-Butyl-2-(3,5-dimethoxyphenyl)cyclohexanone (12). Prepared according to the general procedure using $Pd(OAc)_2$ (0.082 g, 0.35 mmol, 0.02 equiv), tBu$_3$P (1.0 M in toluene, 0.44 mL, 0.44 mmol, 0.025 equiv), NaOtBu (2.62 g, 26.7 mmol, 1.5 equiv), 1-bromo-3,5-dimethoxybenzene (3.96 g, 17.7 mmol, 1.0 equiv) and *tert*-butylcyclohexanone (3.05 g, 19.5 mmol, 1.1 equiv) in THF (30 mL) at 65 °C for 18 h. Chromatography (1/6 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.47, 1/4 EtOAc/hexanes). Yield 62% (3.17 g, 10.9 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.58-1.67 (m, 1H), 1.71-1.86 (m, 2H), 2.16-2.34 (m, 2H), 2.45-2.59 (m, 2H), 3.554-3.61 (m, 1H), 3.80 (s, 6H), 6.33 (d, J = 2.3 Hz, 2H), 6.40 (t, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.5, 32.6, 36.7, 41.7, 47.4, 55.3, 57.2, 98.8, 107.0, 141.5, 160.7, 210.1; IR (neat) 2957, 1713, 1599, 1462, 1429, 1204, 1151, 1065 cm^{-1}; HRMS calcd for $C_{18}H_{27}O_3$ (M^+ + H) 291.1960, found 291.1956.

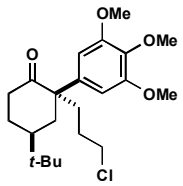


(2R,4S)-4-*tert*-Butyl-2-(3-chloropropyl)-2-(4-nitrophenyl)cyclohexanone (15). According to the general procedure, the reaction of NaH (0.35 g, 8.8 mmol, 1.1 equiv), HMPA (1.70 mL, 9.60 mmol, 1.2 equiv), **8** (2.20 g, 8.0 mmol, 1.0 equiv) and 1-chloro-3-iodopropane (3.43 mL, 32.0 mmol, 4.0 equiv) in THF (40 mL) for 18 h afforded after chromatography (1/15 EtOAc/hexanes) the title compound as solid (Mp = 101-102 °C, R_f = 0.37, 1/10 EtOAc/hexanes). Yield 41% (1.17 g, 3.3 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.26-1.38 (m, 1H), 1.56-1.85 (m, 3H), 1.90 (t, *J* = 12.5 Hz, 1H), 2.08-2.36 (m, 4H), 2.46-2.56 (m, 1H), 2.59-2.70 (m, 1H), 3.46-3.58 (m, 2H), 7.46 (d, *J* = 9.0 Hz, 2H), 8.20 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 26.9, 27.4, 32.5, 32.8, 38.5, 38.8, 41.8, 44.9, 56.4, 123.2, 128.7, 146.6, 149.7, 212.0; IR (neat) 2961, 2870, 1709, 1597, 1518, 1468, 1348, 1232, 912, 856, 735 cm^{-1}; HRMS calcd for $C_{19}H_{30}ClN_2O_3$ (M^+ + H) 369.1945, found 369.1962.



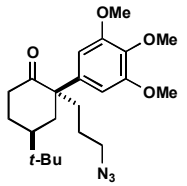
(2R,4S)-2-(3-Azidopropyl)-4-*tert*-butyl-2-(4-nitrophenyl)cyclohexanone (22). According to the general procedure the reaction of chloride **15** (0.65 g, 1.85 mmol, 1.0 equiv), NaN_3 (0.60 g, 9.2 mmol, 5.0 equiv) in DMF (20 mL) at 80 °C for 2.5 h afforded after chromatography (1/4 EtOAc/hexanes) the title compound as solid

(Mp = 94-95 °C, R_f = 0.53, 1/4 EtOAc/hexanes). Yield 88% (0.59 g, 1.63 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.04-1.16 (m, 1H), 1.42-1.54 (m, 1H), 1.56-1.68 (m, 1H), 1.72-1.81 (m, 1H), 1.90 (t, *J* = 12.6 Hz, 1H), 2.06-2.26 (m, 4H), 2.50 (dq, *J* = 3.7, 14.5 Hz, 1H), 2.57-2.68 (m, 1H), 3.21-3.29 (m, 2H), 7.45 (d, *J* = 8.9 Hz, 2H), 8.19 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 26.8, 27.4, 32.5, 32.6, 38.5, 28.7, 41.8, 51.3, 56.5, 123.2, 128.7, 146.5, 149.7, 212.0; IR (neat) 2960, 2870, 2097, 1709, 1597, 1518, 1348, 856 cm^{-1}; HRMS calcd for $C_{19}H_{27}N_4O_3$ (M^+ + H) 359.2083, found 359.2061.

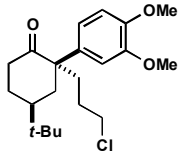


(2R,4S)-4-*tert*-Butyl-2-(3-chloropropyl)-2-(3,4,5-trimethoxyphenyl) cyclohexanone (16). According to the general procedure, the reaction of NaH (0.30 g, 7.6 mmol, 1.1 equiv), HMPA (1.45 mL, 8.3 mmol, 1.2 equiv), **9** (2.20 g, 6.9 mmol, 1.0 equiv) and 1-chloro-3-iodopropane (2.89 mL, 27.5 mmol, 4.0 equiv) in THF (30 mL) for 22 h afforded after chromatography (1/8 EtOAc/hexanes) the title compound as oil (R_f = 0.45, 1/4 EtOAc/hexanes). Yield 40% (1.08 g, 2.7 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.33-1.44 (m, 1H), 1.58-1.75 (m, 3H), 1.93-2.21 (m, 5H), 2.36-2.56 (m, 2H), 3.43-3.57 (m, 2H), 3.86 (s, 9H), 6.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 27.1, 27.3, 32.6, 33.4, 37.8, 38.1, 41.9, 45.4, 55.9, 56.3, 60.8,

105.0, 137.0, 137.4, 152.9, 214.1; IR (neat) 2960, 1715, 1590, 1520, 1420, 1255, 1135, 1015 cm^{-1}; HRMS calcd for $C_{22}H_{34}ClO_4$ (M^+ + H) 397.2146, found 397.2145.

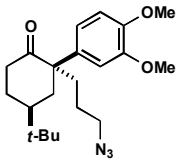


(2R,4S)-2-(3-Azidopropyl)-4-*tert*-butyl-2-(3,4,5-trimethoxyphenyl) cyclohexanone (23). According to the general procedure, the reaction of chloride **16** (1.08 g, 2.72 mmol, 1.0 equiv) and NaN_3 (0.88 g, 13.6 mmol, 5.0 equiv) in DMF (15 mL) at 80 °C for 2.5 h afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil. Yield 99% (1.08 g, 2.7 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.11-1.26 (m, 1H), 1.42-1.78 (m, 3H), 1.88-2.12 (m, 5H), 2.37-2.56 (m, 2H), 3.14-3.32 (m, 2H), 3.84 (s, 9H), 6.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 25.6, 27.3, 32.6, 33.4, 37.2, 38.0, 41.9, 51.7, 55.9, 56.3, 60.8, 104.9, 137.0, 137.3, 152.9, 214.2; IR (neat) 2960, 2100, 1715, 1595, 1520, 1420, 1255, 1140, 1020 cm^{-1}; HRMS calcd for $C_{22}H_{33}N_3O_4Na$ (M^+ + Na) 426.2369, found 426.2376.



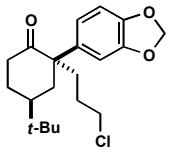
(2R,4S)-4-*tert*-Butyl-2-(3-chloropropyl)-2-(3,4-dimethoxyphenyl) cyclohexanone (17). According to the general procedure, the reaction of NaH (0.176 g, 4.0 mmol, 1.1 equiv), HMPA (0.83 mL, 4.8 mmol, 1.2 equiv), **10** (1.16 g, 4.0

mmol, 1.0 equiv) and 1-chloro-3-iodopropane (1.89 mL, 17.6 mmol, 4.0 equiv) in THF (30 mL) for 17 h afforded after chromatography (1/8 EtOAc/hexanes) the title compound as oil (R_f = 0.41, 1/4 EtOAc/hexanes). Yield 45% (0.66 g, 1.8 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.30-1.42 (m, 1H), 1.58-1.73 (m, 3H), 1.94-2.21 (m, 5H), 2.42-2.54 (m, 2H), 3.41-3.53 (m, 2H), 3.89 (s, 6H), 6.78-6.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 27.1, 27.3, 32.6, 33.3, 37.3, 38.0, 41.9, 45.4, 55.3, 55.8, 56.0, 110.7, 111.2, 119.4, 134.2, 147.8, 148.6, 214.3; IR (neat) 2957, 1707, 1518, 1464, 1256, 1150, 1028 cm^{-1}; HRMS calcd for $C_{21}H_{32}ClO_3$ (M^+ + H) 367.2040, found 367.2062.

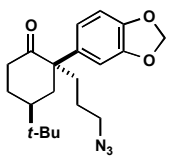


(2R,4S)-2-(3-Azidopropyl)-4-*tert*-butyl-2-(3,4-dimethoxyphenyl) cyclohexanone (24). According to the general procedure, the reaction of chloride **17** (0.57 g, 1.55 mmol, 1.0 equiv) and NaN_3 (0.50 g, 7.76 mmol, 5.0 equiv) in DMF (20 mL) at 80 °C for 2.5 h afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.39, 1/4 EtOAc/hexanes). Yield 87% (0.49 g, 1.30 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.11-1.22 (m, 1H), 1.42-1.52 (m, 1H), 1.58-1.69 (m, 2H), 1.92-2.12 (m, 5H), 2.42-2.53 (m, 2H), 3.16-3.27 (m, 2H), 3.88 (s, 6H), 6.77-6.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 25.8, 27.3, 32.6, 33.3, 36.9, 37.9, 41.9, 51.7, 55.4, 55.8, 56.0, 110.7, 111.2, 119.3, 134.1, 147.9, 148.6, 214.4; IR

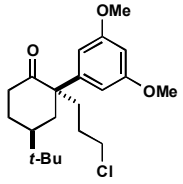
(neat) 2957, 2868, 2097, 1709, 1518, 1464, 1258, 1150, 1028 cm^{-1}; HRMS calcd for $C_{21}H_{31}N_3O_3Na$ (M^+ + Na) 396.2263, found 396.2265.



(2R,4S)-2-(Benzo[d][1,3]dioxol-5-yl)-4-*tert*-butyl-2-(3-chloropropyl) cyclohexanone (18). According to the general procedure, the reaction of NaH (0.096 g, 2.4 mmol, 1.1 equiv), HMPA (0.46 mL, 2.65 mmol, 1.2 equiv), **1l** (0.60 g, 2.2 mmol, 1.0 equiv) and 1-chloro-3-iodopropane (0.94 mL, 8.8 mmol, 4.0 equiv) in THF (20 mL) for 17 h afforded after chromatography (1/20 EtOAc/hexanes) the title compound as oil (R_f = 0.32, 1/10 EtOAc/hexanes). Yield 37% (0.28 g, 0.81 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.33-1.41 (m, 1H), 1.58-1.72 (m, 3H), 1.91-2.17 (m, 5H), 2.49 (t, *J* = 7.5 Hz, 2H), 3.42-3.53 (m, 2H), 5.97 (s, 2H), 6.71-.6.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 27.1, 27.3, 32.6, 33.3, 37.6, 38.0, 41.8, 45.3, 55.5, 101.1, 107.8, 108.4, 120.3, 136.6, 146.2, 147.7, 214.0; IR (neat) 2959, 1709, 1504, 1489, 1433, 1240, 1040 cm^{-1}; HRMS calcd for $C_{20}H_{31}ClO_3N$ (M^+ + NH_4) 368.1992, found 368.1983.

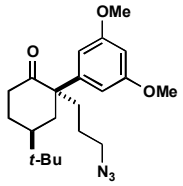


(2R,4S)-2-(3-Azidopropyl)-2-(benzo[d][1,3]dioxol-5-yl)-4-*tert*-butyl cyclohexanone (25). According to the general procedure, the reaction of chloride **18** (0.20 g, 0.57 mmol, 1.0 equiv) and NaN_3 (0.19 g, 2.85 mmol, 5.0 equiv) in DMF (20 mL) at 80 °C for 2.5 h afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.30, 1/10 EtOAc/hexanes). Yield 86% (0.18 g, 0.49 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.11-1.23 (m, 1H), 1.43-1.52 (m, 1H), 1.60-1.68 (m, 2H), 1.92-2.12 (m, 5H), 2.43-2.52 (m, 2H), 3.18-3.32 (m, 2H), 5.96 (s, 2H), 6.70-6.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 26.1, 27.3, 32.6, 33.2, 37.4, 38.0, 41.8, 51.6, 55.6, 101.1, 107.9, 108.3, 120.2, 135.6, 146.2, 147.7, 214.0; IR (neat) 2959, 2097, 1709, 1489, 1204 cm^{-1}; HRMS calcd for $C_{20}H_{31}N_4O_3$ ($M^+ + NH_4$) 375.2396, found 375.2401.



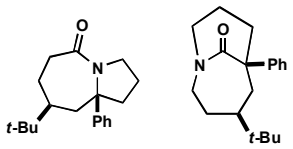
(2R,4S)-4-*tert*-Butyl-2-(3-chloropropyl)-2-(3,5-dimethoxyphenyl) cyclohexanone (19). According to the general procedure, the reaction of NaH (0.46 g, 11.4 mmol, 1.1 equiv), HMPA (2.17 mL, 12.4 mmol, 1.2 equiv), **12** (3.0 g, 10.3 mmol, 1.0 equiv) and 1-chloro-3-iodopropane (4.4 mL, 41.2 mmol, 4.0 equiv) in THF (40 mL) for 14 h afforded after chromatography (1/33 EtOAc/hexanes) the title compound as oil (R_f = 0.32, 1/10 EtOAc/hexanes). Yield 43% (1.64 g, 4.5 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.33-1.45 (m, 1H), 1.56-1.72 (m, 3H), 1.96-

2.21 (m, 5H), 2.41-2.54 (m, 2H), 3.42-3.54 (m, 2H), 3.80 (s, 6H), 6.38 (t, J = 2.1 Hz, 1H), 6.44 (d, J = 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 27.2, 27.3, 32.6, 33.3, 37.1, 38.0, 41.8, 45.4, 55.3, 55.9, 98.1, 106.0, 144.3, 160.6, 213.9; IR (neat) 2957, 1709, 1595, 1456, 1423, 1205, 1157, 1065 cm^{-1}; HRMS calcd for $C_{21}H_{32}ClO_3$ (M^+ + H) 367.2040, found 367.2041.

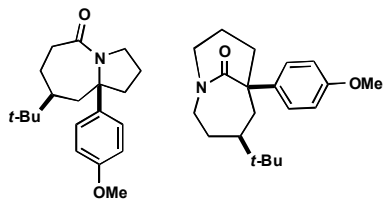


(2R,4S)-2-(3-Azidopropyl)-4-*tert*-butyl-2-(3,5-dimethoxyphenyl) cyclohexanone (26). According to the general procedure, the reaction of chloride **19** (1.42 g, 3.9 mmol, 1.0 equiv) and NaN_3 (1.26 g, 19.3 mmol, 5.0 equiv) in DMF (20 mL) at 80 °C for 2.5 h afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.26, 1/10 EtOAc/hexanes). Yield 89% (1.28 g, 3.4 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.17-1.28 (m, 1H), 1.42-1.70 (m, 3H), 1.88-2.12 (m, 5H), 2.38-2.56 (m, 2H), 3.16-3.38 (m, 2H), 3.79 (s, 6H), 6.34 (t, J = 2.1 Hz, 1H), 6.42 (d, J = 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 25.7, 27.3, 32.6, 33.2, 36.8, 37.9, 41.8, 51.7, 55.3, 55.9, 98.0, 106.0, 144.3, 160.6, 214.0; IR (neat) 2957, 2097, 1709, 1595, 1456, 1205, 1157, 1064 cm^{-1}; HRMS calcd for $C_{21}H_{35}N_4O_3$ (M^+ + NH_4) 391.2709, found 391.2707.

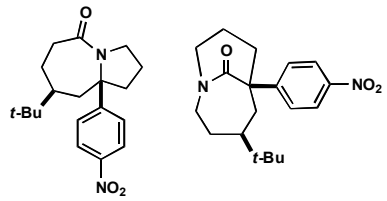
Optimization of Product Distribution in Schmidt Reaction with Azide 20. According to the general procedure azide **20** was reacted with acids specified in Table 6. The reactions were monitored by TLC, and worked-up after consumption of the starting material. Analysis of crude reaction mixtures by ^{1}H NMR indicated ratio of **27** to **34**.



(8S,9aR)-8-*tert*-Butyl-9a-phenylhexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (27) and **(4R,6R)-4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-one (34)**. According to the general procedure, the reaction of azide **20** (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 **27** (0.0185 g, 0.065 mmol, yield 22%) as oil (R_f = 0.40, 1/1 EtOAc/hexanes) and lactam **34** (0.0502 g, 0.0176 mmol, yield 61%) as oil (R_f = 0.70, 1/1 EtOAc/hexanes). Analysis of the crude reaction mixture by ^{1}H NMR indicated 26:74 ratio of **27** to **34**. Spectroscopic properties matched those previously described.[188]

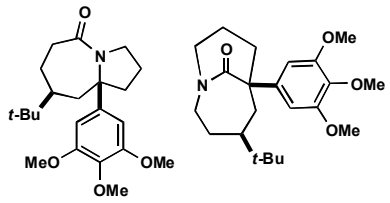


(8S,9aR)-8-*tert*-Butyl-9a-(4-methoxyphenyl)hexahydro-1H-pyrrolo[1,2-a] azepin-5(6H)-one (28) and **(4R,6R)-4-*tert*-Butyl-6-(4-methoxyphenyl)-1-azabicyclo[4.3.1]decan-10-one (35)**. According to the general procedure, the reaction of azide **21** (0.0841 g, 0.25 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 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 **28** (0.0090 g, 0.028 mmol, yield 11%) as oil and lactam **35** (0.0556 g, 0.0177 mmol, yield 71%) as white solid (Mp = 135-136 °C), recrystallization from EtOAc afforded crystals suitable for X-ray analysis. Analysis of the crude reaction mixture by ^1H NMR indicated 12:88 ratio of **28** to **35**. Spectroscopic properties matched those previously described.[188]



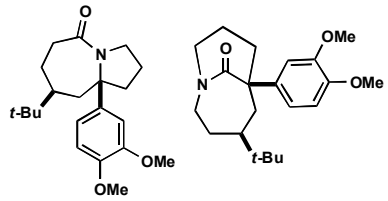
(8S,9aR)-8-*tert*-Butyl-9a-(4-nitrophenyl)hexahydro-1H-pyrrolo[1,2-a] azepin-5(6H)-one (29) and **(4R,6R)-4-*tert*-Butyl-6-(4-nitrophenyl)-1-azabicyclo[4.3.1]decan-10-one (36).** According to the general procedure, the reaction of azide **22** (0.0872 g, 0.24 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M in 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 **29** (0.0301 g, 0.091 mmol, yield 38%) as white solid (Mp = 177-178 °C, R_f = 0.53, 1/1 EtOAc/hexanes) and lactam **36** (0.0312 g, 0.095 mmol, yield 39%, R_f = 0.84, 1/1 EtOAc/hexanes) as white solid

(Mp = 135-136 °C). Analysis of the crude reaction mixture by ^{1}H NMR indicated 51:49 ratio of **29** to **36**. Compound **29**: ^{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 333.2008. Compound **36**: ^{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 333.2044.



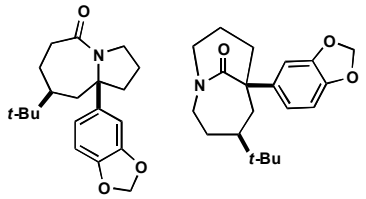
(8S,9aR)-8-*tert*-Butyl-9a-(3,4,5-trimethoxyphenyl)hexahydro-1H-pyrrolo [1,2-a]azepin-5(6H)-one (30) and **(4R,6R)-4-*tert*-Butyl-6-(3,4,5-trimethoxyphenyl)-1-azabicyclo[4.3.1]decan-10-one (37).** According to the general

procedure, the reaction of azide **23** (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 **30** (0.0136 g, 0.036 mmol, yield 19%) as oil (R_f = 0.28, 1/1 EtOAc/hexanes) and lactam **37** (0.0473 g, 0.126 mmol, yield 66%, R_f = 0.53, 1/1 EtOAc/hexanes) as solid (Mp = 158-159 °C). Analysis of the crude reaction mixture by ^{1}H NMR indicated 21:79 ratio of **30** to **37**. Compound **30**: ^{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 **37**: ^{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.



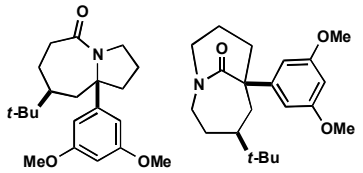
(8S,9aR)-8-*tert*-Butyl-9a-(3,4-dimethoxyphenyl)hexahydro-1H-pyrrolo [1,2-a]azepin-5(6H)-one (21) and **(4R,6R)-4-*tert*-Butyl-6-(3,4-dimethoxyphenyl)-1-azabicyclo[4.3.1]decan-10-one (38).** According to the general procedure, the reaction of azide **24** (0.0849 g, 0.23 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M in hexanes, 0.34 mL, 1.5 equiv) in CH_2Cl_2 (4.2 mL, 0.05 M) for 24 h afforded after chromatography 1/2 hexanes/EtOAc-EtOAc lactam **31** (0.0143 g, 0.041 mmol, yield 18%) as oil (R_f = 0.27, 1/1 EtOAc/hexanes) and lactam **38** (0.0520 g, 0.150 mmol, yield 65%, R_f = 0.55, 1/1 EtOAc/hexanes) as solid (Mp = 105-106 °C). Analysis of the crude reaction mixture by ^{1}H NMR indicated 22:78 ratio of **31** to **38**. Compound **31**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 9H), 1.29 (m, 2H), 1.42 (q, *J* = 10.6 Hz, 1H), 1.55 (q, *J* = 10.1, 1H), 1.71 (m, 1H), 1.90 (m, 1H), 2.09 (d, *J* = 6.8 Hz, 2H), 2.16-2.33 (m, 2H), 2.42 (d, *J* = 13.8 Hz, 1H), 3.57-3.72 (m, 2H), 3.88 (s, 6H), 6.68-6.73 (m, 2H), 6.82 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 24.7, 27.1, 32.6, 33.0, 39.4, 41.5, 43.0, 47.5, 55.9, 56.1, 68.3, 108.3, 110.8, 117.1, 139.7, 147.9, 149.0, 172.4; IR (neat) 2955, 1634, 1514, 1450, 1257, 1140 cm^{-1}; HRMS calcd for $C_{21}H_{32}NO_3$ (M^+ + H) 346.2382, found 346.2397. Compound **38**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.47-1.68 (m, 2H), 1.82-2.12 (m, 6H), 2.50 (d, *J* = 11.9 Hz, 1H), 2.60-2.68 (m, 1H), 3.36 (m, 1H), 3.71 (dd, *J* = 3.2, 11.3 Hz, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 3.95 (m, 1H), 6.84-6.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

22.6, 26.0, 28.0, 34.1, 37.7, 43.1, 44.5, 50.2, 54.7, 55.9, 55.9, 56.0, 110.2, 111.3, 117.8, 140.6, 147.5, 148.7, 184.6; IR (neat) 2955, 1666, 1518, 1460, 1252, 1150, 1045 cm^{-1}; HRMS calcd for $C_{21}H_{32}NO_3$ (M^+ + H) 346.2382, found 346.2373.



(8S,9aR)-9a-(Benzo[d][1,3]dioxol-5-yl)-8-*tert*-butylhexahydro-1H-pyrrolo [1,2-a]azepin-5(6H)-one (32) and **(4R,6R)-6-(Benzo[d][1,3]dioxol-5-yl)-4-*tert*-butyl-1-azabicyclo[4.3.1]decan-10-one (39).** According to the general procedure, the reaction of azide **25** (0.1005 g, 0.28 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M in hexanes, 0.42 mL, 1.5 equiv) in CH_2Cl_2 (5.2 mL, 0.05 M) for 24 h afforded after chromatography 1/2 hexanes/EtOAc lactam **32** (0.0123 g, 0.037 mmol, yield 13%) as oil (R_f = 0.56, 1/1 EtOAc/hexanes) and lactam **39** (0.0669 g, 0.203 mmol, yield 72%, R_f = 0.81, 1/1 EtOAc/hexanes) as solid (Mp = 162-163 °C). Analysis of the crude reaction mixture by ^1H NMR indicated 17:83 ratio of **32** to **39**. Compound **32**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.30 (m, 2H), 1.41-1.57 (m, 2H), 1.68-1.75 (m, 1H), 1.91 (m, 1H), 2.06-2.11 (m, 2H), 2.20 (dt, *J* = 6.4, 12.9 Hz, 1H), 2.30 (m, 1H), 2.41 (d, *J* = 13.8 Hz, 1H), 3.60-3.71 (m, 2H), 5.98 (s, 2H), 6.64 (dd, *J* = 1.9, 8.1 Hz, 1H), 6.72 (d, *J* = 1.8 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 24.7, 27.1, 32.7, 33.0, 39.5, 41.4, 43.1, 47.5, 68.4, 101.2, 105.7, 107.9, 117.9, 141.2, 146.4, 148.0, 172.3; IR (neat) 2959, 2870, 1634, 1487, 1440, 1234,

1050 cm^{-1}; HRMS calcd for $C_{20}H_{28}NO_3$ (M^+ + H) 330.2069, found 330.2065. Compound **39**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.50 (m, 1H), 1.58 (t, *J* = 11.5 Hz, 1H), 1.82-2.08 (m, 6H), 2.45 (d, *J* = 11.8 Hz, 1H), 2.57-2.66 (m, 1H), 3.34 (m, 1H), 3.69 (dd, *J* = 3.2, 11.0 Hz, 1H), 3.93 (m, 1H), 5.94 (s, 2H), 6.77-6.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 26.0, 28.0, 34.1, 37.7, 43.0, 44.5, 50.2, 54.7, 56.0, 100.9, 107.2, 108.2, 118.9, 141.8, 145.7, 147.6, 184.4; IR (neat) 2959, 1666, 1504, 1487, 1240, 1040, 731 cm^{-1}; HRMS calcd for $C_{20}H_{28}NO_3$ (M^+ + H) 330.2069, found 330.2072.



(8S,9aR)-8-*tert*-Butyl-9a-(3,5-dimethoxyphenyl)hexahydro-1H-pyrrolo [1,2-a]azepin-5(6H)-one (33) and **(4R,6R)-4-*tert*-Butyl-6-(3,5-dimethoxyphenyl)-1-azabicyclo[4.3.1]decan-10-one (40).** According to the general procedure, the reaction of azide **26** (0.0802 g, 0.21 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M in hexanes, 0.32 mL, 1.5 equiv) in CH_2Cl_2 (4.0 mL, 0.05 M) for 24 h afforded after chromatography 1/2 hexanes/EtOAc lactam **33** (0.0185 g, 0.054 mmol, yield 25%) as oil (R_f = 0.42, 1/1 EtOAc/hexanes) and lactam **40** (0.0470 g, 0.136 mmol, yield 65%, R_f = 0.72, 1/1 EtOAc/hexanes) as solid (Mp = 117-118 °C). Analysis of the crude reaction mixture by ^1H NMR indicated 27:73 ratio of **33** to **40**. Compound **33**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 9H), 1.23-1.35 (m, 2H), 1.46 (m, 1H), 1.51-1.58

(m, 1H), 1,71 (m, 1H), 1.89 (m, 1H), 2.02-2.18 (m, 2H), 2.21-2.31 (m, 2H), 2.38 (d, *J* = 14.0 Hz, 1H), 3.57-3.71 (m, 2H), 3.79 (s, 6H), 6.32-6.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 24.7, 27.1, 32.6, 32.9, 39.1, 41.4, 42.9, 47.5, 55.4, 68.7, 97.8, 103.6, 149.9, 160.9, 172.3; IR (neat) 2955, 2916, 1634, 1597, 1454, 1421, 1157 cm^{-1}; HRMS calcd for $C_{21}H_{32}NO_3$ (M^+ + H) 346.2383, found 346.2382. Compound **40**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.49 (m, 1H), 1.61 (t, *J* = 11.8 Hz, 1H), 1.81-2.08 (m, 6H), 2.47 (d, *J* = 12.1 Hz, 1H), 3.34 (t, *J* = 11.1 Hz, 1H), 3.68 (m, 1H), 3.80 (s, 6H), 3.89-3.97 (m, 1H), 6.36 (t, *J* = 2.1 Hz, 1H), 6.51 (d, *J* = 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 26.0, 28.0, 34.1, 37.5, 43.0, 44.0, 50.2, 54.7, 55.3, 56.4, 97.8, 104.7, 150.1, 160.7, 184.2; IR (neat) 2957, 1670, 1595, 1456, 1155 cm^{-1}; HRMS calcd for $C_{21}H_{32}NO_3$ (M^+ + H) 346.2383, found 346.2396.

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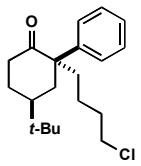
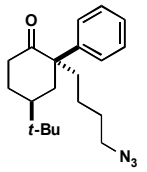
Influence of Stoichiometry of Lewis Acid on Product Distribution in Cation-π Directed Schmidt Reaction (Table 8). According to the general procedure azides were reacted with 1.0, 1.5, 2.0 and 3.0 equiv of $MeAlCl_2$ and 2.0 equiv of BF_3•CH_3CN for 24 h at rt. Aqueous work-up and analysis of the crude reaction mixtures by ^{1}H NMR indicated ratio of bridged to fused lactams.



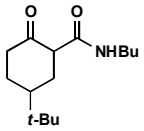
(2R,4S)-4-*tert*-Butyl-2-(4-chlorobutyl)-2-phenylcyclohexanone (41). According to the general procedure, the reaction of NaH (0.0956 g, 2.39 mmol, 1.1 equiv), HMPA (0.46 mL, 2.60 mmol, 1.2 equiv), **6** (0.50 g, 2.17 mmol, 1.0 equiv) and 1-chloro-4-iodobutane (1.08 mL, 8.68 mmol, 4.0 equiv) in THF (30 mL) for 20 h afforded after chromatography (1/50 EtOAc/hexanes) the title compound as oil (R_f = 0.51, 1/10 EtOAc/hexanes). Yield 46% (0.322 g, 1.00 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 0.90-1.04 (m, 1H), 1.34-1.48 (m, 1H), 1.58-1.68 (m, 2H), 1.75 (p, *J* = 7.0 Hz, 2H), 1.93-2.18 (m, 5H), 2.50 (m, 2H), 3.42-3.54 (m, 2H), 7.23-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 26.2, 27.4, 32.6, 32.8, 35.0, 37.4, 38.2, 41.9, 44.6, 56.2, 126.6, 127.4, 128.2, 142.1, 214.2; IR (neat) 2954, 1710, 1465, 1444, 1365, 1224, 1141 cm^{-1}; HRMS calcd for $C_{20}H_{30}ClO$ (M^+ + H) 321.1985, found 325.1903.



(2R,4S)-2-(4-Azidobutyl)-4-*tert*-butyl-2-phenylcyclohexanone (42). According to the general procedure the reaction of chloride **41** (0.296 g, 0.92 mmol, 1.0 equiv), NaN_3 (0.60 g, 9.2 mmol, 10.0 equiv) in DMF (20 mL) at 80 °C for 2.5 h afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.39, 1/10 EtOAc/hexanes). Yield 90% (0.270 g, 0.82 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88-1.02 (m, 1H), 0.97 (s, 9H), 1.26-1.38 (m, 1H), 1.52-1.69 (m, 4H),

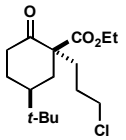
1.93-2.16 (m, 5H), 2.47-2.54 (m 2H), 3.16-3.37 (m, 2H), 7.24-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 26.1, 27.3, 29.2, 32.6, 35.4, 37.6, 38.2, 41.9, 51.1, 56.2, 126.6, 127.4, 128.2, 142.1, 214.2; IR (neat) 2952, 2868, 2094, 1710, 1465, 1444, 1365, 1257 cm^{-1}; HRMS calcd for $C_{20}H_{30}N_3O$ (M^+ + H) 328.2389, found 328.2384.

Attempted Schmidt Reaction with Azide 42. According to the general procedure **42** (0.100 g, 0.30 mmol, 1.0 equiv) was reacted with $MeAlCl_2$ (1.0 M in hexanes, 0.61 mL, 0.61 mmol, 2.0 equiv) in CH_2Cl_2 (5.5 mL, 0.05 M) at rt for 24 h. Analysis of the crude reaction mixture by NMR indicated only the presence of starting material. Note: the reaction of **42** with $TiCl_4$ (5.0 equiv, toluene, 105 °C, 18 h) or $Sc(OTf)_3$ (0.5 equiv, H_2O, 180 °C, 3 h)[397] did not afford the desired lactams; only starting material and decomposition products were observed when crude reaction mixtures were analyzed by NMR.



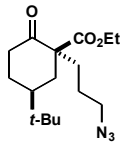
5-*tert*-Butyl-N-butyl-2-oxocyclohexanecarboxamide (44). The compound was prepared following a procedure by Hendi *et al.*[393] To a solution of LDA prepared from diisopropylamine (4.8 mL, 34.0 mmol, 1.05 equiv) and *n*-BuLi (1.55 M in hexanes, 20.9 mL, 32.4 mmol, 1.0 equiv) in Et_2O (80 mL) at -78 °C for 15 min, 4-*tert*-butylcyclohexanone (5.05 g, 32.4 mmol, 1.0 equiv) was added in Et_2O (20 mL) at -78 °C, and the stirring was continued for 20 min. butyl isocyanate (3.65 mL, 32.4

mmol, 1.0 equiv) was added in Et_2O (10 mL) at -78 °C. After the reaction mixture was stirred at -78 °C for 2 h, the reaction was allowed to slowly warm up to rt. After the reaction was stirred for the next 2 h, the reaction was quenched with sat. NH_4Cl (50 mL). The aqueous layer was extracted with ether (3 x 100 mL), combined organic layers were washed with brine (1 x 100 mL), dried and concentrated. Chromatography (1/4 EtOAc/hexanes) afforded the title compound as solid (Mp = 83 -84 °C). Yield 67% (5.49 g, 21.7 mmol). The compound exists as a mixture of keto-enol tautomers and amide rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81-0.95 (m, 12H), 1.16-1.65 (m, 8H), 1.83 (t, *J* = 11.8 Hz, 1H), 1.92-2.12 (m, 1H), 2.24 (d, *J* = 7.5 Hz, 1H), 2.28-2.58 (m, 1H), 3.08-3.30 (m, 2H), 5.27 (s, 0.5H), 6.05 (s, 0.1H), 7.43 (s, 0.3H), 14.16 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 13.7, 13.8, 20.0, 20.1, 20.1, 23.1, 23.9, 26.2, 27.3, 27.4, 27.5, 27.6, 28.4, 28.9, 30.3, 31.5, 31.5, 31.8, 32.3, 32.4, 32.4, 32.6, 32.7, 33.4, 38.9, 39.0, 39.1, 39.5, 40.3, 42.0, 42.2, 44.3, 46.7, 54.6, 55.8, 96.5, 167.5, 169.4, 169.8, 172.6, 211.0, 211.2; IR (neat) 3320, 2940, 2850, 1705, 1625, 1530, 1355, 1295, 1215 cm^{-1}; HRMS calcd for $C_{15}H_{28}O_2$ (M^+ + H) 254.2120, found 254.2108.

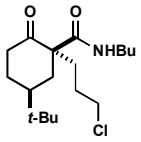


(1S,5S)-Ethyl 5-*tert*-butyl-1-(3-chloropropyl)-2-oxocyclohexane carboxylate (45). According to the general procedure, the reaction of NaH (0.039 g, 0.97 mmol, 1.1 equiv), HMPA (0.19 mL, 1.06 mmol, 1.2 equiv), **43** (0.20 g, 0.88

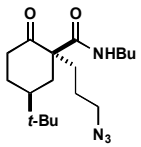
mmol, 1.0 equiv) and 1-chloro-3-iodopropane (0.38 mL, 3.52 mmol, 4.0 equiv) in THF (15 mL) for 24 h afforded after chromatography (1/50 EtOAc/hexanes) the title compound as oil. Yield 62% (0.165 g, 0.55 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, *J* = 2.9 Hz, 9H), 1.27 (dt, *J* = 3.0, 7.1 Hz, 3H), 1.46-1.68 (m, 3H), 1.81-2.17 (m, 6H), 2.36-2.52 (m, 2H), 3.47-3.62 (m, 2H), 4.13-4.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 26.5, 27.4, 27.5, 30.3, 32.5, 33.7, 38.4, 41.5, 45.1, 60.4, 61.2, 172.3, 209.3; IR (neat) 2940, 1720, 1700, 1440, 1355, 1240 cm^{-1}; HRMS calcd for $C_{16}H_{28}ClO_3$ (M^+ + H) 303.1727, found 303.1717.



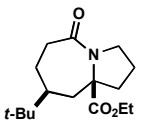
(1S,5S)-Ethyl 1-(3-azidopropyl)-5-*tert*-butyl-2-oxocyclohexanecarboxylate (47). According to the general procedure, the reaction of chloride **45** (0.100 g, 0.33 mmol, 1.0 equiv) and NaN_3 (0.11 g, 1.65 mmol, 5.0 equiv) in DMF (5 mL) at 80 °C for 2.5 h afforded after chromatography (1/10 EtOAc/hexanes) the title compound as oil. Yield 81% (0.083 g, 0.27 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 1.5 Hz, 9H), 1.22-1.32 (dt, *J* = 2.0, 7.2 Hz, 3H), 1.37-1.76 (m, 4H), 1.82-2.18 (m, 5H), 2.44 (s, 2H), 3.24-3.38 (m, 2H), 4.13-4.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 24.0, 26.4, 27.4, 30.1, 32.5, 33.7, 38.4, 41.6, 51.5, 60.5, 61.2, 172.2, 209.3; IR (neat) 2940, 2080, 1720, 1700, 1440, 1360, 1240, 1180 cm^{-1}; HRMS calcd for $C_{16}H_{28}N_3O_3$ (M^+ + H) 310.2131, found 310.2137.



(1S,5S)-5-*tert*-Butyl-N-butyl-1-(3-chloropropyl)-2-oxocyclohexane carboxamide (46). To a suspension of NaH (0.103 g, 2.56 mmol, 1.1 equiv) in THF (15 mL), amide **44** (0.59 g, 2.33 mmol, 1.0 equiv) was added in THF (5.0 mL) dropwise at 0 °C, and the reaction mixture was stirred at rt for 40 min. 1-chloro-3-iodopropane (0.38 mL, 3.50 mmol, 1.5 equiv) was added neat and the reaction was stirred at rt for 9 h. Work-up analogous to the described above followed by chromatography (1/6 EtOAc/hexanes) afforded the title compound as oil. Yield 47% (0.363 g, 1.10 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 0.80-1.05 (m, 12H), 1.05-1.18 (m, 0.5H), 1.22-1.58 (m, 6H), 1.59-1.78 (m, 3.5H), 1.92-2.22 (m, 2.5H), 2.32-2.71 (m, 2.5H), 3.09-3.59 (m 4H), 5.83 (s, 0.25H), 8.29 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 13.6, 13.7, 20.0, 20.1, 26.7, 27.1, 27.3, 27.4, 27.7, 31.4, 31.5, 32.4, 33.4, 34.3, 35.0, 36.9, 39.0, 39.5, 40.6, 41.3, 43.1, 44.6, 45.1, 57.0, 59.9, 169.3, 171.9, 212.4, 215.6; IR (neat) 3330, 2940, 1680, 1635, 1525, 1455, 1355 cm^{-1}; HRMS calcd for $C_{18}H_{33}ClNO_2$ (M^+ + H) 330.2200, found 330.2192.



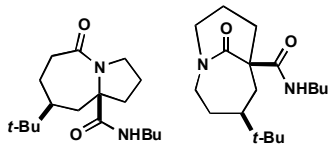
(1S,5S)-1-(3-Azidopropyl)-5-*tert*-butyl-N-butyl-2-oxocyclohexane carboxamide (48). According to the general procedure, the reaction of chloride **46** (0.280 g, 0.85 mmol, 1.0 equiv) and NaN_3 (0.28 g, 4.2 mmol, 5.0 equiv) in DMF (10 mL) at 80 °C for 2 h afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil. Yield 98% (0.281 g, 0.83 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of rotamers) 0.81-0.97 (m, 12H), 1.03-1.16 (m, 0.5H), 1.22-1.74 (m, 9.5H), 1.81-2.10 (m, 2.5H), 2.30-2.65 (m, 2.5H), 3.11-3.25 (m, 4H), 5.74 (s, 0.25H), 8.00 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 13.7, 13.7, 20.0, 20.2, 23.8, 24.2, 26.6, 27.2, 27.4, 27.4, 31.4, 31.5, 32.5, 33.4, 34.2, 34.5, 34.8, 37.0, 39.1, 39.6, 40.6, 41.5, 43.1, 45.1, 51.1, 51.6, 57.1, 60.0, 60.1, 169.2, 171.9, 212.7, 215.8; IR (neat) 3330, 2070, 1675, 1625, 1510, 1450, 1350, 1240 cm^{-1}; HRMS calcd for $C_{18}H_{33}N_4O_2$ (M^+ + H) 337.2603, found 337.2591.



(8S,9aR)-Ethyl 8-*tert*-butyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-9a-carboxylate (49). According to the general procedure, the reaction of azide **47** (0.180 g, 0.58 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M in hexanes, 1.32 mL, 2.2 equiv, added in two portions at the beginning of the reaction and after 2 h) in CH_2Cl_2 (10.0 mL, 0.05 M) for 6 h afforded after chromatography (100% EtOAc) lactam **49** (0.131 g, 0.47 mmol, yield 80%) as oil. Analysis of the crude reaction mixture by NMR did not indicate the formation of bridged isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 9H),

1.16-1.43 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.61-1.76 (m, 2H), 1.78-1.93 (m, 3H), 2.10 (d, J = 14.4 Hz, 1H), 2.27-2.48 (m, 3H), 3.50-3.66 (m, 2H), 4.16-4.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.3, 24.3, 26.9, 32.6, 32.6, 33.6, 39.3, 40.6, 47.2, 61.6, 68.4, 171.8, 174.5; IR (neat) 2950, 1720, 1635, 1440, 1410, 1360, 1250, 1110 cm^{-1}; HRMS calcd for $C_{16}H_{28}NO_3$ (M^+ + H) 282.2069, found 282.2076.

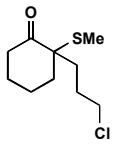
Note: the Schmidt reaction of azide **47** (0.089 g, 0.29 mmol, 1.0 equiv) and TfOH (0.13 mL, 1.44 mmol, 5.0 equiv) in CH_2Cl_2 (10 mL) for 1 h at rt afforded **49** in 92% yield (0.077 g, 0.27 mmol). The Schmidt reaction of azide **47** (0.081 g, 0.26 mmol, 1.0 equiv) in TFA (3.0 mL, excess) for 2 h at rt afforded **49** in 88% yield (0.064 g, 0.23 mmol). The Schmidt reaction of azide **47** (0.103 g, 0.33 mmol, 1.0 equiv) and BF_3•OEt_2 (0.046 mL, 0.37 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) for 5 h at rt afforded **49** in 78% yield (0.072 g, 0.26 mmol); Analysis of crude reaction mixtures by NMR did not indicate formation of the bridged isomer.



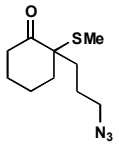
(8S,9aR)-8-*tert*-Butyl-N-butyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-9a-carboxamide (50) and **(4R,6R)-4-*tert*-Butyl-N-butyl-10-oxo-1-azabicyclo[4.3.1] decane-6-carboxamide (51).** According to the general procedure, the reaction of azide **48** (0.16 g, 0.47 mmol, 1.0 equiv) and TfOH (0.21 mL, 5.0 equiv) in CH_2Cl_2 (10.0 mL, 0.05 M) for 23 h afforded after chromatography (100% EtOAc-10% MeOH/CH_2Cl_2) lactam **50** (eluting with EtOAc, 0.077 g, 0.25 mmol, yield 52%) as

oil and lactam **51** (eluting with MeOH/CH_2Cl_2, 0.0192 g, 0.062 mmol, yield 13%) as oil. Compound **50**: ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers, major rotamer) δ 0.88 (s, 9H), 0.93 (t, *J* = 7.3 Hz, 3H), 1.02-1.11 (m, 1H), 1.29-1.44 (m, 3H), 1.45-1.53 (m, 2H), 1.57-1.69 (m, 2H), 1.78-1.91 (m, 3H), 2.25 (d, *J* = 14.9 Hz, 1H), 2.29-2.41 (m, 2H), 2.45 (dd, *J* = 6.2, 6.3 Hz, 1H), 3.18-3.39 (m, 2H), 3.50-3.59 (m, 1H), 3.61-3.68 (m, 1H), 6.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers, major rotamer) δ 13.7, 20.1, 20.4, 24.5, 26.9, 31.7, 32.7, 32.9, 33.9, 39.3, 39.5, 40.9, 48.1, 70.3, 172.9, 174.4; IR (neat) 3330, 1950, 1650, 1615, 1520, 1440, 1415, 1360, 1170 cm^{-1}; HRMS calcd for $C_{18}H_{33}N_2O_2$ (M^+ + H) 309.2542, found 309.2552. Compound **51**: ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 0.76-1.00 (m, 12H), 1.15-1.49 (m, 6H), 1.71-2.05 (m, 3H), 2.16-2.34 (m, 2H), 2.39-2.83 (m, 3H), 3.14-3.40 (m, 3H), 3.69-3.79 (m, 1H), 3.92-4.02 (m, 1H), 5.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 13.7, 20.0, 23.3, 26.9, 27.2, 27.5, 27.7, 27.8, 30.0, 20.9, 31.6, 31.7, 32.3, 32.5, 34.6, 37.9, 38.3, 39.2, 39.4, 39.6, 42.7, 44.8, 58.9, 59.2, 61.2, 62.0, 172.0, 172.9, 179.2, 180.5; IR (neat) 3320, 2940, 1645, 1625, 1520, 1455, 1145, 1100 cm^{-1}; HRMS calcd for $C_{18}H_{33}N_2O_2$ (M^+ + H) 309.2542, found 309.2558. Note: the reaction of **48** (0.323 g, 0.96 mmol) and $MeAlCl_2$ (1.0 M in hexanes, 1.44 mL, 1.5 equiv) in CH_2Cl_2 (15 mL, 0.06 M) for 5 h at rt afforded **50** in 77% yield (0.237 g, 0.74 mmol). Analysis of crude reaction mixtures by NMR did not indicate formation of the bridged isomer **51**.

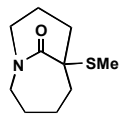
Cation−n control of regiochemistry in Schmidt reaction

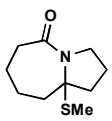


2-(3′-Chloropropyl)-2-(methylthio)cyclohexanone (56). To a suspension of potassium hydride (0.56 g, 14.1 mmol, 2.5 equiv) in 15 mL of THF was added 2-(methylthio)cyclohexanone **55**[395] (0.81 g, 5.6 mmol, 1.0 equiv) dropwise in 5 mL of THF at room temperature and the resulting solution was stirred for 10 min. 1-Chloro-3-iodopropanone (1.80 mL, 16.8 mmol, 3.0 equiv) was added in one portion and the solution was stirred for 48 h at room temperature followed by reflux for 30 min. The reaction was cooled to room temperature, diluted with ether (20 mL) and quenched with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with ether (2 x 20 mL), and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. Chromatography (4% EtOAc/hexanes) afforded the title compound as a colorless oil (R_f = 0.46, 10% EtOAc/hexanes). Yield 47% (0.579 g, 2.63 mmol). Note: the crude reaction mixture is unstable and must be chromatographed immediately after work-up. The title compound is unstable at room temperature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55-2.07 (complex, 13H), 2.21 (dddd, J = 2.0, 2.2, 4.2, 15.2 Hz, 1H), 3.10 (dt, J = 6.0, 14.9 Hz, 1H), 3.50-3.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 20.9, 26.4, 26.9, 30.6, 36.2, 36.8, 45.4, 56.1, 206.6; IR (neat) 2937, 2862, 1697, 1445, 1124 cm^{-1}; HRMS calcd for $C_{10}H_{17}ClOSNa$ (M^+ + Na) 243.0586, found 243.0582.



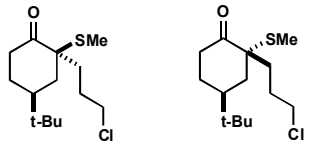
2-(3′-Azidopropyl)-2-(methylthio)cyclohexanone (57). *Caution! Low molecular weight alkylazides are potential explosion hazards and should be used with appropriate caution.* 2-(3′-Chloropropyl)-2-(methylthio)cyclohexanone **56** (0.52 g, 2.4 mmol, 1.0 equiv) and NaN_3 (0.77 g, 11.8 mmol, 5.0 equiv) were combined in DMF (20 mL), and the mixture was heated to 80 °C for 2 h. Ether (150 mL) was added, and the mixture was washed with water (4 x 50 mL) and brine (1 x 50 mL). The organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography (3% EtOAc/hexanes) afforded the compound as yellowish oil (R_f = 0.41, 10% EtOAc/hexanes). Yield 82% (0.449 g, 1.98 mmol). Note: the title compound is unstable at room temperature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49-1.91 (complex, 10H), 1.92-2.10 (m, 3H), 2.24 (dddd, J = 2.0, 2.2, 4.2, 15.2 Hz, 1H), 3.13 (dt, J = 6.0, 14.7 Hz, 1H), 3.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 20.9, 23.1, 26.4, 30.4, 36.2, 36.9, 51.7, 56.2, 206.7; IR (neat) 2937, 2862, 2095, 1697, 1448, 1257, 1124 cm^{-1}; HRMS calcd for $C_{10}H_{21}N_4OS$ ($M^+ + NH_4$) 245.1436, found 245.1438.



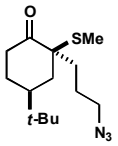


6-(Methylthio)-1-azabicyclo[4.3.1]decan-10-one (58) and 9a-(Methylthio)hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (59). To a solution of azide **57** (0.0910 g, 0.40 mmol, 1.0 equiv) in CH_2Cl_2 (8.0 mL, 0.05 M) was added

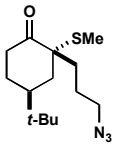
TfOH (0.18 mL, 2.0 mmol, 5.0 equiv) in one portion at 0 °C and the resulting solution was stirred at 0° C for 2.5 min. The reaction was quenched with saturated $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was washed with brine (1 x 20 mL), dried (Na_2SO_4), and concentrated. Analysis of the crude reaction mixture by ^1H NMR indicated 80:20 ratio of **58** to **59**. Flash chromatography (1/2 EtOAc/hexanes, followed by EtOAc) afforded compound **58** as a pale yellow oil (R_f = 0.57, 1/1 EtOAc/hexanes), yield 65% (0.0525 g, 0.26 mmol) and compound **59** as a colorless oil (R_f = 0.31, 1/1 EtOAc/hexanes), yield 15% (0.0120 g, 0.06 mmol). Compound **58**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.53-1.79 (complex, 4H), 1.80-1.99 (complex, 4H), 2.05-2.14 (complex, 4H), 2.22-2.29 (m, 1H), 2.80-2.86 (m, 1H), 3.18-3.24 (m, 1H), 3.43 (dt, *J* =2.8, 12.0 Hz, 1H), 3.86-3.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 22.5, 24.3, 26.5, 36.4, 40.1, 47.9, 50.6, 57.0, 182.4; IR (neat) 2927, 2860, 1686, 1445, 1173 cm^{-1}; HRMS calcd for $C_{10}H_{18}NOS$ (M^+ + H) 200.1109, found 200.1107. Compound **59**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.45-1.57 (m, 1H), 1.62-1.90 (complex, 4H), 1.97-2.14 (complex, 6H), 2.16-2.23 (m, 1H), 2.41-2.47 (m, 1H), 2.50-2.56 (m, 1H), 3.20 (dt, *J* = 2.2, 13.8 Hz, 1H), 3.48-3.57 (m, 1H), 3.68-3.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 21.1, 23.7, 24.9, 37.2, 39.3, 43.1, 49.6, 72.7, 174.7; IR (neat) 2926, 1632, 1429, 1406 cm^{-1}; HRMS calcd for $C_{10}H_{18}NOS$ (M^+ + H) 200.1109, found 200.1105.



(2S,4S)-4-*tert*-Butyl-2-(3-chloropropyl)-2-(methylthio)cyclohexanone (61) and (2R,4S)-4-*tert*-Butyl-2-(3-chloropropyl)-2-(methylthio)cyclohexanone (62). According to the procedure for **56** the reaction of **60**[381] (2.05g, 10.3 mmol, 1.0 equiv), KH (1.03 g, 25.7 mmol, 2.5 equiv) and 1-chloro-3-iodopropane (3.31 mL, 30.8 mmol, 3.0 equiv) in THF (30 mL) at rt for 48 h, followed by reflux for 0.5 h afforded after chromatography (1/50 EtOAc/hexanes) **61** as colorless oil (R_f = 0.57, 1/10 EtOAc/hexanes), yield ca. 6% (0.174 g, 0.63 mmol), and **62** as colorless oil (R_f = 0.51, 1/10 EtOAc/hexanes), yield ca. 6%, purity ca. 80% (0.190 g, 0.68 mmol). Compound **61**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 9H), 1.32 (m, 1H), 1.60 (t, *J* = 13.6 Hz, 1H), 1.68-1.78 (m, 2H), 1.81-1.97 (m, 3H), 1.89 (s, 3H), 1.98-2.08 (m, 2H), 2.24-2.33 (m, 1H), 2.80-2.88 (m, 1H), 3.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 24.6, 27.1, 27.1, 29.3, 32.6, 36.1, 36.2, 42.7, 45.2, 55.6, 208.1; IR (neat) 3453, 2959, 1700, 1441, 1368, 1229 cm^{-1}; HRMS calcd for $C_{14}H_{26}ClOS$ (M^+ + H) 277.1393, found 277.1379. Compound **62**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 9H), 1.31-1.46 (m, 1H), 1.55-2.06 (m, 8H), 1.81 (s, 3H), 2.22-2.29 (m, 1H), 3.08-3.18 (m, 1H), 3.51-3.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 27.0, 27.3, 27.5, 30.9, 32.2, 36.6, 37.3, 41.6, 45.3, 55.4, 206.6; IR (neat) 2917, 1698, 1437, 1420, 1368, 1233, 1169 cm^{-1}; HRMS calcd for $C_{14}H_{25}ClOSNa$ (M^+ + Na) 299.1212, found 299.1197.

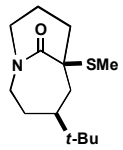


(2S,4S)-2-(3-Azidopropyl)-4-*tert*-butyl-2-(methylthio)cyclohexanone (63). According to the general procedure the reaction of **61** (0.16 g, 0.58 mmol, 1.0 equiv) and NaN_3 (0.19 g, 2.90 mmol, 5.0 equiv) in DMF (20 mL) at 80 °C for 2 h afforded after chromatography (1/20 EtOAc/hexanes) the title compound as colorless oil (R_f = 0.41, 1/10 EtOAc/hexanes). Yield 63% (0.104 g, 0.37 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.38 (m, 1H), 1.54-1.78 (m, 5H), 1.88 (s, 3H), 1.84-1.92 (m, 2H), 1.99-2.06 (m, 1H), 2.21-2.30 (m, 1H), 2.78-2.88 (m, 1H), 3.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 23.4, 24.5, 27.1, 29.1, 32.6, 36.1, 36.1, 42.8, 51.6, 55.5, 208.0; IR (neat) 3439, 2959, 2095, 1704, 1368, 1256 cm^{-1}; HRMS calcd for $C_{14}H_{25}N_3OSNa$ (M^+ + Na) 306.1616, found 306.1619.



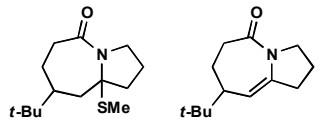
(2R,4S)-2-(3-Azidopropyl)-4-*tert*-butyl-2-(methylthio)cyclohexanone (64). According to the general procedure the reaction of **62** (0.15 g, 0.54 mmol, 1.0 equiv) and NaN_3 (0.17 g, 2.70 mmol, 5.0 equiv) in DMF (20 mL) at 80 °C for 2 h afforded after chromatography (1/50 EtOAc/hexanes) the title compound as colorless oil (R_f = 0.42, 1/10 EtOAc/hexanes). Yield 76% (0.117 g, 0.41 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 9H), 1.35 (m, 1H), 1.48-1.66 (m, 3H), 1.69-1.77 (m, 1H), 1.81 (s,

3H), 1.82-1.98 (m, 2H), 2.00-2.08 (m, 2H), 2.22-2.30 (m, 1H), 3.13 (dt, *J* = 5.8, 15.0 Hz, 1H), 3.26-3.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 23.2, 27.3, 27.5, 30.6, 32.2, 36.6, 37.2, 41.6, 51.8, 55.5, 206.5; IR (neat) 2959, 2095, 1698, 1468, 1368, 1256, 1234 cm^{-1}; HRMS calcd for $C_{14}H_{25}N_3OSNa$ (M^+ + Na) 306.1616, found 306.1606.



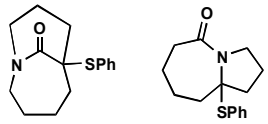
(4S,6S)-4-*tert*-Butyl-6-(methylthio)-1-azabicyclo[4.3.1]decan-10-one (65). According to the procedure for **57**, the reaction of **63** (0.0344, 0.12 mmol, 1.0 equiv, single diastereoisomer) and TfOH (0.055 mL, 0.61 mmol, 5.0 equiv) in CH_2Cl_2 (2.4 mL, 0.05 M) for 60 s at 0 °C afforded after chromatography (1/3 EtOAc/hexanes) the title compound as white solid (Mp = 141 °C, R_f = 0.70, 1/1 EtOAc/hexanes). Yield 74% (0.0226 g, 0.09 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 9H), 1.42 (m, 2H), 1.62-1.84 (m, 3H), 1.86-1.93 (m, 1H), 2.02-2.15 (m, 2H), 2.22 (s, 3H), 2.43 (m, 1H), 2.58 (m, 1H), 3.23 (dt, *J* = 3.3, 11.4 Hz, 1H), 3.56-3.61 (m, 1H), 3.85 (dd, *J* = 5.8, 13.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 23.4, 26.3, 27.8, 33.9, 36.5, 43.4, 45.6, 50.0, 54.7, 57.9, 182.6; IR (neat) 2952, 2916, 1680, 1465, 1236 cm^{-1}; HRMS calcd for $C_{14}H_{26}NOS$ (M^+ + H) 256.1735, found 256.1734. The analysis of the above crude reaction mixture by ^{1}H NMR indicated 86:7:7 ratio of **65**:**66**:**67**. **66** and **67** were not isolated. The Schmidt reaction of **63** (0.0303 g, 0.11 mmol, 1.0 equiv) carried out with BF_3•Et_2O (1.04 M, 0.31 mL, 3.0 equiv) in CH_2Cl_2 (2.1 mL, 0.05 M),

at rt for 2 h afforded the title compound in 69% yield (0.0187 g, 0.073 mmol). The analysis of the crude reaction mixture by ^{1}H NMR indicated 88:4:8 ratio of **65**:**66**:**67**.



8-*tert*-Butyl-9a-(methylthio)hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (66) and 8-*tert*-Butyl-2,3,7,8-tetrahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (67). According to the procedure for **57**, the reaction of **64** (0.0356, 0.13 mmol, 1.0 equiv, single diastereoisomer) and TfOH (0.055 mL, 0.63 mmol, 5.0 equiv) in CH_2Cl_2 (2.5 mL, 0.05 M) for 60 s at 0 °C, afforded after chromatography (1/4-1/1 EtOAc/hexanes) **66** (mixture of diastereoisomers, resulting from acid-promoted elimination-addition) as oil (R_f = 0.15, 1/4 EtOAc/hexanes), yield 57% (0.0184 g, 0.072 mmol) and **67** as oil (R_f = 0.31, 1/4 EtOAc/hexanes), yield 18% (0.0047 g, 0.023 mmol). Analysis of the crude reaction mixture by TLC and NMR did not indicate the formation of the bridged lactam. Note: compound **66** is very unstable; decomposition was observed during solvent removal, at rt over time, and during chromatography on SiO_2. Compound **66** (major isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.36 (m, 2H), 1.80-2.28 (m, 5H), 2.01 (s, 3H), 2.28 (m, 1H), 2.40-2.48 (m, 1H), 2.53-2.62 (m, 1H), 3.16 (m, 1H), 3.46-3.54 (m, 1H), 3.68-3.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 21.0, 24.6, 27.7, 33.1, 36.5, 40.9, 43.5, 45.6, 49.4, 72.5, 174.6; IR (neat) 2956, 2918, 1635, 1413, 1365, 1226, 1194, 1107 cm^{-1}; HRMS calcd for $C_{14}H_{25}NOSNa$ (M^+ + Na) 278.1555, found 278.1523. Compound **67**: ^{1}H

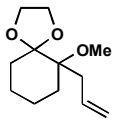
NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 9H), 1.67 (m, 1H), 1.77-1.89 (m, 2H), 1.98-2.13 (m, 2H), 2.41-2.51 (m, 2H), 2.54-2.72 (m, 2H), 3.58-3.66 (m, 1H), 3.68-3.76 (m, 1H), 5.00 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.8, 27.7, 33.6, 34.2, 36.3, 48.3, 50.2, 107.0, 137.9, 173.6; IR (neat) 3382, 2917, 2847, 1650, 1576, 1542, 1385, 1123 cm^{-1}; HRMS calcd for $C_{13}H_{21}NONa$ (M^+ + Na) 230.1521, found 230.1507. Interestingly, the analogous amide **59**, which differs only by the lack of the *t*-butyl substituent was found to be much more stable. The elimination was not observed in the course of the Schmidt reaction or during chromatography on SiO_2.



Note: the azide **72** is known.[173] There is an error in this reference; the single isomer obtained in the original report was incorrectly assigned as **74** (compound **25** in this reference). We now reassign the major product as **73** due to the IR and ^{13}C NMR signatures of the carbonyl group in this molecule (1680 cm^{-1} and 181.9 ppm, respectively). In addition, we have been able to isolate legitimate **73** in the repeated reaction as shown below.

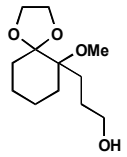
6-(Phenylthio)-1-azabicyclo[4.3.1]decan-10-one (73) and 9a-(Phenylthio) hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (74). According to the general, the reaction of **72** (0.102 g, 0.35 mmol, 1.0 equiv) and TfOH (0.16 mL, 1.76 mmol, 5.0 equiv) in CH_2Cl_2 (7.0 mL, 0.05 M) for 2.5 min at 0 °C afforded after chromatography (1/2 EtOAc/hexanes) **73** as oil (R_f = 0.62, 1/1 EtOAc/hexanes), yield 35% (0.0322 g,

0.12 mmol), and **74** as oil (R_f = 0.38, 1/1 EtOAc/hexanes), yield 32% (0.0288 g, 0.11 mmol). Compound **73**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34-1.48 (m, 1H), 1.62-1.69 (m, 2H), 1.78-1.88 (m, 3H), 1.93-2.06 (m, 3H), 2.37 (dd, *J* = 6.3, 14.4 Hz, 1H), 2.78 (dt, *J* = 5.6, 13.7, 1H), 3.24-3.38 (m, 2H), 3.94 (dt, *J* = 6.4, 13.8 Hz, 1H), 7.28-7.34 (m, 3H), 7.60-7.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 23.6, 25.7, 36.3, 41.4, 49.7, 50.1, 61.5, 128.4, 128.7, 133.0, 135.9, 181.9; IR (neat) 2920, 1680 cm^{-1}; HRMS calcd for $C_{15}H_{20}NOS$ (M^+ + H) 262.1266, found 262.1262. Compound **74**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47-1.68 (m, 3H), 1.71-1.84 (m, 2H), 1.88-1.98 (m, 1H), 1.99-2.06 (m, 1H), 2.20-2.32 (m, 2H), 2.37-2.45(m, 1H), 2.60 (dd, *J* = 5.7, 14.0 Hz, 1H), 3.27 (t, *J* = 13.8 Hz, 1H), 3.45-3.56 (m, 2H), 7.32-7.43 (m, 3H), 7.48-7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 23.7, 24.9, 37.2, 40.9, 44.0, 49.6, 77.0, 129.1, 129.3, 132.1, 136.8, 174.6; IR (neat) 2930, 1625, 1430, 1395, 1190 cm^{-1}; HRMS calcd for $C_{15}H_{20}NOS$ (M^+ + H) 262.1266, found 262.1257.

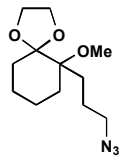


6-Allyl-6-methoxy-1,4-dioxaspiro[4.5]decane (76). A solution of ketone **75**[382] (5.35 g, 31.8 mmol, 1.0 equiv), ethylene glycol (3.7 mL, 63.7 mmol, 2.0 equiv), *p*TsOH (0.30 g, 1.60 mmol, 0.05 equiv) and benzene (20 mL) was heated under Dean-Stark trap for 15 h. The reaction mixture was cooled to rt, washed with sat. $NaHCO_3$ (1 x 20 mL), dried over Na_2SO_4 and concentrated. Chromatography (1/10 Et_2O/Hexanes) afforded the title compound as oil (R_f = 0.25, 1/3 Et_2O/hexanes).

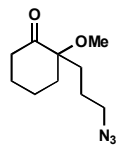
Yield 44% (2.95 g, 13.9 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37-1.62 (m, 6H), 1.78-1.88 (m, 2H), 2.23 (ddt, *J* = 1.2, 7.4, 15.3 Hz, 1H), 2.56 (ddt, *J* = 1.4, 6.8, 15.2 Hz, 1H), 3.32 (s, 3H), 3.92 (m, 4H), 3.88-4.02 (m, 2H), 5.87-5.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 23.0, 31.1, 31.9, 34.8, 50.1, 64.3, 65.0, 79.2, 111.4, 116.0, 135.0; IR (neat) 2937, 2882, 1180, 1088 cm^{-1}; HRMS calcd for $C_{12}H_{20}O_3Na$ (M^+ + Na) 235.1310, found 235.1320.



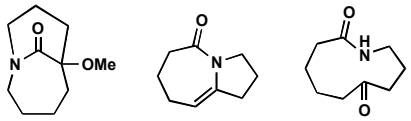
3-(6-Methoxy-1,4-dioxaspiro[4.5]decan-6-yl)propan-1-ol (77). To a solution of **76** (2.27 g, 10.7 mmol, 1.0 equiv) in THF (40 mL), BH_3 (2.0 M, THF, 8.1 mL, 16.1 mmol, 1.5 equiv) was added dropwise at 0 °C. After stirring for 30 min at rt, H_2O (7.1 mL), followed by NaOH (3.0 M, H_2O, 11.6 mL) and H_2O_2 (30%, 7.8 mL) were added at 0 °C. After stirring for 2 h at rt, the reaction mixture was extracted with EtOAc (3 x 100 mL), dried (Na_2SO_4) and concentrated. Chromatography (1/1 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.30, 1/1 EtOAc/hexanes). Yield 60% (1.49 g, 6.5 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (m, 1H), 1.41-1.66 (m, 8H), 1.73-1.86 (m, 3H), 2.11 (br, 1H), 3.28 (s, 3H), 3.60 (m, 2H), 3.86-3.97 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 22.9, 26.0, 26.5, 31.2, 32.1, 50.4, 63.6, 64.3, 65.0, 79.0, 111.8; IR (neat) 3404, 2949, 1180, 1086, 955 cm^{-1}; HRMS calcd for $C_{12}H_{22}O_4Na$ (M^+ + Na) 253.1416, found 253.1409.



6-(3-Azidopropyl)-6-methoxy-1,4-dioxaspiro[4.5]decane (78). To a solution of **77** (1.10 g, 4.8 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL), Et_3N (1.0 mL, 7.2 mmol, 1.5 equiv), followed by MsCl (0.56 mL, 7.2 mmol, 1.5 equiv) were added at 0 °C. After stirring for 1 h at rt, the reaction was quenched with sat. $NaHCO_3$ (20 mL), extracted with CH_2Cl_2 (3 x 50 mL), washed with brine (1 x 20 mL), dried and concentrated. To the solution of the crude mesylate (4.8 mmol, 1.0 equiv) in DMF (20 mL), NaN_3 (1.56 g, 24.0 mmol, 5.0 equiv) was added and the reaction was stirred at 80 °C for 2 h. Ether (150 mL) was added, and the mixture was washed with water (4 x 50 mL) and brine (1 x 50 mL). The organic layer was dried (Na_2SO_4) and concentrated. *Caution! An explosion occurred during solvent removal under reduced pressure;* the title compound was used in the next step without further purification, and it was not concentrated to dryness. (R_f = 0.57, 1/4 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-1.58 (m, 6H), 1.61-1.69 (m, 2H), 1.72-1.86 (m, 3H), 3.26 (m, 4H), 3.86-3.96 (m, 4H), 4.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 22.9, 22.9, 27.1, 30.9, 32.1, 50.1, 52.3, 64.2, 64.9, 78.8, 111.6; IR (neat) 2953, 2095, 1178, 1086 cm^{-1}; HRMS calcd for $C_{12}H_{21}N_3O_3Na$ (M^+ + Na) 278.1480, found 278.1494.

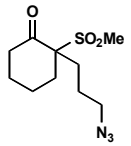


2-(3-Azidopropyl)-2-methoxycyclohexanone (79). To a solution of crude **78** (4.5 mmol, 1.0 equiv) in CH_3CN/H_2O (98%, 10 mL), $LiBF_4$ (1.0 M, CH_3CN, 4.5 mL, 1.0 equiv) was added at rt, and the resulting mixture was stirred at rt for 7 days. Workup with H_2O/Et_2O, followed by chromatography (1/4 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.50, 1/4 EtOAc/hexanes). Yield 65% (three steps) (0.62 g, 2.9 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.48-1.78 (m, 6H), 1.89-2.04 (m, 3H), 2.14-2.22 (m, 1H), 2.27-2.34 (m, 1H), 2.66-2.75 (m, 1H), 3.17 (s, 3H), 3.29-3.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 22.1, 27.8, 28.0, 37.0, 39.4, 50.7, 51.7, 82.1, 212.5; IR (neat) 2942, 2097, 1717, 1457, 1258, 1073 cm^{-1}; HRMS calcd for $C_{10}H_{17}N_3O_2Na$ (M^+ + Na) 234.1218, found 234.1210.



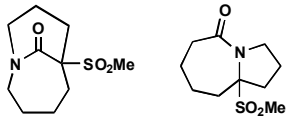
6-Methoxy-1-azabicyclo[4.3.1]decan-10-one (80), 2,3,7,8-Tetrahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (81) and Azecane-2,7-dione (82). According to the general procedure, the reaction of **79** (0.0827 g, 0.39 mmol, 1.0 equiv) and TfOH (0.18 mL, 1.96 mmol, 5.0 equiv) in CH_2Cl_2 (7.6 mL, 0.05 M) for 1 min at 0 °C afforded after purification by PTLC (EtOAc) **80** as oil (R_f = 0.49, EtOAc/hexanes), yield 23% (0.0167 g, 0.091 mmol), **81** as oil (R_f = 0.52, EtOAc), yield 23% (0.0136 g, 0.090 mmol), and **82** as oil (R_f = 0.39, EtOAc), yield 29% (0.0189 g, 0.11 mmol). Compound **80**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.56-2.01 (m, 10H), 2.26-2.33 (m, 1H), 2.69-2.78 (m, 1H), 3.28 (dt, *J* = 2.9, 11.4 Hz, 1H), 3.39 (s, 3H), 3.87-3.97 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.4, 25.0, 32.2, 41.4, 49.1, 50.5, 51.9, 83.7, 183.0; IR (neat) 2931, 1682, 1445, 1177 cm^{-1}; HRMS calcd for $C_{10}H_{18}NO_2$ (M^+ + H) 184.1338, found 184.1327. Compound **81**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-1.92 (m, 4H), 2.22-2.31 (m, 2H), 2.51-2.58 (m, 2H), 2.59-2.65 (m, 2H), 3.70 (t, *J* = 7.2 Hz, 2H), 4.91 (t, *J* = 4.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 21.4, 29.0, 34.5, 37.8, 49.0, 104.3, 137.1, 173.0; IR (neat) 2927, 1647, 1396, 1223 cm^{-1}; HRMS calcd for $C_9H_{14}NO$ (M^+ + H) 152.1075, found 152.1066. Compound **82**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of ketone and enol tautomers) 1.47-2.25 (m, 10H), 2.49 (dd, *J* = 6.9, 14.0 Hz, 1H), 2.87 (t, *J* = 13.7 Hz, 1H), 3.17 (br, 1H), 3.31-3.42 (m, 1H), 3.77-3.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ketone peaks) 22.2, 24.3, 27.6, 36.9, 39.5, 41.0, 41.5, 173.9, 215.1; IR (neat) 3350, 2932, 1701, 1616, 1456, 1437, 1196, 1183, 980 cm^{-1}; HRMS calcd for $C_9H_{16}NO_2$ (M^+ + H) 170.1181, found 170.1177.



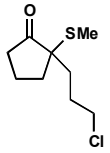
2-(3-Azidopropyl)-2-(methylsulfonyl)cyclohexanone (83). To a solution of **57** (0.0549 g, 0.24 mmol, 1.0 equiv) in CH_2Cl_2 (4.0 mL) *m*CPBA (77%, 0.11 g, 0.48 mmol, 2.0 equiv) was added at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was washed with saturated $NaHCO_3$ (5 x 10 mL), brine (1 x 10 mL), dried and concentrated. Chromatography (1/1 EtOAc/hexanes) afforded the title compound

as oil (R_f = 0.75, 1/1 EtOAc/hexanes). Yield 78% (0.0486 g, 0.19 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (m, 1H), 1.61-1.80 (m, 3H), 1.84-2.08 (m, 3H), 2.09-2.22 (m, 2H), 2.53 (dt, *J* = 4.5, 16.7 Hz, 1H), 2.63-2.72 (m, 1H), 2.80 (m, 1H), 2.89 (s, 3H), 3.27-3.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 23.6, 24.5, 28.5, 30.4, 37.2, 40.8, 51.2, 74.3, 206.6; IR (neat) 2947, 2098, 1701, 1298, 1126 cm^{-1}; HRMS calcd for $C_{10}H_{17}N_3O_3SNa$ (M^+ + Na) 282.0888, found 282.0897.



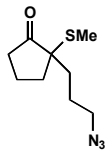
6-(Methylsulfonyl)-1-azabicyclo[4.3.1]decan-10-one (84) and 9a-(Methylsulfonyl)hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (85). According to the general procedure, the reaction of **83** (0.0990 g, 0.38 mmol, 1.0 equiv) and TfOH (0.17 mL, 1.91 mmol, 5.0 equiv) in CH_2Cl_2 (7.5 mL, 0.05 M) for 30 s at 0 °C afforded after purification by PTLC (EtOAc) **84** as oil (R_f = 0.46, EtOAc), yield 48% (0.0418 g, 0.18 mmol), and **85** as oil (R_f = 0.21, EtOAc), yield ca. 13% (0.0117 g, 0.051 mmol). Note: compound **85** is very unstable; decomposition was observed during solvent removal, at rt over short periods of time, and during chromatography on SiO_2. Despite numerous attempts to obtain analytically pure **85**, samples of **85** were always contaminated by elimination side products. Compound **84**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70-2.03 (m, 7H), 2.06-2.11 (m, 1H), 2.44 (dd, *J* = 8.4, 14.9 Hz, 1H), 2.75-2.83 (m, 1H), 2.87-2.96 (m, 1H), 3.19 (s, 3H), 3.31-3.46 (m, 2H), 3.92-4.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 24.1, 26.0, 28.6, 34.5, 38.4, 48.3,

50.6, 72.3, 177.7; IR (neat) 3416, 1666, 1288, 1134 cm^{-1}; HRMS calcd for $C_{10}H_{17}NO_3SNa$ (M^+ + Na) 254.0827, found 254.0830. Compound **85**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.50-2.45 (m, 8H), 2.64 (ddd, *J* = 2.0, 7.8, 15.0 Hz, 1H), 2.75 (d, *J* = 13.6 Hz, 1H), 2.78-2.92 (m, 2H), 2.82 (s, 3H), 3.82-3.95 (m, 1H), 4.10 (ddt, *J* = 1.9, 9.6, 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 26.6, 30.7, 36.0, 36.3, 37.4, 48.1, 58.6, 89.4, 172.6 ; IR (neat) 2930, 1651, 1454, 1296, 1130 cm^{-1}; HRMS calcd for $C_{10}H_{21}N_2O_3S$ (M^+ + NH_4) 249.1273, found 249.1270.

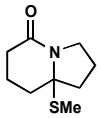


2-(3-Chloropropyl)-2-(methylthio)cyclopentanone (87). According to the procedure for **56**, the reaction of **86** (1.0 g, 7.7 mmol, 1.0 equiv), KH (0.77 g, 19.2 mmol, 2.5 equiv), and 1-chloro-3-iodopropane (2.50 mL, 23.1 mmol, 3.0 equiv) in THF (20 mL) for 48 h at rt, followed by reflux for 30 min, afforded after chromatography (1/20 EtOAc/hexanes, followed by 1/10 Et_2O/cyclohexanes) **87** as oil (R_f = 0.41, 1/10 EtOAc/hexanes), yield 37% (0.59 g, 2.9 mmol). Note: the crude reaction mixture is unstable and must be chromatographed immediately after work-up. The title compound is unstable at room temperature. ^1H NMR (400 MHz, $CDCl_3$) δ 1.47-1.58 (m, 1H), 1.66-1.77 (m, 1H), 1.84-2.21 (m, 7H), 1.91 (s, 3H), 2.59-2.69 (m, 1H), 3.51-3.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7, 18.2, 27.8, 28.4,

35.2, 35.4, 45.1, 54.8, 210.3; IR (neat) 2958, 1720, 1445, 1161 cm^{-1}; HRMS calcd for $C_9H_{16}ClOS$ (M^+ + H) 207.0610, found 207.0632.

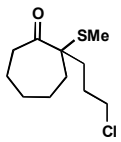


2-(3-Azidopropyl)-2-(methylthio)cyclopentanone (88). According to the general procedure, The reaction of **87** (0.32 g, 1.55 mmol, 1.0 equiv) and NaN_3 (0.54 g, 8.30 mmol, 5.0 equiv) in DMF (20 mL) at 80 °C for 2.5 h, afforded after chromatography (1/4 Et_2O/hexanes, followed by 1/20 EtOAc/hexanes) the title compound as oil (R_f = 0.33, 1/10 EtOAc/hexanes), yield 77% (0.26 g, 1.23 mmol). Note: the title compound is unstable at room temperature, and it decomposes slowly at -20 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.42-1.56 (m, 2H), 1.81-2.20 (m, 7H), 1.90 (s, 3H), 2.58-2.68 (m, 1H), 3.27-3.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7, 18.1, 24.1, 28.2, 35.1, 35.4, 51.5, 54.9, 210.3; IR (neat) 2953, 2097, 1722, 1259, 1163 cm^{-1}; HRMS calcd for $C_9H_{19}N_4OS$ (M^+ + NH_4) 231.1280, found 231.1295.



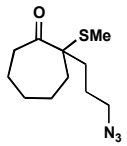
8a-(Methylthio)hexahydroindolizin-5(1H)-one (89). According to the general procedure, the reaction of **88** (0.0404 g, 0.19 mmol, 1.0 equiv) and TfOH (0.085 mL, 0.95 mmol, 5.0 equiv) in CH_2Cl_2 (3.8 mL, 0.05 M) at 0 °C for 60 s

afforded after purification by PTLC (EtOAc) the title compound as oil (R_f = 0.30, 1/1 EtOAc/hexanes), yield 43% (0.0151 g, 0.082 mmol). Note: the title compound is very unstable; decomposition was observed during solvent removal (temp. must be kept below 35 °C to prevent significant decomposition), at rt over short periods of time, and during chromatography on SiO_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54-1.62 (m, 2H), 1.71-1.87 (m, 2H), 1.88-1.96 (m, 1H), 2.00 (s, 3H), 2.22-2.38 (m, 4H), 2.42-2.54 (m, 1H), 3.43-3.51 (m, 1H), 3.68-3.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 17.8, 20.7, 30.5, 33.6, 39.6, 45.1, 73.7, 169.6; IR (neat) 2953, 2918, 1643, 1437, 1400, 1340, 1184 cm^{-1}; HRMS calcd for $C_9H_{16}NOS$ (M^+ + H) 186.0953, found 186.0941. Reactions of **88** with BF_3•Et_2O (2.0 equiv, rt, 15 h) and $TiCl_4$ (2.0 equiv, rt, 2 h) afforded **89** in 40% and 48% yields, respectively. Analysis of crude reaction mixtures by NMR did not indicate the formation of the bridged amide.

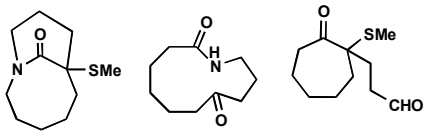


2-(3-Chloropropyl)-2-(methylthio)cycloheptanone (91). According to the procedure for **56**, the reaction of **90** (1.0 g, 6.3 mmol, 1.0 equiv), KH (0.63 g, 15.8 mmol, 2.5 equiv), and 1-chloro-3-iodopropane (2.03 mL, 18.9 mmol, 3.0 equiv) in THF (20 mL) for 48 h at rt, followed by reflux for 30 min, afforded after chromatography (1/25 EtOAc/hexanes) **90** as oil (R_f = 0.48, 1/10 EtOAc/hexanes), yield 64% (0.95 g, 4.0 mmol). Note: the crude reaction mixture is unstable and must be chromatographed immediately after work-up. The title compound is unstable at

room temperature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12-1.23 (m, 1H), 1.35 (q, *J* = 8.7 Hz, 2H), 1.42-1.52 (m, 1H), 1.54-1.63 (m, 1H), 1.77 (s, 3H), 1.71-1.94 (m, 5H), 1.96-2.07 (m, 2H), 2.33 (q, *J* = 7.6 Hz, 1H), 3.07 (dt, *J* = 2.6, 11.8 Hz, 1H), 3.51-3.59 (m, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 24.5, 25.9, 26.3, 27.2, 30.2, 32.1, 38.9, 45.3, 57.7, 206.0; IR (neat) 2926, 1686, 1460, 1443, 1155 cm^{-1}; HRMS calcd for $C_{11}H_{20}ClOS$ (M^+ + H) 235.0923, found 235.0942.

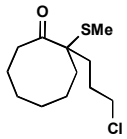


2-(3-Azidopropyl)-2-(methylthio)cycloheptanone (92). According to the general procedure, the reaction of **91** (0.85 g, 3.8 mmol, 1.0 equiv) and NaN_3 (1.25 g, 19.2 mmol, 5.0 equiv) in DMF (20 mL) at 80 °C for 2.5 h, afforded after chromatography (1/20 EtOAc/hexanes) the title compound as oil (R_f = 0.46, 1/10 EtOAc/hexanes), yield 85% (0.74 g, 3.1 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10-1.21 (m, 1H), 1.35 (q, *J* = 9.9 Hz, 2H), 1.44-1.60 (m, 3H), 1.75 (s, 3H), 1.64-2.04 (m, 6H), 2.32 (q, *J* = 7.4 Hz, 1H), 3.01-3.10 (m, 1H), 3.25-3.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 23.2, 24.5, 25.7, 26.3, 30.2, 32.1, 38.9, 51.6, 57.7, 206.1; IR (neat) 2926, 2858, 2097, 1686, 1456, 1259, 1155 cm^{-1}; HRMS calcd for $C_{11}H_{19}N_3OS$ (M^+) 241.1249, found 241.1272.

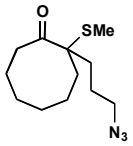


7-(Methylthio)-1-azabicyclo[5.3.1]undecan-11-one (93), Azacycloundecane-2,8-dione (94), and 3-(1-(Methylthio)-2-oxocycloheptyl)propanal (95). According to the general procedure, the reaction of **92** (0.0435 g, 0.18 mmol, 1.0 equiv) and TfOH (0.080 mL, 0.90 mmol, 5.0 equiv) in CH_2Cl_2 (3.6 mL, 0.05 M) at 0 °C for 30 min afforded after purification by chromatography (1/2 EtOAc/hexanes) **93** as oil (R_f = 0.44, 1/1 EtOAc/hexanes), yield 62% (0.0237 g, 0.11 mmol), **94** as oil (R_f = 0.10 1/1 EtOAc/hexanes), yield 11% (0.0038 g, 0.021 mmol), and **95** as oil (R_f = 0.84 1/1 EtOAc/hexanes), yield 20% (0.0075 g, 0.035 mmol). Compound **93**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.55 (m, 2H), 1.65-1.77 (m, 3H), 1.86-2.21 (m, 6H), 2.18 (s, 3H), 2.25-2.32 (m, 1H), 2.74 (dd, *J* = 4.5, 13.5 Hz, 1H), 3.21-3.28 (m, 1H), 3.61 (dt, *J* = 3.2, 11.9 Hz, 1H), 4.60 (dt, *J* = 3.6, 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 22.6, 24.8, 24.8, 32.2, 34.8, 48.3, 48.8, 50.0, 54.3, 178.1; IR (neat) 2925, 2856, 1650, 1488, 1444, 1351, 1193 cm^{-1}; HRMS calcd for $C_{11}H_{20}NOS$ (M^+ + H) 214.1266, found 214.1264. Compound **94**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46-1.54 (m, 2H), 1.62-1.71 (m, 4H), 1.96-2.11 (m, 4H), 2.38-2.49 (m, 4H), 3.41 (q, *J* = 6.0 Hz, 2H), 5.46 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 23.4, 24.1, 26.6, 38.8, 39.4, 40.2, 42.7, 174.1, 213.6; IR (neat) 3314, 2930, 1699, 1635, 1551, 1439, 1408, 1211, 1124 cm^{-1}; HRMS calcd for $C_{10}H_{18}NO_2$ (M^+ + H) 184.1338, found 184.1331. Compound **95**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15-1.25 (m, 1H), 1.33-1.42 (m, 1H), 1.45-1.54 (m, 1H), 1.77 (s, 3H), 1.72-2.01 (m,

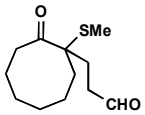
6H), 2.25-2.42 (m, 2H), 2.46-2.56 (m, 1H), 2.57-2.68 (m, 1H), 3.09 (t, J = 12.1 Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 20.9, 24.5, 26.4, 30.2, 32.2, 38.8, 39.0, 57.8, 201.5, 206.0; IR (neat) 2926, 2856, 2721, 1722, 1688, 1456, 1443, 1155 cm^{-1}; HRMS calcd for $C_{11}H_{19}O_2S$ (M^+ + H) 215.1106, found 215.1103. Reactions of **92** with BF_3•Et_2O (3.0 equiv, rt, 48 h) and $TiCl_4$ (3.0 equiv, reflux, 24 h) afforded **93** and **94** in 71% and 13%, and 22% and 43% yields, respectively.



2-(3-Chloropropyl)-2-(methylthio)cyclooctanone (97). According to the procedure for **56**, the reaction of **96** (1.0 g, 5.8 mmol, 1.0 equiv), KH (0.58 g, 14.5 mmol, 2.5 equiv), and 3-chloro-1-iodopropane (1.87 mL, 17.4 mmol, 3.0 equiv) in THF (35 mL) for 48 h at rt, followed by reflux for 30 min, afforded after chromatography (1/40 EtOAc/hexanes) **97** as oil (R_f = 0.54, 1/10 EtOAc/hexanes), yield 75% (1.09 g, 4.4 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81-0.93 (m, 1H), 1.18-1.29 (m, 1H), 1.39-1.50 (m, 1H), 1.55-2.06 (m, 10H), 1.73 (s, 3H), 2.15-2.24 (m, 2H), 3.14 (dt, J = 3.2, 13.1 Hz, 1H), 3.61 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 23.9, 24.6, 25.2, 26.0, 27.1, 28.7, 30.7, 36.4, 45.4, 58.1, 209.2; IR (neat) 2938, 1694, 1447, 1318, 1231, 1125 cm^{-1}; HRMS calcd for $C_{12}H_{21}ClOSNa$ (M^+ +Na) 271.0899, found 271.0899.

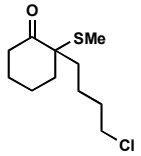


2-(3-Azidopropyl)-2-(methylthio)cyclooctanone (98). According to the general procedure, the reaction of **97** (1.08 g, 4.4 mmol, 1.0 equiv) and NaN_3 (1.42 g, 21.8 mmol, 5.0 equiv) in DMF (20 mL) at 80 °C for 2 h, afforded after chromatography (1/30 EtOAc/hexanes) the title compound as oil (R_f = 0.41, 1/10 EtOAc/hexanes), yield 90% (1.0 g, 3.9 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77-0.88 (m, 1H), 1.21 (q, *J* = 12.4 Hz, 1H), 1.38-1.93 (m, 11H), 1.68 (s, 3H), 2.11-2.21 (m, 2H), 3.11 (dt, *J* = 1.7, 12.2 Hz, 1H), 3.34 (t, *J* = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 23.2, 23.5, 24.5, 25.2, 26.0, 28.6, 30.6, 36.4, 51.7, 58.1, 209.2; IR (neat) 2929, 2094, 2682, 1467, 1446, 1259, 1116 cm^{-1}; HRMS calcd for $C_{12}H_{21}N_3OSNa$ (M^+ +Na) 278.1303, found 278.1309.

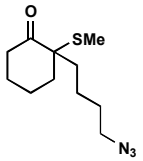


3-(1-(Methylthio)-2-oxocyclooctyl)propanal (99). According to the general procedure, the reaction of **98** (0.159 g, 0.62 mmol, 1.0 equiv) and TfOH (0.28 mL, 3.1 mmol, 5.0 equiv) in CH_2Cl_2 (12.2 mL, 0.05 M) at 0 °C for 1 h, followed by rt for 30 min afforded after purification by chromatography (1/4 EtOAc/hexanes) the title compound as oil as oil (R_f = 0.48, 1/4 EtOAc/hexanes). Yield 30% (0.0412 g, 0.18 mmol). Note: the title compound is unstable; facile decomposition was observed at rt. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81-0.93 (m, 1H), 1.19-1.30 (m, 1H), 1.40-1.94 (m,

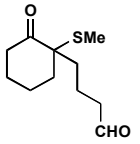
8H), 1.70 (s, 3H), 2.16-2.46 (m, 4H), 2.62-2.71 (m, 1H), 3.14 (dt, *J* = 3.0, 12.6 Hz, 1H), 9.85 (d, J = 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 19.3, 24.4, 25.2, 26.0, 28.7, 30.6, 36.5, 38.7, 58.0, 201.6, 209.2; IR (neat) 2928, 2722, 1723, 1682, 1468, 1447, 1117, 1083 cm^{-1}; HRMS calcd for $C_{12}H_{20}O_2SNa$ (M^+ +Na) 251.1082, found 251.1083. Note: no conversion was observed in reactions of **98** with BF_3•Et_2O, $TiCl_4$ and TFA at temperatures ranging from rt to 45 °C by analysis of crude reaction mixtures by NMR.



2-(4-Chlorobutyl)-2-(methylthio)cyclohexanone (100). According to the procedure for **56**, the reaction of **55** (0.50 g, 3.5 mmol, 1.0 equiv), KH (0.15 g, 3.8 mmol, 1.1 equiv), and 4-chloro-1-iodopropane (1.30 mL, 10.4 mmol, 3.0 equiv) in THF (20 mL) for 48 h at rt, followed by reflux for 30 min, afforded after chromatography (1/40 EtOAc/hexanes) **100** as oil (R_f = 0.44, 1/10 EtOAc/hexanes), yield 67% (0.54 g, 2.3 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.42 (m, 1H), 1.52-1.89 (m, 8H), 1.80 (s, 3H), 1.92-2.11 (m, 3H), 2.18-2.27 (m, 1H), 3.12 (dt, *J* = 5.8, 14.3 Hz, 1H), 3.57 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 20.7, 21.0, 26.4, 32.3, 32.9, 36.1, 36.9, 44.9, 56.4, 206.8; IR (neat) 2937, 2862, 1693, 1446, 1417, 1317, 1124 cm^{-1}; HRMS calcd for $C_{11}H_{19}ClOSNa$ (M^+ +Na) 257.0743, found 257.0768.

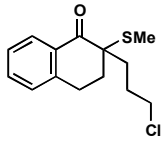


2-(4-Azidobutyl)-2-(methylthio)cyclohexanone (101). According to the general procedure, the reaction of **100** (0.51 g, 2.2 mmol, 1.0 equiv) and NaN_3 (0.71 g, 10.9 mmol, 5.0 equiv) in DMF (20 mL) at 80 °C for 2 h, afforded after chromatography (1/20 EtOAc/hexanes) the title compound as oil (R_f = 0.47, 1/10 EtOAc/hexanes), yield 86% (0.45 g, 1.9 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22-1.34 (m, 1H), 1.42-1.87 (m, 8H), 1.77 (s, 3H), 1.92-2.08 (m, 3H), 2.16-2.24 (m, 1H), 3.09 (dt, *J* = 6.2, 14.0 Hz, 1H), 3.29 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 20.6, 21.0, 26.3, 29.2, 32.7, 36.1, 36.9, 51.3, 56.4, 206.7; IR (neat) 2941, 2864, 2092, 1693, 1446, 1273, 1255, 1122 cm^{-1}; HRMS calcd for $C_{11}H_{19}N_3OSNa$ (M^+ +Na) 264.1147, found 264.1147.



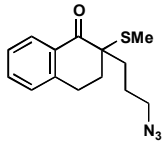
4-(1-(Methylthio)-2-oxocyclohexyl)butanal (102). According to the general procedure, the reaction of **101** (0.0769 g, 0.32 mmol, 1.0 equiv) and TfOH (0.14 mL, 1.6 mmol, 5.0 equiv) in CH_2Cl_2 (6.4 mL, 0.05 M) at 0 °C for 1.5 h afforded after purification by chromatography (1/4 EtOAc/hexanes) the title compound as oil as oil (R_f = 0.19, 1/10 EtOAc/hexanes). Yield 53% (0.0359 g, 0.17 mmol). Note: the title compound is unstable; rapid decomposition was observed at rt. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 1.47-1.89 (m, 7H), 1.80 (s, 3H), 1.94-2.12 (m, 3H), 2.18-2.27 (m, 1H), 2.50 (t, *J* = 6.6 Hz, 2H), 3.12 (dt, *J* = 6.0, 14.7 Hz, 1H), 9.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 16.1, 21.0, 26.4, 32.6, 36.0, 36.9, 44.0, 56.4, 202.1, 206.7; IR (neat) 2928, 2863, 2724, 1720, 1694, 1447, 1420, 1227, 1125 cm^{-1}; HRMS calcd for $C_{11}H_{19}O_2S$ (M^+ +H) 215.1106, found 215.1105. No conversion or decomposition was observed in reactions of **101** with BF_3•Et_2O or $TiCl_4$ at temperatures ranging from rt to 45 °C by analysis of crude reaction mixtures by NMR.

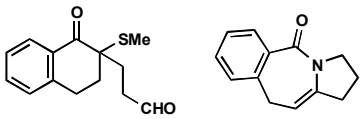


2-(3-chloropropyl)-2-(methylthio)-3,4-dihydronaphthalen-1(2H)-one (104). According to the procedure for **56**, the reaction of **103** (1.0 g, 5.2 mmol, 1.0 equiv), KH (0.52 g, 13.0 mmol, 2.5 equiv), and 3-chloro-1-iodopropane (1.70 mL, 15.6 mmol, 3.0 equiv) in THF (35 mL) for 48 h at rt, followed by reflux for 30 min, afforded after chromatography (1/40 EtOAc/hexanes) **104** as oil (R_f = 0.61, 1/10 EtOAc/hexanes), yield 55% (0.76 g, 2.8 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76-1.88 (m, 1H), 1.92 (s, 3H), 1.94-2.06 (m, 2H), 2.12-2.25 (m, 2H), 2.33 (dt, *J* = 4.8, 13.0 Hz, 1H), 2.83 (dq, *J* = 2.4, 17.2 Hz, 1H), 3.32 (m, 1H), 3.57-3.69 (m, 2H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.48 (dt, *J* = 1.4, 7.4 Hz, 1H), 8.14 (dd, *J* = 1.2, 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2, 25.3, 27.2, 30.9, 32.3, 45.3, 52.8, 126.8, 128.5, 128.5, 130.8, 133.1, 142.2, 190.7; IR (neat) 2920, 1670, 1601, 1454, 1429, 1292, 1231 cm^{-1}; HRMS calcd for $C_{14}H_{18}ClOS$ (M^+ +H) 269.0767, found

269.0747. Note: the reaction of **103** with 1.1 equiv of KH instead of 2.5 equiv afforded **104** in 54% yield.

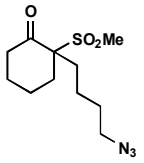


2-(3-azidopropyl)-2-(methylthio)-3,4-dihydronaphthalen-1(2H)-one (105). According to the general procedure, the reaction of **104** (0.71 g, 2.7 mmol, 1.0 equiv) and NaN_3 (0.86 g, 13.3 mmol, 5.0 equiv) in DMF (20 mL) at 80 °C for 2 h, afforded after chromatography (1/30 EtOAc/hexanes) the title compound as oil (R_f = 0.56, 1/10 EtOAc/hexanes), yield 67% (0.49 g, 1.8 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53-1.66 (m, 1H), 1.75-1.97 (m, 2H), 1.91 (s, 3H), 2.06 (dt, *J* = 3.9, 12.2 Hz, 1H), 2.17-2.25 (m, 1H), 2.34 (dt, *J* = 4.9, 13.7 Hz, 1H), 2.84 (dq, *J* = 2.1, 17.2 Hz, 1H), 3.26-3.45 (m, 3H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 8.3 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2, 23.5, 25.3, 30.6, 32.3, 51.7, 52.9, 126.8, 128.4, 128.5, 130.8, 133.1, 142.2, 190.7; IR (neat) 2094, 1666, 1600, 1454, 1351, 1292, 1234 cm^{-1}; HRMS calcd for $C_{14}H_{17}N_3OSNa$ (M^+ +Na) 298.0990, found 298.0968.

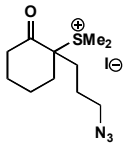


3-(2-(methylthio)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanal (106) and 2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a]azepin-5(10H)-one (107). According to

the general procedure, the reaction of **105** (0.1249 g, 0.45 mmol, 1.0 equiv) and TfOH (0.20 mL, 2.3 mmol, 5.0 equiv) in CH_2Cl_2 (9.0 mL, 0.05 M) at 0 °C for 0.5 h afforded after purification by chromatography (1/10 EtOAc/hexanes) **106** as oil (R_f = 0.38, 1/4 EtOAc/hexanes), yield 10% (0.0116 g, 0.05 mmol) and **107** as oil (R_f = 0.29, 1/4 EtOAc/hexanes), yield 14% (0.0124 g, 0.06 mmol). Compound **106**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 3H), 2.04-2.15 (m, 2H), 2.20 (dt, *J* = 4.9, 13.7 Hz, 1H), 2.32 (m, 1H), 2.40-2.62 (m, 2H), 2.72-2.79 (m, 1H), 3.23 (m, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 9.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3, 25.3, 25.7, 32.3, 38.7, 52.8, 126.9, 128.5, 128, 5, 130.8, 133.3, 142.2, 190.8, 201.4; IR (neat) 2922, 1665, 1601, 1454, 1429, 1298, 1235, 1129 cm^{-1}; HRMS calcd for $C_{14}H_{16}O_2SNa$ (M^+ +Na) 271.0769, found 271.0777. Compound **107**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (m, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 3.13 (d, *J* = 6.8 Hz, 2H), 3.87 (t, *J* = 7.3 Hz, 2H), 5.23 (t, *J* = 6.8 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 7.23 (dt, *J* = 1.0, 7.7 Hz, 1H), 7.34 (dt, *J* = 1.4, 7.4 Hz, 1H), 7.86 (dd, *J* = 1.2, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 31.1, 31.8, 48.8, 106.0, 126.4, 126.7, 130.9, 132.0, 133.5, 140.9, 142.0, 168.4; IR (neat) 2924, 1626, 1572, 1454, 1377, 1352, 1221, 1154 cm^{-1}; HRMS calcd for $C_{13}H_{14}NO$ (M^+ +H) 200.1075, found 200.1075. Note: <20% conversion was observed when the reaction was carried out with TfOH (5.0 equiv) for 60 s at 0 °C. No conversion was observed in reactions of **105** with BF_3•Et_2O or $TiCl_4$ at temperatures ranging from rt to 45 °C. Analysis of crude reaction mixtures did not indicate the formation of the bridged amide.

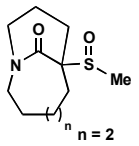


2-(4-azidobutyl)-2-(methylsulfonyl)cyclohexanone (108). According to the procedure for **83**, the reaction of **101** (0.0623 g, 0.26 mmol, 1.0 equiv) and *m*CPBA (77%, 0.12 g, 0.53 mmol, 2.50 equiv) in CH_2Cl_2 (10 mL) at 0 °C for 1 h, afforded after purification by chromatography (1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.70, 1/1 EtOAc/hexanes). Yield 76% (0.0536 g, 0.20 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24-1.36 (m, 1H), 1.42-1.83 (m, 6H), 1.93-2.22 (m, 4H), 2.53 (dt, *J* = 4.7, 16.6 Hz, 1H), 2.64-2.73 (m, 1H), 2.80 (m, 1H), 2.88 (s, 3H), 3.31 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 21.4, 24.4, 28.3, 29.2, 32.8, 37.1, 40.9, 50.9, 74.6, 206.8; IR (neat) 2945, 2097, 1703, 1298, 1126 cm^{-1}; HRMS calcd for $C_{11}H_{19}N_3O_3SNa$ (M^+ + Na) 296.1045, found 296.1034. Note: only decomposition was observed in the reaction of **108** with TfOH (5.0 equiv) under standard conditions.



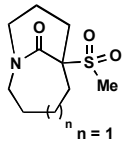
(1-(3-azidopropyl)-2-oxocyclohexyl)dimethylsulfonium iodide (109). To a solution of **57** (0.0492 g, 0.22 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) MeI (0.14 mL, 2.2 mmol, 10 equiv) was added, followed by $AgBF_4$ (0.0440 g, 0.22 mmol, 1.0 equiv) at rt and the resulting mixture was stirred at rt for 24 h. TLC analysis showed presence of starting material, 10 more equiv of MeI and 1.0 equiv of $AgBF_4$ were added and

stirring was continued for 2 h at rt. The reaction mixture was filtered and concentrated to afford the title compound which was used in the next step without further purification. Yield 27% (0.0218 g, 0.06 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63-1.75 (m, 2H), 1.98-2.38 (m, 7H), 2.62-2.85 (m, 3H), 2.81 (s, 3H), 2.85 (s, 3H), 3.38-3.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 21.1, 21.2, 23.1, 25.9, 29.1, 30.9, 39.3, 49.9, 74.6, 206.2; HRMS calcd for $C_{11}H_{20}N_3O_3S$ (M^+ + H) 242.1327, found 242.1328. Note: only decomposition was observed in the reaction of **109** with TfOH (5.0 equiv) under standard conditions.

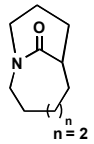


7-(Methylsulfinyl)-1-azabicyclo[5.3.1]undecan-11-one (110). To a solution of **93** (0.0248 g, 0.12 mmol) in CH_2Cl_2 (10 mL) *m*CPBA (77%, 0.0261 g, 0.12 mmol, 1.0 equiv) in CH_2Cl_2 (3.0 mL) was added at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was washed with sat. $NaHCO_3$ (2 x 10 mL), brine (1 x 10 mL), dried, concentrated and purified by chromatography (EtOAc) to give the title compound as oil as oil (R_f = 0.61, EtOAc). Yield 72% (0.0196 g, 0.09 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 1.47-2.25 (m, 21H), 2.25-2.32 (m, 1H), 2.40 (s, 3H), 2.44 (s, 3H), 2.71-2.93 (m, 4H), 3.25-3.35 (m, 2H), 3.61-3.76 (m, 2H), 4.52-4.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 23.1, 23.6, 23.9, 24.3, 24.3, 24.6, 25.0, 31.8, 32.2, 32.4, 33.8, 41.9, 47.1, 47.8, 48.2, 49.6, 49.7,

66.0, 67.7, 175.0, 176.8; IR (neat) 2930, 1636, 1447, 1289, 1277, 1210, 1026 cm^{-1}; HRMS calcd for $C_{11}H_{19}O_2SNa$ (M^+ +Na) 252.1034, found 252.1030.

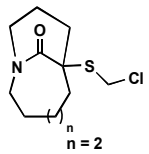


6-(Methylsulfonyl)-1-azabicyclo[4.3.1]decan-10-one (111). According to the procedure for **110** the reaction of **58** (0.0220 g, 0.11 mmol, 1.0 equiv) and *m*CPBA (0.0490 g, 0.22 mmol, 2.0 equiv) in CH_2Cl_2 (4.0 mL) at 0 °C for 1.5 h, afforded after purification by chromatography (EtOAc) the title compound. Yield 67% (0.0170 g, 0.075 mmol). Spectroscopic properties matched those previously described.

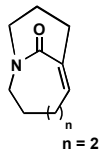


1-Azabicyclo[5.3.1]undecan-11-one (112). To a solution of **93** (0.0328 g, 0.15 mmol, 1.0 equiv) in dioxane (10 mL) Raney Ni (ca. 0.200 g) was added and the reaction mixture was heated to reflux for 1 h. The reaction mixture was cooled to rt, filtered through a cotton pad and concentrated. Known amount of benzene was added as the internal standard, and the reaction was analyzed by ^1H NMR. Yield 86%. Purification by PLTC (EtOAc) afforded the title compound as oil (R_f = 0.40-0.55, EtOAc). Yield 43% (0.0110 g, 0.066 mmol). Note: the compound is unstable on

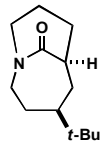
silica. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.57 (m, 3H), 1.61-.89 (m, 6H), 1.92-2.14 (m, 2H), 2.18-2.26 (m, 1H), 2.69-2.82 (m, 2H), 3.18-3.26 (m, 1H), 3.66 (dt, *J* = 2.7, 11.8 Hz, 1H), 4.58 (dt, *J* = 3.8, 13.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 23.5, 25.3, 26.4, 32.3, 41.9, 41.9, 48.0, 49.6, 181.2; IR (neat) 2931, 2856, 1627, 1492, 1446, 1357, 1284, 1203, 1188, 1172 cm^{-1}; HRMS calcd for $C_{10}H_{18}NO$ (M^+ + H) 168.1388, found 168.1387.



7-(Chloromethylthio)-1-azabicyclo[5.3.1]undecan-11-one (113). To a solution of **93** (0.0323 g, 0.15 mmol) in CCl_4 (10 mL) N–Chlorosuccinimide (0.0227 g, 0.17 mmol, 1.1 equiv) was added at rt and the reaction mixture was stirred at rt for 2 h. The reaction mixture was filtered, concentrated and purified by chromatography (1/2 EtOAc/hexanes) to afford the title compound as oil (R_f = 0.60, 1/1 EtOAc/hexanes). Yield 58% (0.0220 g, 0.09 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.1.48-1.60 (m, 2H), 1,72-1.84 (m, 2H), 1.84-2.06 (m, 4H), 2.15 (m, 2H), 2.38 (m, 2H), 2.79 (dd, *J* = 4.6, 13.5 Hz, 1H), 3.27-3.39 (m, 1H), 3.65 (dt, *J* = 4.2, 11.5 Hz, 1H), 4.63 (dt, *J* = 3.6, 13.0 Hz, 1H), 4.92 (d, *J* = 12.6 Hz, 1H), 5.45 (d, *J* = 12.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 24.7, 24.7, 32.4, 34.5, 48.7, 48.7, 48.9, 49.9, 55.9, 177.7; IR (neat) 2930, 2854, 1640, 1445, 1434, 1354, 1333, 1208, 1198, 1046 cm^{-1}; HRMS calcd for $C_{11}H_{18}ClNOSNa$ (M^+ + Na) 270.0695, found 270.0698.



1-Azabicyclo[5.3.1]undec-6-en-11-one (114). A solution of **110** (0.0174 g, 0.076 mmol, 1.0 equiv) in toluene (10 mL) was heated to reflux for 72 h. The reaction mixture was cooled to rt and concentrated. Purification by chromatography (1/2 EtOAc/hexanes-EtOAc) afforded the title compound as oil (R_f = 0.70, EtOAc). Yield 36% (0.0045 g, 0.027 mmol). Monitoring of the reaction by NMR showed that only one of the diasteroisomeric sulfoxides underwent efficient elimination. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08-1.20 (m, 1H), 1.56-1.92 (m, 4H), 2.04-2.17 (m, 3H), 2.25-2.32 (m, 1H), 2.81 (t, *J* = 12.1 Hz, 1H), 2.87-2.99 (m, 2H), 3.16-3.23 (m, 1H), 4.33 (t, *J* = 14.1 Hz, 1H), 6.17 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 25.6, 30.5, 35.1, 36.6, 46.6, 56.1, 125.0, 141.8, 184.7; IR (neat) 2921, 2847, 1684, 1638, 1468, 1443, 1397, 1352, 1314, 1165, 1027 cm^{-1}; HRMS calcd for $C_{10}H_{16}NO$ (M^+ + H) 166.1232, found 166.1232. Note: a similar reaction of the phenyl sulfoxide prepared from **73** under thermal conditions led only to decomposition products, suggesting that [5.3.1] scaffold is the lower limit for a reasonable stability of compounds containing adjacent bridgehead olefin and bridgehead amide at the one-carbon bridge.



(4R,6S)-4-tert-butyl-1-azabicyclo[4.3.1]decan-10-one (115). According to the procedure for **112**, the reaction of **65** (0.0203 g, 0.08 mmol, 1.0 equiv) and Raney Ni (ca. 0.200 g) in dioxane (10 mL) at reflux for 1 h, afforded 1.3 to 1.0 mixture of cis (bottom) and trans (top) isomers. Purification by PTLC (1/3 EtOAc/hexanes) allowed for isolation of **115** as film in 19% yield (0.0031 g, 0.0015 mmol). Cis isomer decomposed during purification. Note: the compound is unstable on silica. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.12-1.18 (m, 2H), 1.60-1.72 (m, 4H), 1.88-1.93 (m, 1H), 2.12-2.73 (m, 2H), 2.74 (q, J = 6.6 Hz, 1H), 3.00-3.08 (m, 2H), 3.45-3.53 (m, 1H), 3.81-3.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 27.6, 28.1, 29.7, 32.6, 33.9, 44.0, 45.3, 46.6, 52.4, 188.9; IR (neat) 2949, 2926, 1699, 1462, 1394, 1365, 1165 cm^{-1}; HRMS calcd for $C_{13}H_{24}NO$ (M^+ + H) 210.1858, found 210.1842.

NMR study with azides 57, 61 and 62. General Procedure: NMR tube was charged with azide (1.0 equiv), CD_2Cl_2 and benzene as the internal standard. Reference spectrum was recorded, cap was removed, the tube was flushed argon, BF_3•Et_2O (3.0 equiv) was added at rt, the tube was flushed with argon and sealed. The reaction was monitored by NMR. After 24 h at rt the septum was removed and 0.20 mL of D_2O was added at rt. The tube was gently shaken and analyzed by NMR.

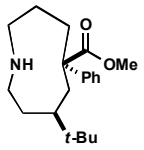
Reaction of azide 57: According to the general procedure, the reaction of **57** (0.0117 g, 0.052 mmol, 1.0 equiv), CD_2Cl_2 (0.70 mL) and $BF_3•Et_2O$ (0.98 M in CD_2Cl_2, 0.15 mL, 0.16 mmol, 3.0 equiv) for 24 h afforded **58** in 64% yield.

Reaction of azide 61: According to the general procedure, the reaction of **61** (0.0107 g, 0.038 mmol, 1.0 equiv), CD_2Cl_2 (0.70 mL) and $BF_3•Et_2O$ (0.94 M in CD_2Cl_2, 0.12 mL, 0.11 mmol, 3.0 equiv) for 24 h afforded **65** in 84% yield.

Reaction of azide 62: According to the general procedure, the reaction of **62** (0.01114 g, 0.040 mmol, 1.0 equiv), CD_2Cl_2 (0.70 mL) and $BF_3•Et_2O$ (1.0 M in CD_2Cl_2, 0.12 mL, 0.12 mmol, 3.0 equiv) for 24 h afforded **66** in 79% yield.

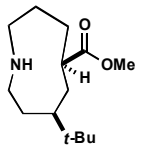
Transannular cyclization strategy

General procedure for hydrolysis of bridged amides: To a solution of amide (1.0 equiv) in MeOH (10 mL), HCl (4.0 M in dioxanes, 1.0 mL) was added at rt (pH = 1), and the reaction mixture was stirred at rt for appropriate time. The reaction was quenched with sat. NH_4Cl (10 mL), extracted with CH_2Cl_2 (3 x 50 mL), dried, and concentrated. Chromatography provided the title amino esters. Note: minor quantities (<10%) of some of the esters close spontaneously to bridged amides when put under high vacuum. This process can be easily monitored by TLC (R_f of bridged amides = 0.2-0.5, 1/4 EtOAc/hexanes; R_f of aminoesters = 0.3-0.6, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$).

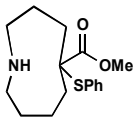


(7R)-Methyl 7-*tert*-butyl-5-phenylazonane-5-carboxylate (116). According to the general procedure, the reaction of amide **34** (0.0150 g, 0.053 mmol, 1.0 equiv) and HCl (4.0 M in dioxanes, 1.0 mL) in MeOH (10 mL) for 24 h at rt, afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title product as oil (R_f = 0.32, $NH_4OH/MeOH/CH_2Cl_2$), yield 89% (0.0151 g, 0.048 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 0.41 (s, 9H), 1.23-1.37 (m, 1H), 1.39-1.46 (m, 1H), 1.51-1.71 (m, 2H), 1.77-1.93 (m, 2H), 2.14-2.25 (m, 2H), 2.73-2.82 (m, 2H), 2.82-2.96 (m, 3H), 3.67 (s, 3H), 7.18-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 25.4, 27.3, 32.8, 34.0,

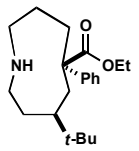
35.3, 37.7, 43.1, 46.3, 52.1, 55.2, 126.8, 126.9, 128.3, 144.8, 177.6; IR (neat) 2949, 2870, 1728, 1668, 1479, 1446, 1366, 1244, 1200, 1186, 1078, 910 cm^{-1}; HRMS calcd for $C_{20}H_{32}NO_2$ (M^+ + H) 318.2433, found 318.2424. Note: about 6% of the product closed to the parent amide **34** (diagnostic peak ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9H).



(7R)-Methyl 7-*tert*-butylazonane-5-carboxylate (117). According to the general procedure, the reaction of amide **3** (0.0250 g, 0.12 mmol, 1.0 equiv) and HCl (4.0 M in dioxanes, 1.5 mL) in MeOH (10 mL) for 13 h at rt, afforded after chromatography (1/15/85 NH_4OH/MeOH/CH_2Cl_2) the title product as oil (R_f = 0.26, NH_4OH/MeOH/CH_2Cl_2), yield 77% (0.0221 g, 0.092 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.13-1.23 (m, 1H), 1.43-1.62 (m, 3H), 1.66-1.96 (m, 4H), 1.98-2.08 (m, 1H), 2.68-2.88 (m, 5H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 24.7, 27.5, 27.6, 31.3, 32.3, 42.6, 43.9, 44.8, 48.3, 51.5, 177.6; IR (neat) 2947, 2868, 1734, 1684, 1475, 1435, 1366, 1161 cm^{-1}; HRMS calcd for $C_{14}H_{28}NO_2$ (M^+ + H) 242.2120, found 242.2094. Note: the compound was contaminated by <5% of the parent amide.

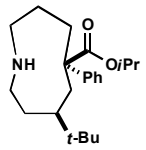


Methyl 5-(phenylthio)azonane-5-carboxylate (118). According to the general procedure, the reaction of amide **73** (0.0151 g, 0.058 mmol, 1.0 equiv) and HCl (4.0 M in dioxanes, 1.5 mL) in MeOH (10 mL) for 8 h at rt, afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title product as oil (R_f = 0.39, $NH_4OH/MeOH/CH_2Cl_2$), yield 84% (0.0143 g, 0.049 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.44-1.56 (m, 3H), 1.57-1.66 (m, 1H), 1.73-1.92 (m, 3H), 1.96-2.06 (m, 2H), 2.13-2.22 (m, 1H), 2.69-2.78 (m, 1H), 2.79-2.89 (m, 3H), 3.08 (br, 1H), 3.69 (s, 3H), 7.27-7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 21.3, 26.4, 27.2, 28.1, 41.8, 47.4, 52.0, 60.2, 128.7, 129.4, 131.0, 136.8, 173.9; IR (neat) 2943, 2918, 2849, 1724, 1580, 1472, 1437, 1364, 1248, 1194, 1144, 1087, 1040 cm^{-1}; HRMS calcd for $C_{16}H_{24}NO_2S$ (M^+ + H) 294.1528, found 294.1521. Note: the spontaneous closure was not observed.



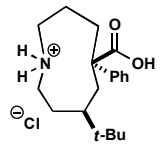
(7R)-Ethyl 7-*tert*-butyl-5-phenylazonane-5-carboxylate (119). According to the general procedure, the reaction of amide **34** (0.0250 g, 0.088 mmol, 1.0 equiv) and HCl (4.0 M in dioxanes, 1.5 mL) in EtOH (10 mL) for 24 h at rt, afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title product as oil (R_f = 0.31, $NH_4OH/MeOH/CH_2Cl_2$), yield 95% (0.0276 g, 0.083 mmol). ^1H NMR (400 MHz,

$CDCl_3$) δ 0.41 (s, 9H), 1.18 (dt, *J* = 0.8, 7.1 Hz, 3H), 1.24-1.36 (m, 1H), 1.37-1.44 (m, 1H), 1.53-1.70 (m, 2H), 1.73-1.91 (m, 2H), 2.12-2.25 (m, 2H), 2.50 (br, 1H), 1.67-2.94 (m, 5H), 4.02-4.12 (m, 1H), 4.18-4.28 (m, 1H), 7.17-7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.9, 25.3, 27.3, 33.0, 34.0, 35.3, 37.7, 43.2, 46.4, 55.1, 60.6, 126.6, 127.0, 128.2, 145.0, 177.1; IR (neat) 3375, 2951, 2870, 1724, 1599, 1580, 1478, 1447, 1366, 1242, 1168, 1078, 911, 860 cm^{-1}; HRMS calcd for $C_{21}H_{33}NO_2Na$ (M^+ + Na) 354.2409, found 354.2434. Note: the spontaneous closure was not observed.

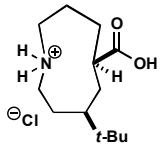


(7R)-Isopropyl 7-*tert*-butyl-5-phenylazonane-5-carboxylate (120). According to the general procedure, the reaction of amide **34** (0.0202 g, 0.071 mmol, 1.0 equiv) and HCl (4.0 M in dioxanes, 5.0 mL) in *i*PrOH (10 mL) for 24 h at rt, afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title product as oil (R_f = 0.21, $NH_4OH/MeOH/CH_2Cl_2$), yield 37% (0.0091 g, 0.026 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 0.41 (s, 9H), 0.86-0.99 (m, 1H), 1.08 (d, *J* = 6.2 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.24-1.38 (m, 1H), 1.39-1.46 (m, 1H), 1.54-1.72 (m, 2H), 1.78-1.88 (m, 1H), 2.12-2.22 (m, 2H), 2.68-2.98 (m, 5H), 5.02-5.11 (m, 1H), 7.16-7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 21.6, 21.7, 25.2, 27.3, 32.6, 34.0, 35.1, 37.6, 42.9, 46.2, 55.0, 67.7, 126.5, 127.0, 128.1, 145.0, 176.4; IR (neat) 3380, 2955,

2916, 1849, 1719, 1576, 1539, 1418, 1385, 1244, 1109 cm^{-1}; HRMS calcd for $C_{22}H_{36}NO_2$ (M^+ + H) 346.2746, found 346.2728. Note: the spontaneous closure was not observed.



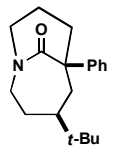
(4R)-4-*tert*-Butyl-6-carboxy-6-phenylazonanium chloride (121). To a solution of amide **34** (0.015 g, 0.053 mmol, 1.0 equiv) in THF (3 mL), HCl (6.0 M in H_2O, 3 mL) was added, and the resulting mixture was stirred at rt for 1.5 h. The solvent was removed to afford the corresponding amino acid (0.0167 g, 0.049 mmol, 93% yield), which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.35 (s, 9H), 1.22-1.50 (m, 2H), 1.61-2.03 (m, 5H), 2.09-2.20 (m, 1H), 2.34-2.43 (m, 1H), 2.97-3.06 (m, 2H), 3.09-3.26 (m, 2H), 7.18-7.36 (m, 5H), 8.65 (s, 1H), 9.54 (s, 1H), 12.6 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.4, 25.7, 26.7, 28.4, 33.9, 34.6, 37.7, 41.1, 44.2, 53.8, 126.7, 126.7, 128.1, 177.0; HRMS calcd for $C_{19}H_{30}NO_2$ (M^+ + H) 304.2277, found 304.2274.



(4R)-4-*tert*-Butyl-6-carboxyazonanium chloride (122). According to the procedure described above, the reaction of amide **3** (0.025 g, 0.12 mmol, 1.0 equiv),

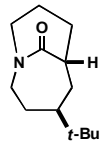
HCl (6.0 M in H_2O, 3 mL) in THF (3 mL) for 1.5 h at rt afforded the title amino acid (0.031 g, 0.12 mmol, 98% yield), which was used in the next step without further purification. Spectroscopic properties matched those previously described.[54]

General procedure for closure to the twisted amides: To a flask charged with aminoester (1.0 equiv) and toluene (5-10 mL), DBU (10 equiv) was added and the reaction mixture was heated to reflux until TLC analysis indicated full conversion to the bridged amide. Typically, 1 h for methyl esters. Solvent removal, followed by chromatography afforded the title amides.

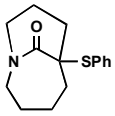


Lactam 34. According to the general procedure, the reaction of aminomethyl ester (0.0278 g, 0.09 mmol, 1.0 equiv) and DBU (0.14 mL, 0.90 mmol, 10 equiv) in toluene (5 mL) for 1 h, afforded after chromatography (1/2 EtOAc/hexanes) the title amide in 92% yield (0.0230 g, 0.081 mmol). Spectroscopic properties matched those previously described. Note: refluxing the aminomethylester in toluene under Dean-Stark trap for 24 h w/o DBU did not lead to any conversion to the bridged amide. Heating the aminoester at 120 °C under vacuum (5 h, no solvent) led to ca. 50% conversion along with decomposition products. Putting the aminomethylester under vacuum for 24 h at rt led to 11% conversion to amide. In addition, leaving the

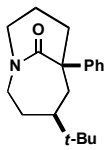
aminoester in a flask open to air for 2 weeks led to ca. 80% conversion to **34**, after 4 weeks 85% conversion.



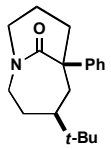
Lactam 3. According to the general procedure, the reaction of aminomethyl ester (0.020 g, 0.083 mmol, 1.0 equiv) and DBU (0.13 mL, 0.83 mmol, 10 equiv) in toluene (5 mL) for 1 h, afforded after chromatography (1/1 EtOAc/hexanes) the title amide in 48% yield (0.0083 g, 0.040 mmol). Spectroscopic properties matched those previously described. Note: lower yield in this case is caused by instability of **3** on SiO_2. NMR indicated clean conversion to the **3**.



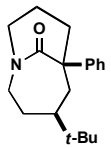
Lactam 73. According to the general procedure, the reaction of aminomethyl ester (0.012 g, 0.041 mmol, 1.0 equiv) and DBU (0.06 mL, 0.41 mmol, 10 equiv) in toluene (5 mL) for 1 h, afforded after chromatography (1/1 EtOAc/hexanes) the title amide in 84% yield (0.0089 g, 0.034 mmol). Spectroscopic properties matched those previously described.



Lactam 34 (From ethyl ester). According to the general procedure, the reaction of aminoethyl ester (0.025 g, 0.076 mmol, 1.0 equiv) and DBU (0.12 mL, 0.76 mmol, 10 equiv) in toluene (10 mL) for 18 h, afforded after chromatography (1/2 EtOAc/hexanes) the title amide in 85% yield (0.0183 g, 0.064 mmol). Note: the reaction is slower than with the methyl ester. Spectroscopic properties matched those previously described.

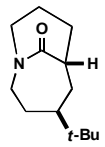


Amide 34 (From ispropyl ester). According to the general procedure, the reaction of aminoisopropyl ester (0.0062 g, 0.018 mmol, 1.0 equiv) and DBU (0.03 mL, 0.18 mmol, 10 equiv) in toluene (10 mL) for 7 days, afforded after chromatography (1/2 EtOAc/hexanes) the title amide in 49% yield (0.0025 g, 0.009 mmol). Note: ^{1}H NMR indicated 75% conversion. Spectroscopic properties matched those previously described.

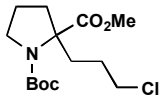


Amide 34 (From carboxylic acid). To a solution of amino acid (0.015 g, 0.044 mmol, 1.0 equiv) in DMSO (5 mL), DCC (1.0 M in CH_2Cl_2, 0.44 mL, 0.44 mmol, 10 equiv), followed by DMAP (0.054 g, 0.44 mmol, 10 equiv) was added and

the resulting mixture was stirred at rt for 20 h. The reaction was quenched with water (10 mL), diluted with ether (100 mL), washed with water (4 x 20 mL), brine (1 x 20 mL), dried and concentrated. Chromatography (1/3 EtOAc/hexanes) afforded the title amide in 79% yield (0.0099 g, 0.035 mmol). Spectroscopic properties matched those previously described.

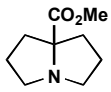


Amide 3 (From carboxylic acid). According to the procedure described above, the reaction of amino acid (0.031 g, 0.12 mmol, 1.0 equiv), DCC (1.0 M in CH_2Cl_2, 1.2 mL, 1.2 mmol, 10 equiv), and DMAP (0.15 g, 1.2 mmol, 10 equiv) in DMSO (5 mL) at rt for 20 h, afforded after chromatography (1/1 EtOAc/hexanes) the title amide in 59% yield (0.0083 g, 0.040 mmol). Spectroscopic properties matched those previously described. Note: lower yield in this case is caused by instability of **3** on SiO_2. NMR indicated clean conversion to the **3**, polymerization was not observed.



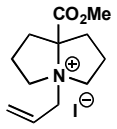
1-*tert*-Butyl 2-methyl 2-(3-chloropropyl)pyrrolidine-1,2-dicarboxylate (124). To a solution of LDA, prepared from *n*BuLi (2.3 M in hexanes, 2.44 mL, 5.6 mmol, 1.3 equiv) and diisopropylamine (0.86 mL, 6.04 mmol, 1.4 equiv) in THF (20 mL) at -78 °C for 20 min, **123** (1.0 g, 4.3 mmol, 1.0 equiv) in THF (10 mL) was

added dropwise at -78 °C. After 20 min 1-chloro-3-iodopropane (0.92 mL, 8.6 mmol, 2.0 equiv) was added, and the dry ice-acetone ice bath was removed. After stirring at rt for 19 h, the reaction mixture was quenched with NH_4Cl (20 mL), extracted with ether (3 x 100 mL), dried and concentrated. Chromatography (1/6 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.31, 1/4 EtOAc/hexanes). Yield 62% (1.07 g, 3.5 mmol). ^1H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.39 (s, 5.7H), 1.42 (s, 3.3H), 1.64-2.14 (m, 7H), 2.29 (dt, *J* = 4.6, 13.9 Hz, 1H), 3.33-3.42 (m, 1H), 3.44-3.75 (m, 4H), 3.68 (s, 1.1 H), 3.69 (s, 1.9H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 22.7, 23.1, 27.1, 27.6, 28.3, 28.4, 32.0, 32.8, 36.2, 37.5, 45.2, 48.5, 48.6, 52.1, 67.0, 67.6, 79.6, 80.2, 153.7, 154.1, 174.8, 175.1; IR (neat) 2974, 2918, 1742, 1697, 1391, 1366, 1163, 1132 cm^{-1}; HRMS calcd for $C_{14}H_{24}ClNO_4Na$ (M^+ + Na) 328.1292, found 328.1286.

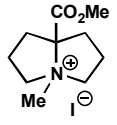


Methyl hexahydro-1H-pyrrolizine-7a-carboxylate (125). To a solution of **124** (0.567 g, 1.85 mmol, 1.0 equiv) in MeOH (15 mL), TMSCl (1.18 mL, 9.26 mmol, 5.0 equiv) was added dropwise at rt, and the reaction mixture was stirred at rt for 24 h. The reaction was quenched with sat. $NaHCO_3$ (10 mL) until pH >8, diluted with CH_2Cl_2 (50 mL), extracted with CH_2Cl_2 (3 x 50 mL), dried, concentrated and purified by chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) to afford the title compound as oil (R_f = 0.61, 1/10/90 NH_4OH/MeOH/CH_2Cl_2). Yield 89% (0.28 g,

1.65 mmol). The compound is known.[119] Described above method for its preparation compares preferably with the literature synthesis.[119]

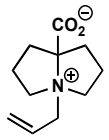


4-Allyl-7a-(methoxycarbonyl)octahydropyrrolizinium iodide (126). To a solution of amine **125** (0.0750 g, 0.44 g, 1.0 mmol) in CH_2Cl_2 (10 mL), allyliodide (0.21 mL, 2.22 mmol, 5.0 equiv) was added and the resulting mixture was stirred at rt for 22 h. Solvent removal afforded the title compound as oil. Yield 98% (0.145 g, 0.43 mmol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18-2.48 (m, 6H), 2.52-2.68 (m, 2H), 3.73-3.93 (m, 4H), 3.81 (s, 3H), 4.02 (d, J = 6.8 Hz, 2H), 5.60 (d, J = 10.0 Hz, 1H), 5.75 (d, J = 16.8 Hz, 1H), 5.92-6.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 33.7, 54.5, 62.0, 63.0, 86.7, 125.6, 129.2, 168.4; IR (neat) 2953, 2916, 2189, 1740, 1456, 1435, 1283, 1234, 1136, 1038, 920, 731 cm^{-1}; HRMS calcd for $C_{12}H_{20}NO_2$ (M^+) 210.1494, found 210.1495.



7a-(Methoxycarbonyl)-4-methyloctahydropyrrolizinium iodide (126a). To a solution of amine **125** (0.10 g, 0.59 g, 1.0 mmol) in CH_2Cl_2 (10 mL), methyliodide (0.37 mL, 5.9 mmol, 10.0 equiv) was added and the resulting mixture was stirred at rt for 21 h. Solvent removal afforded the title compound as solid (mp. = 121-2 °C, R_f = 0.67, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 99% (0.18 g, 0.58 mmol). ^{1}H NMR (400

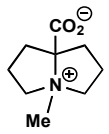
MHz, $CDCl_3$) δ 1.92-2.08 (m, 2H), 2.09-2.24 (m, 4H), 2.29-2.42 (m, 2H), 3.06 (s, 3H), 3.58 (s, 3H), 3.59-3.68 (m, 2H), 3.82-3.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 33.0, 48.7, 54.3, 65.8, 86.2, 168.0; IR (neat) 3477, 2953, 2189, 1738, 1470, 1454, 1286, 1229, 1138, 1011, 920, 731 cm^{-1}; HRMS calcd for $C_{10}H_{18}NO_2$ (M^+) 184.1338, found 184.1297.



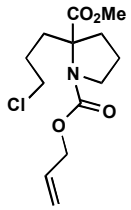
4-Allyloctahydropyrrolizinium-7a-carboxylate (127). To a solution of **126** (0.048 g, 0.14 mmol, 1.0 equiv) in THF (10 mL), NaOMe (0.081 g, 1.42 mmol, 10.0 equiv) was added, and the resulting mixture was heated at reflux for 30 min. Solvent removal and purification by chromatography (1/25/75 NH_3/MeOH/CH_2Cl_2) afforded the title compound as oil (R_f = 0.42, 1/20/80 NH_3/MeOH/CH_2Cl_2). Yield 59% (0.0161 g, 0.083 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 2.08-2.22 (m, 4H), 2.24-2.36 (m, 2H), 2.84-2.92 (m, 2H), 3.28-3.42 (m, 2H), 3.82-3.98 (m, 2H), 4.20 (d, *J* = 7.2 Hz, 2H), 5.57-5.69 (m, 2H), 5.90-6.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 34.2, 61.0, 61.5, 90.4, 126.8, 127.5, 169.6; IR (neat) 3437, 1620, 1462, 1383, 1360, 1013, 955 cm^{-1}; HRMS calcd for $C_{11}H_{18}NO_2$ (M^+) 196.1338, found 196.1317.

Note: the reaction of **126** (0.0568 g, 0.16 mmol, 1.0 equiv) and NaN_3 (0.0547 g, 0.81 mmol, 5.0 equiv) in THF (5 mL) for 30 h at reflux afforded **127** in 49% yield (0.0153 g, 0.08 mmol); the reaction of **126** (0.0705 g, 0.21 mmol, 1.0 equiv) and EtONa (0.147 g, 2.1 mmol, 10.0 equiv) in THF (10 mL) for 72 h at reflux afforded

127 in 55% yield (0.0224 g, 0.11 mmol). To further confirm the structure of **127**, the methyl analogue **126a** (0.0455 g, 0.15 mmol, 1.0 equiv) was subjected to the reaction with MeONa (0.083 g, 1.46 mmol, 10.0 equiv) in THF (10 mL) for 30 min at reflux. Interestingly, in this case, purification by chromatography led only to decomposition, however solvent removal afforded **127a**. A number of other reaction conditions were also tried (for example, reduction with NH_3/Na, Zn/AcOH, $NaCNBH_3$, SmI_2) but did not afford the desired ring-opened product.

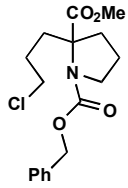


4-Methyloctahydropyrrolizinium-7a-carboxylate (127a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91-2.11 (m, 4H), 2.38-2.52 (m, 4H), 3.06 (s, 3H), 3.60 (t, J =7.3 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.0, 33.8, 47.1, 64.3, 88.1, 170.2; HRMS calcd for $C_9H_{16}NO_2$ (M^+) 170.1181, found 170.1148.



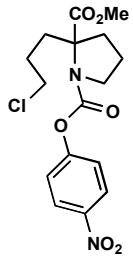
1-Allyl 2-methyl 2-(3-chloropropyl)pyrrolidine-1,2-dicarboxylate (128). To a solution of amine 125 (0.0744 g, 0.44 mmol, 1.0 equiv) in toluene (10 mL), allyl chloroformate (0.14 mL, 1.32 mmol, 3.0 equiv) was added at rt, and the resulting mixture was stirred at 100 °C for 30 min. Solvent removal, followed by

chromatography (1/3 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.35, 1/4 EtOAc/hexanes). Yield 91% (0.117 g, 0.40 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.56-2.34 (m, 9H), 3.40-3.56 (m, 3H), 3.64, 3.67 (s, 3H), 4.43-4.58 (m, 2H), 5.12-5.29 (m, 2H), 5.75-5.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 22.6, 23.1, 27.1, 27.4, 31.7, 32.7, 36.1, 37.4, 45.0, 48.3, 49.1, 52.4, 65.6, 66.0, 67.3, 68.1, 117.0, 117.7, 132.5, 132.9, 154.3, 174.4, 174.7; IR (neat) 2953, 2880, 1742, 1703, 1400, 1339, 1271, 1169, 1127, 995 cm^{-1}; HRMS calcd for $C_{13}H_{21}ClNO_4$ (M^+ + H) 290.1159, found 290.1157.

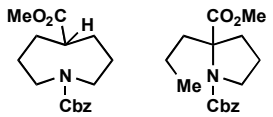


1-Benzyl 2-methyl 2-(3-chloropropyl)pyrrolidine-1,2-dicarboxylate (129). According to the above procedure, the reaction of **125** (0.0603 g, 0.36 mmol) and benzyl chloroformate (0.16 mL, 1.07 mmol, 3.0 equiv) in toluene (10 mL) at 100 °C for 30 min afforded after chromatography (1/4 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.27, 1/4 EtOAc/hexanes). Yield 89% (0.109 g, 0.32 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.57-2.41 (m, 8H), 3.28-3.59 (m, 4H), 3.69 (m, 3H), 5.04-5.18 9m, 2H), 7.28-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 22.7, 23.2, 27.2, 27.5, 31.8, 32.7, 36.1, 37.5, 44.9, 45.1, 48.4, 49.2, 52.2, 52.4, 66.7, 67.1, 67.3, 68.2, 127.6, 127.9, 127.9, 128.4, 128.4, 128.5, 136.2, 136.9, 154.4, 154.5, 174.4, 174.6; IR (neat) 2953, 2880, 1740, 1703,

1406, 1356, 1213, 1169, 1127 cm^{-1}; HRMS calcd for $C_{17}H_{23}ClNO_4$ (M^+ + H) 340.1316, found 340.1325.

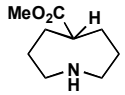


2-Methyl 1-(4-nitrophenyl) 2-(3-chloropropyl)pyrrolidine-1,2-dicarboxylate (130). According to the above procedure, the reaction of **125** (0.040 g, 0.24 mmol) and 4-nitrophenyl chloroformate (0.13 g, 0.62 mmol, 2.6 equiv) in toluene (10 mL) at rt for 4 h afforded after chromatography (1/4 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.76, 1/1 EtOAc/hexanes). Yield 76% (0.0677 g, 0.18 mmol). ^1H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.71-2.52 (m, 8H), 3.42-3.98 (m, 4H), 3.78, 3.85 (s, 3H), 7.26-7.38 (m, 2H), 8.23-8.33 (m, 2H), 7.28-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 22.7, 23.1, 27.2, 27.5, 31.5, 32.8, 36.1, 37.6, 44.8, 49.1, 49.6, 52.8, 52.9 68.4, 69.0, 121.9, 122.2, 122.3, 125.1, 125.2, 125.2, 144.8, 144.9, 151.6, 153.0, 156.0, 156.1, 171.4, 173.6; IR (neat) 2953, 2916, 1728, 1521, 1385, 1344, 1223, 1204, 1111 cm^{-1}; HRMS calcd for $C_{16}H_{19}ClN_2O_6Na$ (M^+ + Na) 393.0829, found 393.0800.

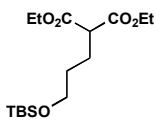


1-Benzyl 5-methyl azocane-1,5-dicarboxylate (131) and 1-Benzyl 2-methyl 2-propylpyrrolidine-1,2-dicarboxylate (131a). To a solution of **125** (0.165 g, 0.98 mmol, 1.0 equiv) in THF (10 mL) at -78 °C, benzyl chloroformate (0.84 mL, 5.6 mmol, 5.7 equiv) was added dropwise. After stirring for 4 h at -78 °C, $NaCNBH_3$ (0.216 g, 3.4 mmol, 3.5 equiv) in THF (5 mL) was added dropwise, the reaction mixture was warmed slowly to rt, and stirred overnight. The reaction mixture was concentrated, the residue taken in CH_2Cl_2 (20 mL), washed with NaOH (1.0 M, 1 x 10 mL), brine (1 x 10 mL), dried and concentrated. Chromatography (1/10-1/4 EtOAc/hexanes) afforded **131a** as oil (R_f = 0.32, 1/4 EtOAc/hexanes), yield 33% (0.0982 g, 0.32 mmol), and **131** as oil (R_f = 0.25, 1/4 EtOAc/hexanes), yield 26% (0.0775 g, 0.25 mmol). Compound **131**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56-2.01 (m, 8H), 2.49-2.58 (m, 1H), 3.13-3.21 (m, 2H), 3.63-3.78 (m, 2H), 3.68 (s, 3H), 7.30-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 25.7, 27.2, 27.9, 43.1, 47.2, 48.1, 51.7, 67.0, 127.0, 127.5, 127.8, 127.9, 128.5, 137.0, 156.0, 177.1; IR (neat) 2947, 2862, 1732, 1697, 1477, 1454, 1420, 1354, 1221, 1144, 1051 cm^{-1}; HRMS calcd for $C_{17}H_{24}ClNO_4$ (M^+ + H) 306.1705, found 306.1702. Compound **131a**: ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 0.88, 0.95 (t, *J* = 7.3 Hz, 3H), 1.11-1.46 (m, 2H), 1.78-1.98 (m, 3H), 2.04-2.18 (m, 2.5H), 2.31 (td, *J* = 4.7, 13.6 Hz, 0.5H), 3.49, 3.70 (s, 3H), 3.41-3.52 (m, 1H), 3.70-3.84 (m, 1H), 5.06-5.20 (m, 2H), 77.27-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 14.3, 14.3, 16.7, 16.9, 22.8, 23.3, 36.1, 37.2, 37.5, 48.4, 49.3, 52.1, 52.3, 66.6, 67.0, 67.8, 68.6, 127.6, 127.8, 128.0, 128.2, 128.4, 128.4, 136.5, 137.0, 154.3, 154.5, 175.0, 175.2; IR (neat) 2959,

2874, 1742, 1705, 1454, 1408, 1356, 1169, 1130, 1097, 912, 743 cm^{-1}; HRMS calcd for $C_{17}H_{24}ClNO_4$ (M^+ + H) 306.1705, found 306.1703.

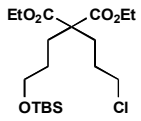


Methyl azocane-5-carboxylate (132). To a solution of **131** (0.130 g, 0.42 mmol, 1.0 equiv) in MeOH (5 mL), Pd/C (5%, 0.18 g) was added, and the resulting solution was stirred under a balloon of H_2 at rt for 1 h. Filtration through Celite, followed by chromatography (1/5/95 NH_3/MeOH/CH_2Cl_2) afforded the title compound as oil (R_f = 0.19, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 71% (0.0511 g, 0.30 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51-1.62 (m, 2H), 1.72-1.86 (m, 4H), 1.93-2.02 (m, 2H), 2.76-2.85 (m, 3H), 2.87-2.98 (m, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 27.4, 44.0, 48.4, 51.5, 177.6; IR (neat) 2916, 2849, 1732, 1576, 1541, 1472, 1435, 1385, 1298, 1159, 1090 cm^{-1}; HRMS calcd for $C_9H_{18}NO_2$ (M^+ + H) 172.1338, found 172.1324. Note: attempted transannular closure of **132** in a manner analogous to the described earlier led only to decomposition of the starting material.



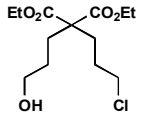
Diethyl 2-(3-(*tert*-butyldimethylsilyloxy)propyl)malonate (133). To a suspension of NaH (60% in mineral oil, 0.42 g, 10.5 mmol, 1.4 equiv) in DMF (8

mL) diethyl malonate (1.60 mL, 10.5 mmol, 1.4 equiv) was added at 0 °C. After the reaction mixture was stirred at rt for 30 min, 3-bromopropoxy-*tert*-butyldimethylsilane (1.82 mL, 7.6 mmol, 1.0 equiv) was added in THF (16 mL) at 0 °C. The resulting mixture was stirred at 55 °C for 72 h, cooled to rt, quenched with sat. NH_4Cl (20 mL), extracted with ether (3 x 50 mL), washed with water (1 x 50 mL), brine (1 x 50 mL), dried and concentrated under reduced pressure. Chromatography (1/20 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.36, 1/10 EtOAc/hexanes). Yield 92% (2.31 g, 7.0 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.85 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 6H), 1.46-1.57 (m, 2H), 1.87-1.97 (m, 2H), 3.33 (t, *J* = 7.6 Hz, 1H), 3.60 (t, *J* = 6.2 Hz, 2H), 4.15 (qd, *J* = 1.0, 7.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, 14.0, 18.2, 25.3, 25.9, 30.3, 51.6, 61.2, 62.4, 169.4; IR (neat) 2955, 2930, 2859, 1753, 1736, 1471, 1370, 1254, 1098, 1032, 837 cm^{-1}; HRMS calcd for $C_{16}H_{32}O_5SiNa$ (M^+ + Na) 355.1917, found 355.1929.



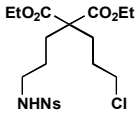
Diethyl 2-(3-(*tert*-butyldimethylsilyloxy)propyl)-2-(3-chloropropyl) malonate (134). To a suspension of NaH (60% in mineral oil, 0.318 g, 8.0 mmol, 1.2 equiv) in THF (5 mL), a solution of malonate (2.2 g, 6.6 mmol, 1.0 equiv) in THF (10 mL) was added dropwise at 0 °C. After the reaction mixture was stirred for 30 min at rt, 1-chloro-3-iodopropane (1.42 mL, 13.2 mmol, 2.0 equiv) was added at 0 °C, the resulting mixture was stirred at rt for 30 min, followed by reflux for 30 min. The

reaction was cooled to rt, quenched with sat. NH_4Cl (20 mL), extracted with ether (3 x 50 mL), washed with water (1 x 50 mL), brine (1 x 50 mL), dried and concentrated under reduced pressure. Chromatography (1/10 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.36, 1/10 EtOAc/hexanes). Yield 74% (2.0 g, 4.9 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.91 (s, 9H), 1.27 (td, *J* = 1.1, 7.1 Hz, 6H), 1.36-1.46 (m, 2H), 1.64-1.75 (m, 2H), 1.91-1.98 (m, 2H), 2.01-2.08 (m, 2H), 3.54 (t, *J* = 6.5 Hz, 2H), 3.62 (t, *J* = 6.2 Hz, 2H), 4.20 (q, *J* = 7.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 14.1, 18.3, 25.9, 27.4, 27.5, 28.9, 29.8, 44.8, 56.8, 61.3, 62.9, 171.5; IR (neat) 2955, 2930, 2857, 1732, 1472, 1464, 1256, 1194, 1098, 1032, 837 cm^{-1}; HRMS calcd for $C_{19}H_{37}ClO_5SiNa$ (M^+ + Na) 431.1996, found 431.1986.

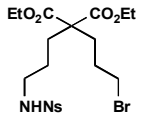


Diethyl 2-(3-chloropropyl)-2-(3-hydroxypropyl)malonate (135). To a solution of ether (0.33 g, 0.80 mmol, 1.0 equiv) in CH_3CN (3 mL) HF•CH_3CN (prepared in a separate vial from 0.2 mL of HF and 1.8 mL of CH_3CN) was added dropwise at 0 °C. After stirring for 20 min at 0 °C, the reaction was carefully quenched with sat. $NaHCO_3$, extracted with ether (3 x 50 mL), washed with brine (1 x 50 mL), dried and concentrated. The product was used in the next step without further purification. Analytical sample was obtained by chromatography (1/1 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.40, 1/1 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 6H), 1.43-1.56 (m, 2H), 1.67-1.77

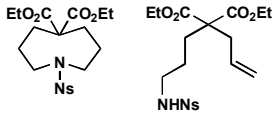
(m, 2H), 1.95-2.12 (m, 4H), 3.55 (t, J = 6.5 Hz, 2H), 3.64-3.69 (m, 2H), 4.21 (q, J = 7.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 27.4, 27.5, 28.9, 30.1, 44.8, 56.8, 61.4, 62.7, 171.4; IR (neat) 3380, 2916, 1728, 1539, 1385, 1300, 1256, 1184, 1049, 1028 cm^{-1}; HRMS calcd for $C_{13}H_{23}ClO_5Na$ (M^+ + Na) 317.1132, found 317.1144.



Diethyl 2-(3-chloropropyl)-2-(3-(2-nitrophenylsulfonamido)propyl) malonate (136). To a 25 ml round-bottom flask charged with alcohol (0.235 g, 0.80 mmol, 1.0 equiv), 2-nitrobenzenesulfonamide (0.51 g, 2.5 mmol, 3.1 equiv), triphenylphosphine (0.37 g, 1.4 mmol, 1.75 equiv) toluene (5 mL) and THF (1 mL), DIAD (0.28 mL, 1.36 mmol, 1.70 equiv) was added dropwise at 0 °C, and the resulting mixture was stirred at rt for 2.5 h. After the solvent was removed under reduced pressure, chromatography (1/5 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.59, 1/1 EtOAc/hexanes). Yield 70% (2 steps, 0.27 g, 0.57 mmol).^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 6H), 1.39-1.51 (m, 2H), 1.55-1.67 (m, 2H), 1.80-1.88 (m, 2H), 1.88-1.96 (m, 2H), 3.08 (q, J = 6.0 Hz, 2H), 3.48 (t, J = 6.1 Hz, 2H), 4.14 (q, J = 6.9 Hz, 4H), 5.44 (t, J = 5.4 Hz, 1H), 7.70-7.76 (m, 2H), 7.79-7.85 (m, 1H), 8.05-8.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 24.6, 27.4, 29.7, 30.2, 43.8, 44.8, 56.6, 61.4, 125.4, 131.0, 132.9, 133.5, 133.7, 148.0, 171.0; IR (neat) 3337, 2957, 2917, 1727, 1542, 1366, 1257, 1167, 1094, 1030 cm^{-1}; HRMS calcd for $C_{19}H_{28}ClN_2O_8S$ (M^+ + H) 479.1255, found 479.1244.

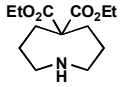


Diethyl 2-(3-bromopropyl)-2-(3-(2-nitrophenylsulfonamido)propyl) malonate (137). A solution of amine (0.0464 g, 0.10 mmol, 1.0 equiv) and LiBr (0.30 g, 3.4 mmol, 35 equiv) in 2-butenone (4 mL) was heated to reflux for 18 h. The reaction was cooled to rt, quenched with water (20 mL), extracted with ether (3 x 50 mL), washed with sat. sodium thiosulfate (1 x 20 mL), brine (1 x 20 mL), dried and concentrated to afford the title compound as oil (R_f = 0.60, 1/1 EtOAc/hexanes), which was used in the next step without further purification. Yield 97% (0.0493 g, 0.094 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 6H), 1.44-1.54 (m, 2H), 1.68-1.77 (m, 2H), 1.85-1.92 (m, 2H), 1.94-2.01 (m, 2H), 3.08-3.16 (m, 2H), 3.33-3.42 (m, 2H), 4.22 (q, *J* = 7.1 Hz, 4H), 5.40 (t, *J* = 5.9 Hz, 1H), 7.73-7.79 (m, 2H), 7.85-7.90 (m, 1H), 8.10-8.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 24.7, 27.5, 29.8, 31.5, 33.3, 43.8, 56.6, 61.5, 125.4, 131.1, 132.8, 133.6, 133.7, 148.1, 171.0; IR (neat) 3331, 2978, 2919, 1726, 1542, 1366, 1345, 1300, 1248, 1167, 1094, 1030 cm^{-1}; HRMS calcd for $C_{19}H_{27}BrN_2O_8SNa$ (M^+ + Na) 545.0569, found 545.0559.

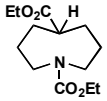


Diethyl 1-(2-nitrophenylsulfonyl)azocane-5,5-dicarboxylate (138) and Diethyl 2-allyl-2-(3-(2-nitrophenylsulfonamido)propyl)malonate (138a). To a stirred solution of Cs_2CO_3 (0.14 g, 0.43 mmol, 4.9 equiv) and *n*Bu_4NI (0.065 g, 0.17

mmol, 2.0 equiv) in CH_3CN (5 mL) at 60 °C, a solution of amine (0.045 g, 0.086 mmol, 1.0 equiv) in CH_3CN (5 mL) was added via syringe pump over 2 h. The reaction mixture was stirred at 60 °C for additional 2 h, cooled to rt, poured into water (50 mL), extracted with ether (3 x 50 mL), washed with brine (1 x 50 mL), dried and concentrated. Chromatography (1/4 EtOAc/hexanes) afforded **138** as oil (more polar compound) in 40% yield (0.0151 g, 0.034 mmol) and **138a** as oil (less polar compound) in 34% yield (0.0128 g, 0.029 mmol). Compound **138**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (td, *J* = 1.6, 7.0 Hz, 6H), 1.75-1.84 (m, 4H), 2.24-2.32 (m, 4H), 3.36 (t, *J* = 5.8 Hz, 4H), 4.21 (qd, *J* = 1.6, 7.1 Hz, 4H), 7.61-7.66 (m, 1H), 7.67-7.75 (m, 2H), 7.94-7.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 24.1, 28.0, 50.2, 57.2, 61.4, 124.1, 130.7, 131.5, 132.9, 133.4, 148.2, 171.8; IR (neat) 2916, 2849, 1724, 1576, 1541, 1385, 1092, 1078 cm^{-1}; HRMS calcd for $C_{19}H_{26}N_2O_8SNa$ (M^+ + Na) 465.1308, found 465.1303. Compound **138a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 6H), 1.46-1.55 (m, 2H), 1.82-1.89 (m, 2H), 2.61 (d, *J* = 7.4 Hz, 2H), 3.10 (q, *J* = 6.8 Hz, 2H), 4.19 (qd, *J* = 1.2, 7.1 Hz, 4H), 5.09 (d, *J* = 11.8 Hz, 2H), 5.34 (t, *J* = 5.6 Hz, 1H), 5.53-5.67 (m, 1H), 7.73-7.79 (m, 2H), 7.86-7.92 (m, 1H), 8.12-8.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 24.6, 29.4, 37.3, 43.9, 56.9, 61.4, 119.3, 125.5, 131.1, 132.1, 132.8, 133.6, 133.6, 148.1, 170.9; IR (neat) 3337, 2924, 1729, 1542, 1366, 1345, 1190, 1167, 1032 cm^{-1}; HRMS calcd for $C_{19}H_{26}N_2O_8SNa$ (M^+ + Na) 465.1308, found 465.1300.

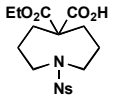


Diethyl azocane-5,5-dicarboxylate (139). To a solution of nosylamine (0.0117 g, 0.028 mmol, 1.0 equiv) and Cs_2CO_3 (0.0259 g, 0.08 mmol, 3.0 equiv) in CH_3CN (4 mL), PhSH (0.006 g, 0.05 mmol, 2.0 equiv) was added, and the resulting mixture was stirred at 55 °C for 30 min. Solvent removal, followed by chromatography (1/10/90 NH_3/MeOH/CH_2Cl_2) afforded the title compound as oil (R_f = 0.38, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 78% (0.0052 g, 0.020 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 6H), 1.56-1.65 (m, 4H), 2.14 (br, 1H), 2.21-2.28 (m, 4H), 2.84 (t, *J* = 6.2 Hz, 4H), 4.19 (q, *J* = 7.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 24.8, 28.2, 48.9, 57.6, 61.1, 172.4; IR (neat) 3380, 2916, 1726, 1576, 1541, 1472, 1385, 1227, 1186, 1094, 1080 cm^{-1}; HRMS calcd for $C_{13}H_{24}NO_4$ (M^+ + H) 258.1705, found 258.1704. Note: deprotection of **138** (0.0104 g, 0.024 mmol, 1.0 equiv) with thioglycolic acid (0.09 mL, 1.2 mmol, 50 equiv) and LiOH (0.058 g, 2.4 mmol, 100 equiv) in DMF (5 mL) at rt for 1 h afforded 1:3 mixture of amine **139** and carbamate **140** in ca. 50% yield (0.003 g, 0.012 mmol).



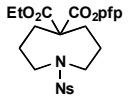
Diethyl azocane-1,5-dicarboxylate (140). According to the procedure described above, the reaction of amine 139 (0.005 g, 0.02 mmol, 1.0 equiv) and DBU (0.03 mL, 0.20 mmol, 10.0 equiv) in toluene (10 mL) at reflux for 24 h afforded after chromatography (1/1 EtOAc/hexanes) the title product as oil (R_f = 0.76, 1/1

EtOAc/hexanes). Yield 62% (0.0031 g, 0.012 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22-1.32 (m, 6H), 1.66-1.88 (m, 6H), 1.90-1.98 (m, 2H), 2.46-2.54 (m, 1H), 3.08-3.18 (m, 2H), 3.57-3.65 (m, 1H), 3.67-3.76 (m, 1H), 4.09-4.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.8, 24.7, 25.7, 27.3, 28.0, 43.3, 47.1, 47.9, 60.3, 61.1, 156.3, 176.8; IR (neat) 2916, 1730, 1697, 1541, 1474, 1420, 1385, 1221, 1177, 1146 cm^{-1}; HRMS calcd for $C_{13}H_{24}NO_4$ (M^+ + H) 258.1705, found 258.1697.

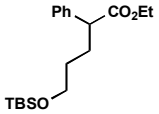


5-(Ethoxycarbonyl)-1-(2-nitrophenylsulfonyl)azocane-5-carboxylic acid (141). To a solution of the malonate (0.0172 g, 0.039 mmol, 1.0 equiv) in THF (2.5 mL), LiOH (0.0374 g, 1.6 mmol, 40 equiv) in H_2O (2.5 mL) was added at rt, and the resulting mixture was stirred at rt for 24 h. The solution was acidified to pH = 2 with sat. $KHSO_4$, extracted with EtOAc (3 x 50 mL), washed with brine (1 x 50 mL), dried and concentrated to provide the title compound as oil (0.0154 g, 0.037 mmol, 96% yield), which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3H), 1.76-1.91 (m, 4H), 2.31 (t, *J* = 5.6 Hz, 4H), 3.28-3.44 (m, 4H), 4.24 (q, *J* = 7.1 Hz, 2H), 7.61-7.66 (m, 1H), 7.67-7.74 (m, 2H), 7.93-7.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 24.1, 28.0, 50.1, 57.2, 61.9, 124.2, 130.7, 131.6, 132.8, 133.5, 148.2, 171.4, 177.0; IR (neat) 3368, 2916, 2849, 1731, 1717, 1700, 1576, 1542, 1385, 1374, 1165, 1077 cm^{-1}; HRMS calcd for $C_{17}H_{22}N_2O_8SNa$ (M^+ + Na) 437.0995, found 437.0993. Note: the selectivity in

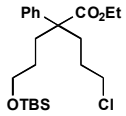
hydrolysis using excess of base is without precedent and likely results from the steric hindrance around the quaternary carbon.



5-Ethyl 5-perfluorophenyl 1-(2-nitrophenylsulfonyl)azocane-5,5-dicarboxylate (142). To a solution of acid (0.0143 g, 0.035 mmol, 1.0 equiv) and pentafluorophenol (0.0096 g, 0.052 mmol, 1.5 equiv) in CH_2Cl_2 (4 mL), EDC (0.0168 g, 0.088 mmol, 2.5 equiv) was added at rt, and the resulting mixture was stirred at rt for 30 min. The reaction was quenched with sat. NH_4Cl (10 mL), extracted with ether (3 x 30 mL), washed with brine (1 x 30 mL), dried and concentrated. Chromatography (1/2 EtOAc/hexanes) afforded the title product as oil (R_f = 0.68, 1/1 EtOAc/hexanes). Yield 75% (0.0153 g, 0.026 mmol).^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.2 Hz, 3H), 1.83-1.92 (m, 4H), 2.44 (t, *J* = 5.7 Hz, 4H), 3.34-3.46 (m, 4H), 4.29 (q, *J* = 7.1 Hz, 2H), 7.63-7.68 (m, 1H), 7.69-7.75 (m, 2H), 7.96-8.02 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 23.8, 28.2, 50.0, 57.5, 62.3, 124.2, 130.8, 131.6, 132.7, 133.5, 137.0, 138.9, 140.1, 142.0, 148.2, 168.2, 170.2; IR (neat) 2917, 2849, 1785, 1736, 1541, 1522, 1374, 1349, 1161, 1109, 995 cm^{-1}; HRMS calcd for $C_{23}H_{21}F_5N_2O_8SNa$ (M^+ + Na) 603.0836, found 603.0836.

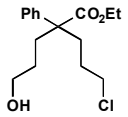


Ethyl 5-(*tert*-butyldimethylsilyloxy)-2-phenylpentanoate (143). To a solution of HMPA (1.0 mL, 6.1 mmol, 2.0 equiv) in THF (10 mL), LHMDS (1.0 M in THF, 3.35 mL, 3.35 mmol, 1.1 equiv) was added at rt, and the reaction mixture was cooled to -78 °C. Phenyl ethyl acetate (0.49 mL, 3.05 mmol, 1.0 equiv) was added in THF (5 mL), and the reaction mixture was stirred at -78 °C for 1 h. (3-Bromopropoxy)-*tert*-butyldimethylsilane (1.09 mL, 4.6 mmol, 1.5 equiv) was added dropwise, the reaction mixture was allowed to slowly warm to rt, and stirred at rt overnight. The reaction was quenched with sat. NH_4Cl (30 mL), extracted with ether (4 x 50 mL), washed with brine (1 x 50 mL), dried and concentrated. Chromatography (1/40 EtOAc/hexanes) afforded the title product as oil (R_f = 0.33, 1/20 EtOAc/hexanes). Yield 89% (0.91 g, 2.7 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.91 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.42-1.58 (m, 2H), 1.82-1.92 (m, 1H), 2.09-2.19 (m, 1H), 3.57 (t, *J* = 7.8 Hz, 1H), 3.62 (td, *J* = 1.8, 6.4 Hz, 2H), 4.08-4.19 (m, 2H), 7.18-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 14.2, 18.4, 26.0, 29.9, 30.7, 51.5, 60.7, 62.8, 127.1, 128.0, 128.6, 139.3, 174.1; IR (neat) 2955, 2930, 2857, 1734, 1472, 1254, 1159, 1098, 837 cm^{-1}; HRMS calcd for $C_{19}H_{32}O_3SiNa$ (M^+ + Na) 359.2018, found 359.2025.



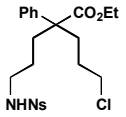
Ethyl 5-(*tert*-butyldimethylsilyloxy)-2-(3-chloropropyl)-2-phenylpentanoate (144). To a solution of ester (0.56 g, 1.67 mmol, 1.0 equiv) in

THF (10 mL) and HMPA (1.5 mL), LDA (0.60 M, 3.87 mL, 2.34 mmol, 1.4 equiv; freshly prepared from 1.1 equiv of DIPA and 1.0 equiv of *n*BuLi in THF) was added at -78 °C. After the reaction mixture was stirred for 1 h at -78 °C, 1-chloro-3-iodopropane (0.54 mL, 5.0 mmol, 3.0 equiv) was added, the reaction mixture was allowed to warm up rt and stirred for next 15 h. NH_4Cl (30 mL), extracted with ether (4 x 50 mL), washed with brine (1 x 50 mL), dried and concentrated. Chromatography (1/33 EtOAc/hexanes) afforded the title product as oil (R_f = 0.45, 1/10 EtOAc/hexanes). Yield 91% (0.63 g, 1.5 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.91 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.32-1.42 (m, 2H), 1.53-1.65 (m, 2H), 1.99-2.22 (m, 4H), 3.51 (t, *J* = 6.5 Hz, 2H), 3.62 (t, *J* = 6.2 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 7.22-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 14.1, 18.3, 26.0, 27.5, 27.6, 30.9, 32.4, 45.3, 53.1, 60.8, 63.2, 126.4, 126.8, 128.4, 142.3, 175.5; IR (neat) 2955, 2930, 2857, 1728, 1472, 1252, 1196, 1098, 1032, 837 cm^{-1}; HRMS calcd for $C_{22}H_{37}ClO_3SiNa$ (M^+ + Na) 435.2098, found 435.2094.



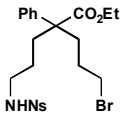
Ethyl 5-chloro-2-(3-hydroxypropyl)-2-phenylpentanoate (145). According to the procedure described for **135**, the reaction of **144** (0.63 g, 1.5 mmol, 1.0 equiv) and HF•CH_3CN (prepared from 0.5 mL of HF and 2.5 mL of CH_3CN) in 5 mL of CH_3CN for 20 min at 0 °C, afforded after chromatography (1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.65, 1/1 EtOAc/hexanes). Yield 93% (0.42 g, 1.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.1 Hz, 3H), 1.32-1.49 (m, 2H), 1.52-1.68 (m, 3H), 2.03-2.25 (m, 4H), 3.52 (t, *J* = 6.4 Hz, 2H), 3.62 (dt, *J* = 1.5, 6.2 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 7.22-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 27.5, 27.6, 31.1, 32.4, 45.3, 53.2, 60.9, 63.0, 126.4, 126.9, 128.4, 142.1, 175.5; IR (neat) 3400, 2917, 2849, 1725, 1576, 1539, 1386, 1235, 1094, 1059, 1032 cm^{-1}; HRMS calcd for $C_{16}H_{23}ClO_3Na$ (M^+ + Na) 321.1233, found 321.1233.

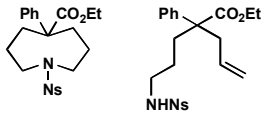


Ethyl 5-chloro-2-(3-(2-nitrophenylsulfonamido)propyl)-2-phenylpentanoate (146). According to the procedure described for **136**, **145** (0.20 g, 0.67 mmol, 1.0 equiv) was reacted with DBAD (0.268 g, 1.14 mmol, 1.7 equiv), triphenylphosphine (0.31 g, 1.17 mmol, 1.75 equiv) and nosylamine (0.424 g, 2.1 mmol, 3.1 equiv) in THF/toluene (1 mL/5 mL) for 3 h. HCl (4.0 M in dioxane, 3.0 mL) was added and the reaction was stirred at rt for 1 h. The reaction was diluted with ether (10 mL), washed with aq. HCl (4.0 M, 2 x 10 mL), water (1 x 20 mL), brine (1 x 20 mL), dried and concentrated. Chromatography (1/3 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.60, 1/1 EtOAc/hexanes). Yield 68% (0.22 g, 0.46 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H), 1.29-1.41 (m, 2H), 1.46-1.64 (m, 2H), 1.96-2.18 (m, 4H), 3.05-3.16 (m, 2H), 3.50 (t, *J* = 6.3 Hz, 2H), 4.09-4.19 (m, 2H), 5.31 (t, *J* = 5.7 Hz, 1H), 7.14-7.36 (m, 5H), 7.70-7.78 (m, 2H), 7.82-7.91 (m, 1H), 8.07-8.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1,

24.7, 27.6, 32.2, 32.5, 44.1, 45.2, 53.2, 61.1, 125.4, 126.3, 127.0, 128.5, 131.0, 132.8, 133.6, 133.7, 141.6, 148.0, 175.0; IR (neat) 3339, 2916, 2849, 1719, 1576, 1541, 1385, 1366, 1165, 1090 cm^{-1}; HRMS calcd for $C_{22}H_{27}ClN_2O_6SNa$ (M^+ + Na) 505.1176, found 505.1176.

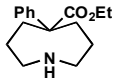


Ethyl 5-bromo-2-(3-(2-nitrophenylsulfonamido)propyl)-2-phenylpentanoate (147). According to the procedure described for **137**, the reaction of chloride **146** (0.0761 g, 0.16 mmol, 1.0 equiv) and LiBr (0.48 g, 5.5 mmol, 35 equiv) in butanone (4 mL) at reflux for 15 h afforded the title product as oil. Yield 96% (0.0797 g, 0.15 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (dt, *J* = 0.8, 7.2 Hz, 3H), 1.31-1.44 (m, 2H), 1.56-1.73 (m, 2H), 2,01 (t, *J* = 8.0 Hz, 2H), 2.08-2.18 (m, 2H), 3.03-3.14 (m, 2H), 3.36 (t, *J* = 6.4 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 5.32 (t, *J* = 6.0 Hz, 1H), 7.14-7.35 (m, 5H), 7.73-7.82 (m, 2H), 7.83-7.89 (m, 1H), 8.08-8.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 24.7, 27.7, 32.2, 33.7, 33.9, 44.1, 53.2, 61.1, 125.4, 126.3, 127.0, 128.5, 131.0, 132.8, 133.6, 133.6, 141.6, 148.0, 175.0; IR (neat) 3345, 2917, 2849, 1719, 1576, 1542, 1418, 1365m 1165, 1092, 913 cm^{-1}; HRMS calcd for $C_{22}H_{27}BrN_2O_6SNa$ (M^+ + Na) 549.0670, found 549.0648.

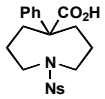


Ethyl 1-(2-nitrophenylsulfonyl)-5-phenylazocane-5-carboxylate (148) and Ethyl 2-(3-(2-nitrophenylsulfonamido)propyl)-2-phenylpent-4-enoate (149). According to the procedure described for **137**, the reaction of **147** (0.0731 g, 0.14 mmol, 1.0 equiv), Cs_2CO_3 (0.22 g, 0.68 mmol, 4.9 equiv) and nBu$_4$NI (0.10 g, 0.28 mmol, 2.0 equiv) in CH_3CN (10 and 5 mL) at 60 °C for 4 h (syringe pump addition for 1.5 h) afforded after chromatography (1/4 EtOAc/hexanes) compound **148** as oil (R_f = 0.59, 1/1 EtOAc/hexanes) in 29% yield (0.0178 g, 0.040 mmol) and compound **149** as oil (R_f = 0.71, 1/1 EtOAc/hexanes) in 39% yield (0.0240 g, 0.054 mmol).Compound **148**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J = 7.1 Hz, 3H), 1.64-1.75 (m, 2H), 1.77-1.88 (m, 2H), 2.30-2.39 (m, 2H), 2.42-2.51 (m, 2H), 3.18-3.27 (m, 2H), 3.52-3.61 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 7.22-7.38 (m, 5H), 7.62-7.66 (m, 1H), 7.68-7.74 (m, 2H), 7.94-7.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 24.2, 30.6, 50.2, 53.8, 61.0, 124.2, 126.3, 126.9, 128.5, 130.6, 131.5, 133.0, 133.4, 143.4, 148.2, 175.7; IR (neat) 2917, 2849, 1717, 1541, 1374, 1161, 1125, 1092 cm^{-1}; HRMS calcd for $C_{22}H_{27}N_2O_6S$ (M^+ + H) 447.1590, found 447.1595. Compound **149**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J = 7.1 Hz, 3H), 1.26-1.39 (m, 2H), 1.98 (dd, J = 5.4, 11.0 Hz, 2H), 2.67-2.74 (m, 1H), 2.79-2.86 (m, 1H), 3.06 (q, J = 6.6 Hz, 2H), 4.07-4.21 (m, 2H), 5.04-5.11 (m, 2H), 5.25 (t, J = 5.7 Hz, 1H), 5.46-5.58 (m, 1H), 7.16-7.35 (m, 5H), 7.71-7.77 (m, 2H), 7.84-7.88 (m, 1H), 8.08-8.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 24.2, 31.8, 39.2, 44.1, 53.2, 61.0, 118.6, 125.4, 126.3, 126.9, 128.5, 131.1, 132.8, 133.3, 133.5, 133.7, 141.6, 148.1, 174.9; IR (neat)

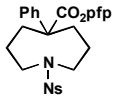
3343, 2979, 2934, 1723, 1541, 1445, 1364, 1345, 1210, 1167, 1127, 1030 cm^{-1}; HRMS calcd for $C_{22}H_{27}N_2O_6S$ (M^+ + H) 447.1590, found 447.1585.



Ethyl 5-phenylazocane-5-carboxylate (150). According to the procedure for **139**, the reaction of **148** (0.0115 g, 0.026 mmol, 1.0 equiv), Cs_2CO_3 (0.025 g, 0.78 mmol, 3.0 equiv) and PhSH (0.006 g, 0.05 mmol, 2.0 equiv) in CH_3CN (5 mL) at 55 °C for 30 min, afforded after chromatography (1/10/90 NH_3/MeOH/CH_2Cl_2) the title compound as film (R_f = 0.24, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 89% (0.0060 g, 0.023 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.1 Hz, 3H), 1.55-1.72 (m, 4H), 2.26-2.39 (m, 2H), 2.42-2.51 (m, 2H), 2.82-2.99 (m, 4H), 3.07 (br, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 7.22-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 24.7, 30.8, 49.0, 54.1, 60.8, 126.4, 126.6, 128.4, 144.1, 176.1; IR (neat) 3368, 2917, 1721, 1542, 1385, 1212, 1183, 1113, 1082 cm^{-1}; HRMS calcd for $C_{16}H_{24}NO_4$ (M^+ + H) 262.1807, found 262.1792. Note: deprotection of **148** (0.0042 g, 0.01 mmol, 1.0 equiv) with thioglycolic acid (0.03 mL, 0.5 mmol, 50 equiv) and LiOH (0.023 g, 0.9 mmol, 100 equiv) in DMF (5 mL) at rt for 1 h afforded **150** in 53% yield (0.0013 g, 0.005 mmol). Note: attempted transannular closure (DBU, toluene, 110 °C, 24 h) led to no conversion to the desired lactam.

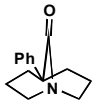


1-(2-Nitrophenylsulfonyl)-5-phenylazocane-5-carboxylic acid (151). A mixture of ester (0.0303 g, 0.068 mmol, 1.0 equiv) and LiOH (0.163 g, 6.8 mmol, 100 equiv) in dioxane/water (6 mL/3 mL) was refluxed for 48 h. The reaction was cooled to rt, quenched with 10% $KHSO_4$ (until pH = 2), extracted with ether (3 x 50 mL), washed with water (1 x 20 mL), brine (1 x 20 mL), dried and concentrated to afford the title product as oil (R_f = 0.26, 1/1 EtOAc/hexanes), which was used in the next step without further purification. Yield 91% (0.0259 g, 0.062 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70-1.88 (m, 4H), 2.29-2.41 (m, 2H), 2.46-2.58 (m, 2H), 3.22-3.32 (m, 2H), 3.48-3.58 (m, 2H), 7.24-7.46 (m, 5H), 7.58-7.66 (m, 1H), 7.68-7.73 (m, 2H), 7.93-7.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 30.3, 50.2, 53.6, 124.2, 126.6, 127.3, 128.7, 130.6, 131.6, 133.0, 133.4, 142.2, 148.2, 181.4; IR (neat) 3416, 2916, 1698, 1542, 1374, 1343, 1162, 1127, 913, 734 cm^{-1}; HRMS calcd for $C_{20}H_{23}N_2O_6S$ (M^+ + H) 419.1268, found 419.1277.



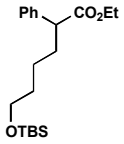
Perfluorophenyl 1-(2-nitrophenylsulfonyl)-5-phenylazocane-5-carboxylate (152). According to the procedure described for **142**, the reaction of acid (0.0240 g, 0.057 mmol, 1.0 equiv), EDC (0.0165 g, 0.086 mmol, 1.5 equiv) and pentafluorophenol (0.0262 g, 0.14 mmol, 2.5 equiv) in CH_2Cl_2 at rt for 30 min, afforded after chromatography (1/2 EtOAc/hexanes) the title compound as oil (R_f = 0.74, 1/1 EtOAc/hexanes).Yield 72% (0.0241 g, 0.041 mmol). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 1.73-1.86 (m, 2H), 1.87-1.98 (m, 2H), 2.44-2.66 (m, 4H), 3.18-3.28 (m, 2H), 3.64-3.72 (m, 2H), 7.31-7.47 (m, 5H), 7.64-7.68 (m, 1H), 7.70-7.76 (m, 2H), 7.97-8.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 30.9, 50.1, 54.7, 124.2, 126.3, 127.7, 128.9, 130.7, 131.6, 132.8, 133.5, 136.7, 139.1, 139.9, 141.5, 142.3, 148.2, 172.4; IR (neat) 2917, 2849, 1771, 1542, 1520, 1385, 1100, 996 cm^{-1}; HRMS calcd for $C_{26}H_{22}F_5N_2O_6S$ (M^+ + H) 585.1118, found 585,1124.

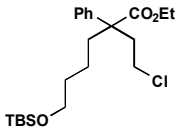


5-Phenyl-1-azabicyclo[3.3.1]nonan-9-one (153). According to the previously described procedure, **152** (0.0155 g, 0.27 mmol, 1.0 equiv) was reacted with Cs_2CO_3 (0.0259 g, 0.80 mmol, 3.0 equiv) and PhSH (0.006 g, 0.05 mmol, 2.0 equiv) in CH_3CN (5 mL) at 55 °C for 30 min. Solvent was removed under reduced pressure, and the reaction was analyzed by ^1H NMR. Yield 57% (vs. 2-nitrophenylphenylsulfide). Note: the compound is unstable, rapid decomposition is observed in $CDCl_3$. Attempted purification led only to the decomposition products. ^1H NMR (400 MHz, $CDCl_3$) (aromatic peaks not resolved) δ 1.55-1.65 (m, 2H), 2.24-2.36 (m, 2H), 2.37-2.43 (m, 4H), 3.36-3.45 (m, 2H), 3.48-3.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (aromatic peaks not resolved) δ 22.3, 40.8, 52.8, 57.0, 199.5; IR (neat) 2919, 2849, 1730.5, 1621, 1518, 1439, 1337, 1304, 1250, 1136 cm^{-1}; HRMS calcd for $C_{14}H_{18}NO$ (M^+ + H) 216.1388, found 216.1391. The structure was confirmed by COSY, NOESY, HMBC and HSQC experiments. Note: attempted

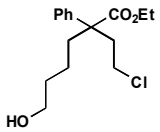
deprotection of **152** with thioglycolic acid and LiOH in DMF led only to decomposition products.



Ethyl 6-(*tert*-butyldimethylsilyloxy)-2-phenylhexanoate (154). According to the procedure described for **143**, the reaction of phenyl ethyl acetate (0.49 mL, 3.05 mmol, 1.0 equiv), LiHMDS (1.0 M in THF, 3.36 mL, 3.36 mmol, 1.1 equiv), HMPA (1.06 mL, 6.1 mmol, 2.0 equiv) and *tert*-Butyl(4-iodobutoxy)dimethylsilane (1.25 mL, 4.57 mmol, 1.5 equiv) in THF (15 mL) for 18 h, afforded after chromatography (1/40 EtOAc/hexanes) the title product as oil (R_f = 0.54, 1/10 EtOAc/hexanes). Yield 69% (0.74 g, 2.1 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.28-1.40 (m, 2H), 1.50-1.61 (m, 2H), 1.77-1.86 (m, 1H), 2.06-2.16 (m, 1H), 3.56 (t, *J* = 7.7 Hz, 1H), 3.60 (t, *J* = 6.5 Hz, 2H), 4.06-4.22 (m, 2H), 7.24-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 14.2, 18.3, 23.9, 26.0, 32.6, 33.5, 51.8, 60.6, 62.9, 127.1, 127.9, 128.6, 139.3, 174.1; IR (neat) 2928, 1732, 1557, 1386, 1154, 1108 cm^{-1}; HRMS calcd for $C_{20}H_{34}O_3SiNa$ (M^+ + Na) 373.2175, found 373.2175.

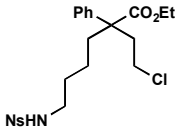


Ethyl 6-(*tert*-butyldimethylsilyloxy)-2-(2-chloroethyl)-2-phenylhexanoate (155). According to the procedure described for **144**, the reaction of ester **154** (0.62 g, 1.76 mmol, 1.0 equiv), LDA (0.94 M in THF, 2.61 mL, 2.46 mmol, 1.4 equiv), 1-bromo-2-chloroethane (0.31 mL, 3.52 mmol, 2.0 equiv), 1-iodo-2-chloroethane (0.51 mL, 5.29 mmol, 3.0 equiv) and HMPA (1.5 mL) in THF for 18 h, afforded after chromatography (1/50 EtOAc/hexanes) the title compound as oil (R_f = 0.48, 1/10 EtOAc/hexanes). Yield 43% (0.125 g, 0.30 mmol, out of theoretical 0.7 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.090 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.17-1.38 (m, 2H), 1.51-1.61 (m, 2H), 1.98-2.16 (m, 2H), 2.42-2.61 (m, 2H), 3.23-3.31 (m, 1H), 3.33-3.41 (m, 1H), 3.62 (t, *J* = 6.3 Hz, 2H), 4.14-4.22 (m, 2H), 7.24-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 14.1, 18.3, 20.8, 26.0, 33.2, 35.3, 38.5, 40.6, 53.7, 61.0, 62.7, 126.3, 127.1, 128.6, 141.5, 174.8; IR (neat) 2955, 2930, 2731, 1337, 1388, 1256, 1104, 836 cm^{-1}; HRMS calcd for $C_{22}H_{37}ClO_3SiNa$ (M^+ + Na) 435.2098, found 435.2101.



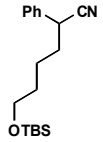
Ethyl 2-(2-chloroethyl)-6-hydroxy-2-phenylhexanoate (156). According to the procedure described earlier, the reaction of **155** (0.121 g, 0.29 mmol, 1.0 equiv) and HF•CH_3CN (prepared from 0.5 mL of HF and 2.5 mL of CH_3CN) in 5.0 mL of CH_3CN at 0 °C for 20 min, afforded after chromatography (1/2 EtOAc/hexanes) the title compound as oil (R_f = 0.32, 1/2 EtOAc/hexanes). Yield 74% (0.0638 g, 0.21

mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (td, J = 2.0, 7.1 Hz, 3H), 1.26-1.37 (m, 2H), 1.53-1.63 (m, 2H), 1.97-2.19 (m, 2H), 3.21-3.31 (m, 1H), 3.34-3.41 (m, 1H), 3.63 (td, J = 1.8, 6.4 Hz, 2H), 4.14-4.26 (m, 2H), 7.24-7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.7, 32.9, 35.4, 38.5, 40.6, 53.7, 61.1, 62.4, 126.2, 127.1, 128.6, 141.3, 174.8; IR (neat) 3430, 2938, 1725, 1651, 1447, 1233, 1175, 1032 cm^{-1}; HRMS calcd for $C_{16}H_{23}ClO_3Na$ (M^+ + Na) 321.1233, found 321.1231.

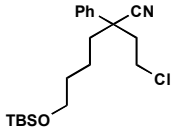


Ethyl 2-(2-chloroethyl)-6-(2-nitrophenylsulfonamido)-2-phenylhexanoate (157). According to the procedure described for **146**, the reaction of **156** (0.0601 g, 0.20 mmol, 1.0 equiv), nosylamine (0.127 g, 0.62 mmol, 3.1 equiv), triphenylphosphine (0.0927 g, 0.35 mmol, 1.75 equiv) and DBAD (0.0820 g, 0.34 mmol, 1.70 equiv) in THF/toluene (1 mL/5 mL) for 3.5 h, followed by treatment with HCl (4.0 M in dioxane, 1.0 mL) for 1 h, afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.60, 1/1 EtOAc/hexanes). Yield 80% (0.0772 g, 0.16 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 3H), 1.06-1.31 (m, 2H), 1.51-1.59 (m, 2H), 1.91-2.06 (m, 2H), 2.33-2.54 (m, 2H), 3.04-3.16 (m, 2H), 3.18-3.26 (m, 1H), 3.32-3.39 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 5.33 (t, J = 5.8 Hz, 1H), 7.16-7.36 (m, 5H), 7.72-7.78 (m, 2H), 7.84-7.89 (m, 1H), 8.10-8.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.5, 30.0, 35.2, 38.5, 40.5, 43.5, 53.6, 61.2, 125.5, 126.2, 127.2, 127.8, 128.7, 131.0, 132.9, 133.7, 141.0, 148.0, 174.6; IR (neat)

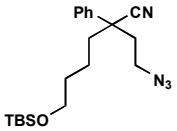
3350, 2917, 1723, 1542, 1366, 1342, 1165, 1092 cm^{-1}; HRMS calcd for $C_{22}H_{27}ClN_2O_6SNa$ (M^+ + Na) 505.1176, found 505.1169. Note: attempted chloride displacement of **157** with LiBr according to previously utilized conditions led to no conversion. Under more forcing conditions (200 equiv of LiBr, 31 h, reflux) lactone **159** was the major product in the reaction mixture.



6-(*tert*-Butyldimethylsilyloxy)-2-phenylhexanenitrile (160). According to the procedure described for **154**, benzyl cyanide (0.50 g, 4.3 mmol, 1.0 equiv) was reacted with LHMDS (1.0 M in THF, 4.73 mL, 4.73 mmol, 1.1 equiv), HMPA (1.50 mL, 8.6 mmol, 2.0 equiv) and *tert*-Butyl(4-iodobutoxy)dimethylsilane (1.41 mL, 5.2 mmol, 1.2 equiv) in THF (20 mL) to afford after chromatography (1/30-1/10 EtOAc/hexanes) the title compound as oil (R_f = 0.68, 1/10 EtOAc/hexanes). Yield 60% (0.79 g, 2.6 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.46-1.66 (m, 4H), 1.86-2.02 (m, 2H), 3.58-3.67 (m, 2H), 3.77-3.84 (m, 1H), 7.26-7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 18.3, 23.5, 26.0, 32.0, 35.7, 37.4, 62.6, 120.9, 127.3, 128.0, 129.1, 136.0; IR (neat) 2951, 2930, 2856, 2241, 1495, 1472, 1454, 1256, 1099, 835 cm^{-1}; HRMS calcd for $C_{18}H_{29}NOSiNa$ (M^+ + Na) 326.1916, found 326.1886.

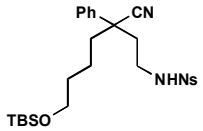


6-(*tert*-Butyldimethylsilyloxy)-2-(2-chloroethyl)-2-phenylhexanenitrile (161). According to the procedure described for **155**, the reaction of **160** (0.70 g, 2.3 mmol, 1.0 equiv), LDA (0.75 M in THF, 4.3 mL, 3.2 mmol, 1.4 equiv), HMPA (3 mL) and 1-bromo-2-chloroethane (1.0 mL, 11.5 mmol, 5.0 equiv) in THF (25 mL) for 15 h afforded after chromatography (1/100-1/20 EtOAc/hexanes) the title compound as oil (R_f = 0.67, 1/10 EtOAc/hexanes). Yield 88% (0.74 g, 2.0 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.86 (s, 9H), 1.16-1.28 (m, 1H), 1.42-1.58 (m, 3H), 1.91-2.12 (m, 2H), 2.34-2.45 (m, 1H), 2.46-2.57 (m, 1H), 3.14-3.24 (m, 1H), 3.51-3.62 (m, 3H), 7.31-7.49 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 18.3, 21.6, 25.9, 32.3, 39.6, 41.1, 43.4, 47.1, 62.5, 121.4, 125.7, 128.2, 129.3, 136.8; IR (neat) 2952, 2928, 2235, 1492, 1459, 1255, 1101, 834 cm^{-1}; HRMS calcd for $C_{20}H_{32}ClNOSiNa$ (M^+ + Na) 388.1839, found 388.1844.



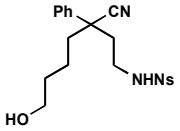
2-(2-Azidoethyl)-6-(*tert*-butyldimethylsilyloxy)-2-phenylhexanenitrile (162). According to the procedure described earlier, the reaction of chloride (0.16 g, 0.44 mmol, 1.0 equiv) and NaN_3 (0.29 g, 4.4 mmol, 10.0 equiv) in DMF (20 mL) at 90 °C for 6 h afforded the title product as oil which was used in the next step without further purification. Yield 86% (0.14 g, 0.38 mmol). ^{1}H NMR (400 MHz, $CDCl_3$)

δ 0.00 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 1.16-1.26 (m, 1H), 1.44-1.61 (m, 3H), 1.91-2.12 (m, 2H), 2.14-2.24 (m, 1H), 2.27-2.36 (m, 1H), 3.06-3.16 (m, 1H), 3.34-3.44 (m, 1H), 3.49-3.64 (m, 2H), 7.28-7.49 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 18.3, 21.7, 25.9, 32.3, 39.5, 41.2, 46.3, 47.6, 62.5, 121.5, 125.7, 128.2, 129.2, 137.0; IR (neat) 2953, 2928, 2857, 2100, 1458, 1256, 1102, 912, 837 cm^{-1}; HRMS calcd for $C_{20}H_{32}N_4OSiNa$ (M^+ + Na) 395.2243, found 395.2237.

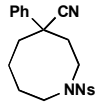


N-(7-(*tert*-Butyldimethylsilyloxy)-3-cyano-3-phenylheptyl)-2-nitrobenzene sulfonamide (164). To a solution of azide **163** (0.14 g, 0.38 mmol, 1.0 equiv) in EtOAc (3 mL), Pd/C (5%, 0.028 g) was added and the resulting mixture was stirred under H_2 balloon at rt for 6 h. The reaction mixture was filtered through celite and concentrated. The crude amine was taken in CH_2Cl_2 (10 mL), Hünig base (0.060 g, 0.46 mmol, 1.2 equiv), followed by nosyl chloride (0.0868 g, 0.38 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) were added and the resulting mixture was stirred at rt for 2 h. The reaction was quenched with water (1 x 20 mL), extracted with EtOAc (3 x 50 mL), washed with brine (1 x 20 mL), dried and concentrated. Chromatography (1/4 EtOAc/hexanes) afforded the title product as oil (R_f = 0.81, 1/1 EtOAc/hexanes). Yield 74% (0.15 g, 0.28 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.00 (s, 3H), 0.84 (s, 9H), 1.10-1.22 (m, 1H), 1.38-1.57 (m, 3H), 1.88-2.06 (m, 2H), 2.26-2.40 (m, 2H), 2.84-2.93 (m, 1H), 3.17-3.27 (m, 1H), 3.47-3.59 (m, 2H), 5.37 (t, *J* = 6.0 Hz,

1H), 7.31-7.45 (m, 5H), 7.67-7.76 (m, 2H), 7.82-7.86 (m, 1H), 7.95-7.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 18.2, 21.6, 25.9, 32.3, 40.3, 40.7, 41.3, 46.4, 62.5, 121.5, 125.5, 125.7, 128.2, 129.3, 131.1, 132.9, 133.1, 133.8, 136.9, 148.0; IR (neat) 3342, 2953, 2928, 2856, 2235, 1541, 1350, 1254, 1169, 1095, 837 cm^{-1}; HRMS calcd for $C_{26}H_{38}N_3O_5SSi$ (M^+ + H) 532.2302, found 532.2307.

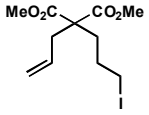


N-(3-Cyano-7-hydroxy-3-phenylheptyl)-2-nitrobenzenesulfonamide (184). According to procedure described for **156**, the reaction of **163** (0.0490 g, 0.092 mmol) and HF•CH_3CN (prepared from 0.3 mL of HF and 1.9 mL of CH_3CN) in 5 mL of CH_3CN at 0 °C for 20 min afforded after chromatography (1/2 EtOAc/hexanes) the title compound as oil (R_f = 0.23, 1/1 EtOAc/hexanes). Yield 96% (0.0369 g, 0.088 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12-1.25 (m, 1H), 1.42-1.62 (m, 3H), 1.91-2.06 (m, 2H), 2.27-2.41 (m, 2H), 2.84-2.93 (m, 1H), 3.16-3.26 (m, 1H), 3.58 (t, *J* = 6.0 Hz, 2H), 5.41 (t, *J* = 6.0 Hz, 1H), 7.34-7.45 (m, 5H), 7.68-7.76 (m, 2H), 7.82-7.87 (m, 1H), 7.95-7.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 32.2, 40.3, 40.6, 41.1, 46.4, 62.3, 121.5, 125.5, 125.7, 128.3, 129.3, 131.1, 132.9, 133.1, 133.7, 136.8, 148.0; IR (neat) 3537, 3342, 2935, 2868, 2237, 1541, 1361, 1344, 1167, 1126, 1074, 911 cm^{-1}; HRMS calcd for $C_{20}H_{23}N_3O_5SNa$ (M^+ + Na) 440.1256, found 440.1257.

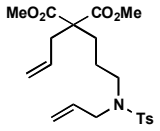


1-(2-Nitrophenylsulfonyl)-4-phenylazocane-4-carbonitrile (165).

According to the procedure described earlier, the reaction of **164** (0.0549 g, 0.13 mmol, 1.0 equiv), triphenylphosphine (0.104 g, 0.39 mmol, 3.0 equiv) and DBAD (0.0917 g, 0.39 mmol, 3.0 equiv) in THF/toluene (2 mL/10 mL) at rt for 4 h afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.67, 1/1 EtOAc/hexanes). Yield 42% (0.0217 g, 0.054 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39-1.55 (m, 2H), 1.92-2.11 (m, 3H), 2.31-2.44 (m, 2H), 2.66-2.74 (m, 1H), 3.14-3.22 (m, 1H), 3.28 (dt, *J* = 5.4, 14.6 Hz, 1H), 3.70 (dt, *J* = 5.2, 14.7 Hz, 1H), 3.76-3.83 (m, 1H), 7.33-7.58 (m, 5H), 7.62-7.65 (m, 1H), 7.69-7.77 (m, 2H), 7.92-7.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 29.0, 34.9, 38.9, 45.5, 46.1, 48.9, 122.8, 124.2, 125.9, 128.1, 129.1, 130.9, 131.4, 131.5, 133.7, 140.8, 148.5; IR (neat) 2929, 2869, 2234, 1544, 1370, 1347, 1168, 913 cm^{-1}; HRMS calcd for $C_{20}H_{21}N_3O_4SNa$ (M^+ + Na) 422.1150, found 422.1137. Note: the yield and purity of the product was found to decrease upon scale-up. Attempted manipulations of the nitrile including hydrolysis and reduction did not afford satisfactory results.



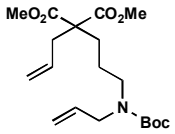
Dimethyl 2-allyl-2-(3-iodopropyl)malonate (168). To a suspension of sodium hydride (60%, suspension in mineral oil) (0.111 g, 2.78 mmol, 1.1 equiv) in 10 mL of THF at 0° C was added dimethyl 2-allylmalonate (0.434 g, 2.52 mmol, 1.0 equiv) dropwise in 10 mL of THF and the resulting solution was stirred at rt for 30 min. 1,3-diiodopropane (1.15 mL, 10.1 mmol, 4.0 equiv) was added in one portion at 0 °C and the resulting solution was stirred for 30 min at room temperature followed by heating to 60-65 °C for 1 h. The reaction was cooled to room temperature, diluted with ether (20 mL) and quenched with brine (10 mL). The aqueous layer was extracted with ether (3 x 50 mL), and the combined organic layers were washed brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. Chromatography (3-5% EtOAc/hexanes) afforded the title compound as a colorless oil (R_f = 0.30, 10% EtOAc/hexanes). Yield 71% (0.609 g, 1.79 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72-1.80 (m, 2H), 1.96-2.02 (m, 2H), 2.64-2.68 (m, 2H), 3.17 (t, *J* = 6.8, 2H), 3.75 (s, 6H), 5.11-5.17 (m, 1H), 5.60-5.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.6, 28.3, 33.5, 37.4, 52.5, 57.0, 119.4, 132.0, 171.3; IR (neat) 2950, 1731, 1435, 1221 cm^{-1}; HRMS calcd for $C_{11}H_{17}IO_4Na$ (M^+ + Na) 363.0069, found 363.0072.



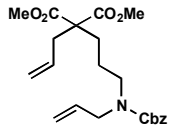
Dimethyl 2-allyl-2-(3-(N-allyl-4-methylphenylsulfonamido)propyl) malonate (169). To a solution of iodide **168** (0.381 g, 1.12 mmol, 1.0 equiv) in DMF (12.0 mL) was added Et_3N (0.31 mL, 2.24 mmol, 2.0 equiv), followed by allylamine

(0.43 mL, 5.61 mmol, 5.0 equiv) under Ar. The septum was sealed with Teflon tape, Ar atmosphere was removed, and the reaction mixture was heated at 60 °C for 30 min. The reaction was cooled to room temperature, diluted with ether (20 mL), quenched with water (10 mL), and extracted with ether (3 x 50 mL). The organic layer was washed with water (4 x 50 mL), and brine (1 x 50 mL), dried (Na_2SO_4), and concentrated. The resulting amine was used in the next step w/o further purification.

To a solution the crude amine (1.12 mmol) in DCM (20 mL), Et_3N (0.23 mL, 1.68 mmol, 1.5 equiv) was added, followed by TsCl (0.265 g, 1.34 mmol, 1.2 equiv). The reaction mixture was stirred for 19 h at rt. The solvent was removed under reduced pressure, and the reaction mixture was purified directly by flash chromatography (1/6-1/4 EtOAc/hexanes) to afford the title compound **169** as a light oil (R_f = 0.25, 1/4 EtOAc/hexanes), yield 75% for two steps (0.353 g, 0.83 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.48 (m, 2H), 1.78-1.84 (m, 2H), 2.44 (s, 3H), 2.62 (d, *J* = 7.4 Hz, 2H), 3.10 (t, *J* = 7.4 Hz, 2H), 3.72 (s, 6H), 3.79 (d, *J* = 6.5 Hz, 2H), 5.06-5.19 (m, 4H), 5.55-5.67 (m, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.0, 29.6, 37.4, 47.2, 50.7, 52.4, 57.3, 118.9, 119.1, 127.2, 129.7, 132.2, 133.2, 136.9, 143.2, 171.4; IR (neat) 2951, 2926, 1734, 1340, 1215, 1159 cm^{-1}; HRMS calcd for $C_{21}H_{29}NO_6SNa$ (M^+ + Na) 446.1613, found 446.1610.

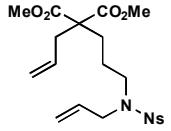


Dimethyl 2-allyl-2-(3-(allyl(tert-butoxycarbonyl)amino)propyl)malonate (170). To a solution of the crude amine obtained as described above (0.60 mmol) in DCM (15 mL), Et_3N (0.12 mL, 0.90 mmol, 1.5 equiv) was added, followed by Boc_2O (0.16 g, 0.72 mmol, 1.2 equiv). The reaction mixture was stirred for 20 h at rt. The solvent was removed under reduced pressure, and the reaction mixture was purified directly by flash chromatography (1/8-1/4 EtOAc/hexanes) to afford the title compound **170** as colorless oil (R_f = 0.43, 1/4 EtOAc/hexanes), yield 59% for two steps (0.13 g, 0.35 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37-1.52 (m, 2H), 1.47 (s, 9H), 1.82-1.88 (m, 2H), 2.66 (d, *J* = 7.4 Hz, 2H), 3.17-3.25 (m, 2H), 3.73 (s, 6H), 3.75-3.85 (m, 2H), 5.07-5.16 (m, 4H), 5.57-5.69 (m, 1H), 7.71-5.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 22.8, 23.1, 28.4, 29.7, 37.2, 46.5, 49.4, 52.4, 57.3, 79.5, 116.4, 119.1, 132.3, 134.3, 155.4, 171.5; IR (neat) 2976, 1735, 1695, 1410, 1244, 1207, 1149 cm^{-1}; HRMS calcd for $C_{19}H_{31}NO_6Na$ (M^+ + Na) 392.2049, found 392.2052.



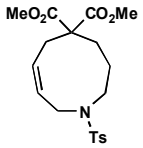
Dimethyl 2-allyl-2-(3-(allyl(benzyloxycarbonyl)amino)propyl)malonate (171). To a solution of the crude amine obtained as described above (0.60 mmol) in DCM (15 mL), Et_3N (0.12 mL, 0.90 mmol, 1.5 equiv) was added, followed by CBzCl

(0.10 mL, 0.72 mmol, 1.2 equiv). The reaction mixture was stirred for 5 h at rt. The solvent was removed under reduced pressure, and the reaction mixture was purified directly by flash chromatography (1/4 EtOAc/hexanes) to afford the title compound **171** as colorless oil (R_f = 0.35, 1/4 EtOAc/hexanes), yield 69% for two steps (0.165 g, 0.41 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (br, 2H), 1.85 (br, 2H), 2.63 (br, 2H), 3.25 (br, 2H), 3.70 (s, 6H), 3.90 (br, 2H), 4.98-5.22 (br, 4H), 5.15 (s, 2H), 5.52-5.86 (m, 2H), 7.29-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 22.6, 23.1, 29.6, 37.3, 46.4, 47.0, 49.5, 50.0, 52.4, 57.3, 67.2, 116.6, 117.1, 119.1, 127.9, 128.5, 132.2, 133.8, 136.8, 156.0, 171.5; IR (neat) 2951, 1734, 1699, 1238, 1215 cm^{-1}; HRMS calcd for $C_{22}H_{30}NO_6$ (M^+ + H) 404.2073, found 404.2067.



Dimethyl 2-allyl-2-(3-(N-allyl-2-nitrophenylsulfonamido)propyl)malonate (172). To a round bottom flask charged with N-allyl-2-nitrobenzenesulfonamide[1] (0.0475 g, 0.20 mmol, 1.0 equiv), K_2CO_3 (0.060 g, 0.43 mmol, 2.2 equiv) and DMF (12 mL), iodide **168** (0.100 g, 0.29 mmol, 1.5 equiv) was added as a solution in DMF (3 mL) at rt, and the reaction mixture was heated at 60 °C for 30 min. The reaction was cooled to room temperature, diluted with ether (20 mL), quenched with water (10 mL), and extracted with ether (3 x 30 mL). The organic layer was washed with water (4 x 20 mL), and brine (1 x 20 mL), dried (Na_2SO_4), and concentrated. Chromatography (1/2 EtOAc/hexanes) afforded the title compound as a colorless oil

(R_f = 0.56, 1/1 EtOAc/hexanes). Yield 90% (0.0801 g, 0.18 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42-1.52 (m, 2H), 1.74-1.80 (m, 2H), 2.61 (d, *J* = 7.4 Hz, 2H), 3.29 (t, *J* = 7.4 Hz, 2H), 3.72 (s, 6H), 3.94 (d, *J* = 6.4 Hz, 2H), 5.06-5.13 (m, 2H), 5.18-5.26 (m, 2H), 5.54-5.76 (m, 2H), 7.63-7.75 (m, 3H), 8.03-8.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 29.5, 37.5, 46.7, 49.8, 52.4, 57.2, 119.2, 119.4, 124.2, 131.0, 131.7, 132.2, 132.7, 133.5, 133.7, 148.0, 171.3; IR (neat) 2952, 1732, 1543, 1352, 1215, 1163 cm^{-1}; HRMS calcd for $C_{20}H_{26}N_2O_8SNa$ (M^+ + Na) 477.1308, found 477.1309.



(Z)-Dimethyl 1-tosyl-3,4,6,9-tetrahydro-1H-azonine-5,5(2H)-dicarboxylate (173). Table 15, entry 1. To a 25 ml round-bottom flask charged with olefin and solvent (c = 0.003 M), 50 mol% of Grubbs 1 catalyst was added as solid under nitrogen. The reaction was stirred at 40 °C for 16 h. The reaction was cooled to rt, 50 mol% of Grubbs 1 catalyst was added, and stirring at 40 °C was continued for next 10 h. The reaction was cooled to rt, solvent was removed under reduced pressure. Known amount of nitromethane was added as the internal standard, and the reaction was analyzed by ^{1}H NMR. Purification by flash chromatography afforded the title product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 2H), 2.15 (s, 2H), 2.45 (s, 3H), 2.7-3.2 (br s, 2H), 3.17 (s, 2H), 3.66 (s, 2H), 3.76 (s, 6H), 5.49 (q, *J* = 10.4 Hz, 1H),

5.81 (m, 1H), 7.33 (d, J = 8.0 Hz), 7.71 (d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.9, 27.8, 30.3, 46.5, 50.8, 52.7, 56.7, 127.3, 128.4, 129.5, 129.7, 135.3, 143.4, 171.6; IR (neat) 2952, 2926, 1733, 1339, 1210, 1160, 1090 cm^{-1}; HRMS calcd for $C_{19}H_{26}NO_6SNa$ (M^+ + Na) 418.1300, found 418.1296.

Optimization of RCM reaction, representative entries from Table 15. Entry 2 and 3. To a 25 ml round-bottom flask charged with olefin and solvent (c = 0.003 M), Fürstner catalyst was added in one portion as solid under nitrogen. The reaction was stirred at rt (entry 2) or 40 °C (entry 3) for specified period of time. Solvent was removed under reduced pressure. Known amount of nitromethane was added as the internal standard, and the reaction was analyzed by ^{1}H NMR.

Entry 4 and 5. To a 25 ml round-bottom flask charged with olefin. Grubbs 2 catalyst followed by solvent (c = 0.003 M) was added as solid under nitrogen. The reaction was stirred at 40 °C (entry 4) or 80 °C (entry 5) for specified period of time. Solvent was removed under reduced pressure. Known amount of nitromethane was added as the internal standard, and the reaction was analyzed by ^{1}H NMR.

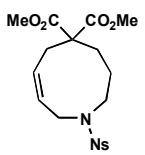
Entry 7. To a 25 ml round-bottom flask charged with olefin. Grubbs 2 catalyst followed by solvent (c = 0.003 M) was added as solid under nitrogen. $Ti(O\textit{i}Pr)_4$ (5 equiv) was added and the reaction was stirred at 80 °C for specified period of time. Solvent was removed under reduced pressure. Known amount of nitromethane was added as the internal standard, and the reaction was analyzed by ^{1}H NMR.

Entry 6 and 10. A 25 ml round-bottom flask charged with olefin and solvent (c = 0.003 M) was heated to 80 °C for 30-45 min. Grubbs 2 (entry 6) or Hoveyda-

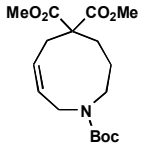
Grubbs 2 catalyst (entry 10) was added in DCE and the reaction was stirred at 80 °C for specified period of time. Solvent was removed under reduced pressure. Known amount of nitromethane was added as the internal standard, and the reaction was analyzed by ^{1}H NMR.

Entry 13. A 25 ml round-bottom flask charged with olefin (0.0150 g, 0.036 mmol, 1.0 equiv) and solvent (c = 0.003 M) was heated to 80 °C for 15 min. Hoveyda-Grubbs 2 catalyst was added in DCE. Argon was bubbled through the reaction while it was stirred at 80 °C for specified period of time. Solvent was removed under reduced pressure. Purification of the residue by flash chromatography (1/7-1/4 EtOAc/Hexanes) afforded the title compound in 87% yield (0.0122 g, 0.031 mmol).

Entry 14. A 25 ml round-bottom flask charged with olefin (0.0144 g, 0.034 mmol, 1.0 equiv) and solvent (c = 0.003 M) was sealed with a septum under argon and heated to 80 °C for 15 min. Hoveyda-Grubbs 2 catalyst was added in DCE. The reaction was stirred at 80 °C for 8 h. A needle was inserted once every hour to open the reaction to air and release ethylene. Solvent was removed under reduced pressure. Purification of the residue by flash chromatography (1/7-1/4 EtOAc/Hexanes) afforded the title compound in 95% yield (0.0127 g, 0.032 mmol).

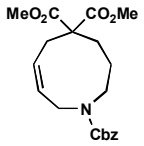


(Z)-Dimethyl 1-(2-nitrophenylsulfonyl)-3,4,6,9-tetrahydro-1H-azonine-5,5(2H)-dicarboxylate (176). A 100 ml round-bottom flask charged with olefin **172** (0.0610 g, 0.134 mmol, 1.0 equiv) and DCE (45 mL, c = 0.003 M) was heated to 80 °C for 15 min. Hoveyda-Grubbs 2 catalyst (0.0042 g, 0.0067 mmol, 0.05 equiv) was added in DCE (1.0 mL). Argon was bubbled through the reaction while it was stirred at 80 °C for 16 h. Solvent was removed under reduced pressure. Purification of the residue by flash chromatography (1/7-1/1 EtOAc/Hexanes) afforded the title compound as an oil (R_f = 0.33, 1/1 EtOAc/hexanes). Yield 93% (0.0532 g, 0.125 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 2H), 2.16 (s, 2H), 2.94 (s, 2H), 3.39 (t, *J* = 6.0 Hz, 2H), 3.76 (s, 6H), 3.85 (d, *J* = 7.0 Hz, 2H), 5.51-5.59 (m, 1H), 5.86-5.94 (m, 1H), 7.60-7.64 (m, 1H), 7.67-7.75 (m, 2H), 7.96-7.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 27.1, 30.4, 46.2, 50.9, 52.7, 56.6, 124.1, 129.0, 129.7, 130.7, 131.5, 132.0, 133.6, 148.5, 171.5; IR (neat) 2952, 2924, 1732, 1541, 1373, 1346, 1207, 1165 cm^{-1}; HRMS calcd for $C_{18}H_{22}N_2O_8SNa$ (M^+ + Na) 449.0994, found 449.0992.



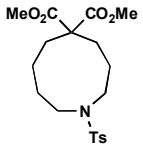
(Z)-1-*tert*-Butyl 5,5-dimethyl 3,4-dihydro-1H-azonine-1,5,5(2H,6H,9H)-tricarboxylate (174). According to the procedure for **176**, the reaction of **170** (0.0840 g, 0.23, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0071 g, 0.011 mmol, 0.05

equiv) in DCE (57 mL = 0.004 M) at 80 °C for 17 h afforded after chromatography (1/7-1/5 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.33, 1/4 EtOAc/hexanes). Yield 85% (0.0662 g, 0.194 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 1.6-2.2 (m, 4H), 2.5-3.0 (m, 2H), 3.37 (s, 2H), 3.75 (s, 6H), 3.75-4.05 (m, 2H), 5.27-5.42 (m, 1H), 5.83-5.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 21.8, 23.1, 26.9, 27.7, 28.5, 28.5, 29.7, 30.4, 30.5, 46.6, 47.8, 49.9, 50.8, 52.6, 52.6, 57.0, 57.3, 79.6, 79.8, 125.9, 126.6, 130.9, 131.2, 155.5, 171.7; IR (neat) 2952, 1733, 1693, 1456, 1411, 1395, 1125, 1170 cm^{-1}; HRMS calcd for $C_{17}H_{27}NO_6Na$ (M^+ + Na) 374.1736, found 364.1706.

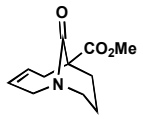


(Z)-1-Benzyl 5,5-dimethyl 3,4-dihydro-1H-azonine-1,5,5(2H,6H,9H)-tricarboxylate (175). According to the procedure for Table 1, entry 14, the reaction of **171** (0.0170 g, 0.042, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0013 g, 0.0021 mmol, 0.05 equiv) in DCE (15 mL = 0.003 M) at 80 °C for 8 h afforded after chromatography (1/7-1/5 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.68, 1/1 EtOAc/hexanes). Yield 89% (0.0141 g, 0.038 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 2H), 2.79 (s, 2H), 3.42 (t, *J* = 6.0 Hz, 2H), 3.76 (s, 6H), 3.85 (s, 2H), 3.92 (d, *J* = 6.2 Hz, 2H), 5.35-5.44 (m, 1H), 5.88-6.01 (m, 1H), 7.31-7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 21.8, 23.0, 26.6, 27.1,

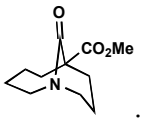
30.7, 30.8, 46.0, 47.3, 50.0, 50.3, 52.6, 52.7, 56.9, 57.0, 67.1, 67.3, 127.0, 127.4, 127.8, 127.9, 128.0, 128.5, 130.5, 130.7, 136.7, 136.9, 155.8, 156.3, 171.6; IR (neat) 2950, 1731, 1699, 1417, 1251, 1230, 1214, 1089 cm^{-1}; HRMS calcd for $C_{20}H_{26}NO_6$ (M^+ + H) 376.1760, found 376.1758.



Dimethyl 1-tosylazonane-5,5-dicarboxylate (177). To a solution of **173** (0.0069 g, 0.0175 mmol, 1.0 equiv) in EtOAc (3 mL), Pd/C (5%), ca. 10 mg was added, and the reaction was stirred under H_2 balloon at rt for 20 h. Filtration through celite pad, followed by chromatography (1/2 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.63, 1/1 EtOAc/hexanes). Yield 96% (0.0067 g, 0.0169 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (m, 4H), 1.79 (m, 2H), 2.14 (t, *J* = 6.4 Hz, 2H), 2.31 (t, *J* = 5.9 Hz, 2H), 2.45 (s, 3H), 2.99-3.05 (m, 4H), 3.73 (s, 6H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 21.2, 21.5, 26.4, 26.7, 28.0, 45.9, 50.4, 52.5, 57.5, 127.5, 129.6, 134.5, 143.3, 172.3; IR (neat) 2952, 2916, 1730, 1338, 1207, 1159, 912, 742 cm^{-1}; HRMS calcd for $C_{19}H_{28}NO_6S$ (M^+ + H) 398.1637, found 398.1636. Note: DEPT, COSY and HSQC in agreement with the assigned structure.

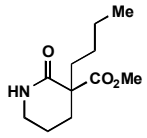


Methyl 10-oxo-1-azabicyclo[4.3.1]dec-3-ene-6-carboxylate (178). To a solution of **176** (0.0206 g, 0.0484 mmol, 1.0 equiv) and Cs_2CO_3 (0.088 g, 0.27 mmol, 5.5 equiv) in CH_3CN (5 mL), thiophenol (0.0297 g, 0.27 mmol, 5.5 equiv) was added, and the resulting mixture was heated at 55-60 $^{\circ}C$ for 2.5 h. Solvent was removed under reduced pressure, and the reaction was analyzed by ^1H NMR Yield 89% (vs. 2-nitrophenylphenylsulfide). Purification by PTLC (1:1 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.57, 1/1 EtOAc/hexanes). Yield 54% (0.0055 g, 0.0263 mmol). Note: the compound is unstable on silica. ^1H NMR (400 MHz, $CDCl_3$) δ 1.78-1.88 (m, 2H), 1.93-2.02 (m, 1H), 2.32-2.40 (m, 1H), 2.50-2.56 (m, 1H), 3.03-3.11 (m, 1H), 3.19 (m, 1H), 3.29-3.37 (m, 1H), 3.41-3.48 (m, 1H), 3.80 (s, 3H), 3.40-3.48 (m, 1H), 5.55-5.62 (m, 1H), 5.67-5.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 34.2, 35.4, 50.4, 52.7, 54.9, 59.5, 126.6, 126.7, 172.8, 181.9; IR (neat) 2916, 1739, 1683, 1458, 1437, 1242, 1182, 1116 cm^{-1}; HRMS calcd for $C_{11}H_{15}NO_3Na$ (M^+ + Na) 232.0949, found 232.0951.



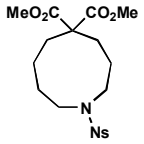
Methyl 10-oxo-1-azabicyclo[4.3.1]decane-6-carboxylate (179). A 10 mL round-bottom flask charged with **174** (0.0245 g, 0.072 mmol, 1.0 equiv), EtOAc (5 mL) and Pd/C (5%, ca. 50 mg) was stirred under H_2 balloon for 22 h at rt. The reaction mixture was filtered through a pad of celite and concentrated. The residue was taken in 8 mL of DCM and 3 mL of TFA was added at rt After stirring for 2 h at

rt, the solvent was removed under reduced pressure, CH_3CN was added, followed by Cs_2CO_3 (0.47 g, 1.44 mmol, 20 equiv), and the reaction mixture was stirred at 60 °C for 3 h. Solvent removal, followed by chromatography (1/2-1/1 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.72, 1/1 EtOAc/hexanes). Yield 73% (0.0111 g, 0.053 mmol). Note: in contrast to **178**, the compound is stable on silica. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64-1.97 (m, 8H), 2.41-2.55 (m, 2H), 2.77-2.84 (m, 1H), 3.30-3.37 (m, 1H), 3.44 (dt, *J* = 4.0, 11.2 Hz, 1H), 3.79 (s, 3H), 3.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 23.7, 26.3, 32.4, 35.4, 49.1, 50.2, 52.5, 58.6, 173.3, 181.0; IR (neat) 2945, 1737, 1680, 1444, 1255, 1240, 1176 cm^{-1}; HRMS calcd for $C_{11}H_{17}NO_3Na$ (M^+ + Na) 234.1106, found 234.1105.

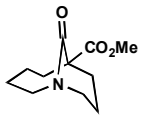


Methyl 3-butyl-2-oxopiperidine-3-carboxylate (180). A 10 mL round-bottom flask charged with **175** (0.0140 g, 0.0373 mmol, 1.0 equiv), MeOH (5 mL) and Pd/C (5%, ca. 30 mg) was stirred under H_2 balloon for 24 h at rt. The reaction mixture was filtered through a pad of celite and concentrated. Purification by chromatography (EtOAc-1/4 MeOH/EtOAc) afforded the title compound as oil (R_f = 0.37, EtOAc). Yield 63% (0.0050 g, 0.024 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.0 Hz, 3H), 1.14-1.39 (m, 4H), 1.79-2.04 (m, 5H), 2.19-2.27 (m, 1H), 3.36 (m, 2H), 3.76 (s, 3H), 5.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.8, 23.1, 26.7, 29.5, 35.4, 42.5, 52.6, 54.0, 170.9, 173.5; IR (neat) 3209, 2954, 1734,

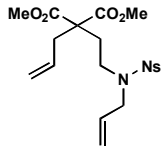
1668, 1558, 1489, 1456, 1197 cm^{-1}; HRMS calcd for $C_{11}H_{20}NO_3$ (M^+ + Na) 214.1443, found 214.1440.



Dimethyl 1-(2-nitrophenylsulfonyl)azonane-5,5-dicarboxylate (181). To a solution of **176** (0.018 g, 0.042 mmol, 1.0 equiv) in THF (5 mL), $Rh(PPh_3)_3Cl$ (0.0195 g, 0.021 mmol, 0.5 equiv) was added under nitrogen. The flask was evacuated (3 x), H_2 atmosphere was established, H_2 was bubbled through the solution for ca. 30 s, and the reaction was stirred under H_2 balloon for 16 h. Solvent was removed under reduced pressure, and the residue was purified by chromatography (1/2-1/1 EtOAc/hexanes) to afford the title compound as oil (R_f = 0.37, 1/1 EtOAc/hexanes). Yield 60% (0.0108 g, 0.025 mmol). Note: traces of the aniline were detected by MS. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58-1.67 (m, 2H), 1.68-1.76 (m, 2H), 1.78-1.86 (m, 2H), 2.16 (t, *J* = 6.4 Hz, 2H), 2.32 (t, *J* = 6.1 Hz, 2H), 3.24-3.32 (m, 4H), 3.73 (s, 6H), 7.57-7.62 (m, 1H), 7.66-7.76 (m, 2H), 7.91-7.5 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 21.5, 26.7, 26.9, 27.8, 46.7, 51.0, 52.6, 57.5, 123.9, 130.7, 131.1, 131.3, 133.6, 149.0, 172.2; IR (neat) 2952, 2918, 1728, 1543, 1373, 1346, 1209, 1167, 912 cm^{-1}; HRMS calcd for $C_{18}H_{24}N_2O_8SNa$ (M^+ + Na) 451.1151, found 451.1139.

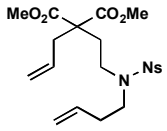


Methyl 10-oxo-1-azabicyclo[4.3.1]decane-6-carboxylate (179). From 181. According to the general procedure, the reaction of **181** (0.0081 g, 0.019 mmol, 1.0 equiv), Cs_2CO_3 (0.062 g, 0.19 mmol, 10 equiv) and PhSH (0.0104 g, 0.095 mmol, 5.0 equiv) in CH_3CN (6 mL) at 60 °C for 2 h afforded after chromatography (1/4-1/1 EtOAc/hexanes) the title compound in 78% yield (0.0031 g, 0.015mmol). Spectroscopic properties matched those previously described.

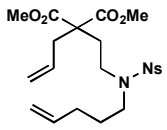


Dimethyl 2-allyl-2-(2-(N-allyl-2-nitrophenylsulfonamido)ethyl)malonate (183). According to the procedure for **172**, the reaction of N-allyl-2-nitrobenzenesulfonamide (0.11 g, 0.45 mmol, 1.0 equiv), K_2CO_3 (0.138 g, 0.99 mmol, 2.2 equiv) and dimethyl 2-allyl-2-(2-bromoethyl)malonate (0.25 g, 0.91 mmol, 2.0 equiv) in DMF (15 mL) at 80 °C for 7 h afforded after chromatography (1/4-1/2 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.66, 1/1 EtOAc/hexanes). Yield 70% (0.139 g, 0.32 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09-2.16 (m, 2H), 2.64 (d, *J* = 7.4 Hz, 2H), 3.25-3.32 (m, 2H), 3.74 (s, 6H), 3.97 (d, *J* = 6.4 Hz, 2H), 5.09-5.32 (m, 4H), 5.55-5.75 (m, 2H), 7.62-7.74 (m, 3H), 8.00-8.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8, 37.6, 42.6, 50.1, 52.6, 56.1, 119.6, 119.7, 125.0,

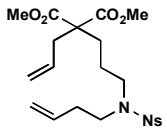
130.9, 131.7, 131.8, 132.5, 133.5, 133.6, 148.0, 170.9; IR (neat) 2952, 1732, 1545, 1371, 1356, 1224, 1163 cm^{-1}; HRMS calcd for $C_{19}H_{25}N_2O_8S$ (M^+ + H) 441.1332, found 441.1332.



Dimethyl 2-allyl-2-(2-(N-(but-3-enyl)-2-nitrophenylsulfonamido)ethyl) malonate (184). According to the procedure for **172**, the reaction of N-(but-3-enyl)-2-nitrobenzenesulfonamide (0.16 g, 0.62 mmol, 1.0 equiv), K_2CO_3 (0.22 g, 1.6 mmol, 2.5 equiv) and dimethyl 2-allyl-2-(2-bromoethyl)malonate (0.52 g, 1.9 mmol, 3.0 equiv) in DMF (15 mL) at 80 °C for 13 h afforded after chromatography (1/4-1/3-1/1 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.77, 1/1 EtOAc/hexanes). Yield 75% (0.21 g, 0.46 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10-2.16 (m, 2H), 2.28-2.36 (m, 2H), 2.66 (d, *J* = 7.4 Hz, 2H), 3.30-3.37 (m, 2H), 3.37-3.42 (m, 2H), 3.76 (s, 6H), 5.02-5.18 (m, 4H), 5.58-5.77 (m, 2H), 7.61-7.74 (m, 3H), 7.99-8.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 32.6, 38.0, 43.2, 47.0, 52.7, 56.1, 117.5, 119.7, 124.2, 130.8, 131.6, 131.9, 133.4, 133.6, 134.2, 148.0, 170.9; IR (neat) 2952, 1732, 1545, 1373, 1350, 1222, 1161 cm^{-1}; HRMS calcd for $C_{20}H_{27}N_2O_8S$ (M^+ + H) 455.1488, found 455.1490.

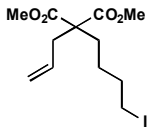


Dimethyl 2-allyl-2-(2-(2-nitro-N-(pent-4-enyl)phenylsulfonamido)ethyl) malonate (185). According to the procedure for **172**, the reaction of 2-nitro-N-(pent-4-enyl)benzenesulfonamide (0.114 g, 0.42 mmol, 1.0 equiv), K_2CO_3 (0.147 g, 1.05 mmol, 2.5 equiv) and dimethyl 2-allyl-2-(2-bromoethyl)malonate (0.35 g, 1.25 mmol, 3.0 equiv) in DMF (15 mL) at 80 °C for 13 h afforded after chromatography (1/4-1/2 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.14, 1/4 EtOAc/hexanes). Yield 68% (0.133 g, 0.28 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61-1.69 (m, 2H), 2.01-2.08 (m, 2H), 2.09-2.16 (m, 2H), 2.66 (d, *J* = 7.4 Hz, 2H), 3.27-3.35 (m, 4H), 3.76 (s, 6H), 4.97-5.05 (m, 2H), 5.09-5.18 (m, 2H), 5.57-5.68 (m, 2H), 5.70-5.81 (m, 2H), 7.60-7.73 (m, 3H), 7.98-8.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 30.6, 31.5, 37.9, 43.2, 47.3, 52.7, 56.1, 115.5, 119.7, 124.2, 130.8, 131.6, 131.9, 133.4, 133.5, 137.2, 148.1, 170.9; IR (neat) 2952, 1732, 1545, 1373, 1350, 1219, 1161 cm^{-1}; HRMS calcd for $C_{21}H_{28}N_2O_8SNa$ (M^+ + H) 491.1164, found 491.1465.

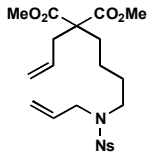


Dimethyl 2-allyl-2-(3-(N-(but-3-enyl)-2-nitrophenylsulfonamido)propyl) malonate (186). According to the procedure for **172**, the reaction of N-(but-3-enyl)-2-nitrobenzenesulfonamide (0.165 g, 0.64 mmol, 1.0 equiv), K_2CO_3 (0.197 g, 1.41 mmol, 2.2 equiv) and iodide **168** (0.33 g, 0.97 mmol, 1.5 equiv) in DMF (20 mL) at 60 °C for 60 min afforded after chromatography (1/4-1/2 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.63, 1/1 EtOAc/hexanes). Yield 95% (0.284 g,

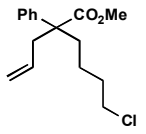
0.61 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.54 (m, 2H), 1.76-1.82 (m, 2H), 2.24-2.33 (m, 2H), 2.62 (d, *J* = 7.4 Hz, 2H), 3.28-3.39 (m, 4H), 3.72 (s, 6H), 5.00-5.13 (m, 4H), 5.54-5.76 (m, 2H), 7.63-7.74 (m, 3H), 8.00-8.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 29.6, 32.5, 37.6, 46.5, 47.1, 52.5, 57.2, 117.5, 119.3, 124.2, 130.8, 131.6, 132.1, 133.4, 133.6, 134.1, 148.0, 171.3; IR (neat) 2952, 1732, 1545, 1373, 1346, 1215, 1159 cm^{-1}; HRMS calcd for $C_{21}H_{29}N_2O_8S$ (M^+ + H) 469.1645, found 469.1654.



Dimethyl 2-allyl-2-(4-iodobutyl)malonate (187). According to the procedure for **168**, the reaction of sodium hydride (60%, suspension in mineral oil) (0.26 g, 6.4 mmol, 1.1 equiv), dimethyl 2-allylmalonate (1.0 g, 5.8 mmol, 1.0 equiv), and 1,4-diiodopropane (2.3 mL, 17.4 mmol, 3.0 equiv) in THF (20 mL) afforded after chromatography (2-5% EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.42, 10% EtOAc/hexanes). Yield 75% (1.54 g, 4.4 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22-1.37 (m, 2H), 1.78-1.92 (m, 4H), 2.67 (d, *J* = 7.4 Hz, 2H), 3.19 (t, *J* = 6.9 Hz, 2H), 3.74 (s, 6H), 5.08-55.14 (m, 2H), 5.57-5.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.3, 24.8, 31.1, 33.3, 37.1, 52.5, 57.4, 119.2, 132.3, 171.6; IR (neat) 2951, 1732, 1435, 1215 cm^{-1}; HRMS calcd for $C_{12}H_{20}IO_4$ (M^+ + H) 355.0406, found 355.0394.

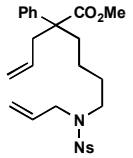


Dimethyl 2-allyl-2-(4-(N-allyl-2-nitrophenylsulfonamido)butyl)malonate (188). According to the procedure for **172**, the reaction of N-allyl-2-nitrobenzenesulfonamide (0.173 g, 0.72 mmol, 1.0 equiv), K_2CO_3 (0.22 g, 1.57 mmol, 2.2 equiv) and iodide **187** (0.38 g, 1.07 mmol, 1.5 equiv) in DMF (15 mL) at 60 °C for 60 min afforded after chromatography (1/4-1/2 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.72, 1/1 EtOAc/hexanes). Yield 88% (0.295 g, 0.63 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05-1.15 (m, 2H), 1.52 (p, *J* = 7.5 Hz, 2H), 1.78-1.87 (m, 2H), 2.58 (d, *J* = 7.4 Hz, 2H), 3.28 (t, *J* = 7.5 Hz, 2H), 3.71 (s, 6H), 3.92 (d, *J* = 6.2 Hz, 2H), 5.04-5.27 (m, 4H), 5.54-5.76 (m, 2H), 7.62-7.75 (m, 3H), 8.01-8.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 27.9, 32.1, 37.1, 46.6, 49.7, 52.4, 57.5, 119.0, 119.2, 124.3, 130.9, 131.6, 132.3, 132.8, 133.5, 133.7, 147.9, 171.5; IR (neat) 2952, 1732, 1543, 1373, 1352, 1211, 1161 cm^{-1}; HRMS calcd for $C_{21}H_{29}N_2O_8S$ (M^+ + H) 469.1645, found 469.1638.



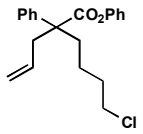
Methyl 2-allyl-6-chloro-2-phenylhexanoate (191). To solution of LDA prepared from diisopropylamine (0.37 mL, 2.62 mmol, 1.15 equiv) and n-butyllithium (2.3 M in hexanes) (1.09 mL, 2.50 mmol, 1.10 equiv) in THF (10 mL),

HMPA (1.0 mL) was added dropwise at -78 °C. After stirring for 30 min at -78 °C methyl allylphenylacetate **189** in THF (5 mL) was added dropwise. After next 45 min at -78 °C, 1-chloro-4-iodobutane (0.42 mL, 3.4 mmol, 1.5 equiv) was added dropwise, and after 15 min the reaction mixture was allowed to warm to room temperature. After stirring for additional 3 h, the reaction was quenched with brine (10 mL). The aqueous layer was extracted with ether (3 x 50 mL), and the combined organic layers were washed brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. Chromatography (1-2-5% EtOAc/hexanes) afforded the title compound as a colorless oil (R_f = 0.47, 10% EtOAc/hexanes). Yield 84% (0.534 g, 1.90 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-1.33 (m, 2H), 1.78 (p, *J* = 7.5 Hz, 2H), 1.98-2.08 (m, 2H), 2.84 (dq, *J* = 7.7, 14 Hz, 2H), 3.52 (dt, *J* = 1.5, 6.6 Hz, 2H), 3.68 (s, 3H), 5.05-5.15 (m, 2H), 5.49-5.61 (m, 1H), 7.24-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 32.9, 33.7, 39.1, 44.6, 52.1, 53.7, 118.5, 126.3, 126.9, 128.4, 133.5, 142.0, 175.8; IR (neat) 2951, 1730, 1496, 1446, 1271, 1217, 1155 cm^{-1}; HRMS calcd for $C_{16}H_{21}ClO_2Na$ (M^+ + Na) 303.1128, found 3303.1117.



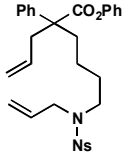
Methyl 2-allyl-6-(N-allyl-2-nitrophenylsulfonamido)-2-phenylhexanoate (193). To a round bottom flask charged with N-allyl-2-nitrobenzenesulfonamide (0.215 g, 0.89 mmol, 1.0 equiv), K_2CO_3 (0.273 g, 1.96 mmol, 2.2 equiv), NaI (0.67g,

4.5 mmol, 5 equiv) and DMF (10 mL), chloride **191** (0.50 g, 1.78 mmol, 2.0 equiv) was added as a solution in DMF (5 mL) at rt, and the reaction mixture was heated at 80 °C for 14 h. The reaction was cooled to room temperature, diluted with ether (20 mL), quenched with water (10 mL), and extracted with ether (3 x 50 mL). The organic layer was washed with water (4 x 50 mL), and brine (1 x 50 mL), dried (Na_2SO_4), and concentrated. Chromatography (1/4-1/3 EtOAc/hexanes) afforded the title compound as a yellow oil (R_f = 0.76, 1/1 EtOAc/hexanes). Yield 72% (0.313 g, 0.64 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96-1.06 (m, 2H), 1.44-1.56 (m, 2H), 1.90-1.99 (m, 2H), 2.74 (dq, *J* = 6.8, 14 Hz, 2H), 3.24 (d, *J* = 7.7 Hz, 2H), 3.65 (s, 3H), 3.91 (d, *J* = 6.2 Hz, 2H), 5.02-5.09 (m, 2H), 5.19 (dt, *J* = 1.2, 10.0 Hz, 2H), 5.44-5.56 (m, 1H), 5.63-5.75 (m, 1H), 7.19-7.38 (m, 5H), 7.62-7.73 (m, 3H), 8.00-8.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 28.1, 34.1, 39.2, 46.8, 49.7, 52.1, 53.7, 118.4, 119.1, 124.2, 126.3, 126.9, 128.4, 130.9, 131.6, 132.8, 133.4, 133.5, 133.8, 141.9, 147.9, 175.8; IR (neat) 2949, 1728, 1545, 1371, 1352, 1163 cm^{-1}; HRMS calcd for $C_{25}H_{30}N_2O_6SNa$ (M^+ + Na) 509.1722, found 509.1724.



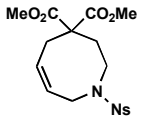
Phenyl 2-allyl-6-chloro-2-phenylhexanoate (192). According to the procedure for **191**, the reaction of LDA (prepared from diisopropylamine (0.27 mL, 1.91 mmol, 1.15 equiv) and n-butyllithium (2.3 M in hexanes) (0.79 mL, 1.83 mmol, 1.10 equiv) in THF (10 mL)), HMPA (1.0 mL), phenyl allylphenylacetate **190** (0.42

g, 1.66 mmol, 1.0 equiv), and 1-chloro-4-iodobutane (0.31 mL, 2.5 mmol, 1.5 equiv) afforded after chromatography (hexanes-1-2-5% EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.35, 10% EtOAc/hexanes). The compound was contaminated with inseparable impurity (ca. 10-15% by ^{1}H NMR). Yield (corrected by impurity) 69% (0.39 g, 1.14 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33-1.52 (m, 2H), 1.83 (p, *J* = 7.0 Hz, 2H), 2.07-2.24 (m, 2H), 2.97 (dq, *J* = 6.6, 14.1 Hz, 2H), 3.52-3.62 (m, 2H), 5.18-5.24 (m, 2H), 5.63-5.74 (m, 1H), 6.94-6.99 (m, 2H), 7.19-7.24 (m, 1H), 7.29-7.45 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 32.9, 33.6, 39.0, 44.7, 53.8, 118.9, 121.4, 125.8, 126.4, 127.1, 128.6, 129.4, 133.1, 141.6, 150.8, 174.0; IR (neat) 2952, 1749, 1593, 1492, 11.92, 1161 cm^{-1}; HRMS calcd for $C_{21}H_{23}ClO_2Na$ (M^+ + Na) 365.1284, found 365.1251.

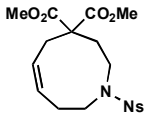


Phenyl 2-allyl-6-(N-allyl-2-nitrophenylsulfonamido)-2-phenylhexanoate (194). According to the procedure for **193**, the reaction of N-allyl-2-nitrobenzenesulfonamide (0.109 g, 0.45 mmol, 1.0 equiv), K_2CO_3 (0.138 g, 0.99 mmol, 2.2 equiv), NaI (0.34 g, 2.3 mmol, 5 equiv) and chloride **192** (0.39 g, 1.14 mmol, 2.5 equiv) in DMF (15 mL) at 80 °C for 14 h afforded after chromatography (1/5-1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.74, 1/1 EtOAc/hexanes). Yield 65% (0.161 g, 0.29 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10- 1.20 (m, 2H),

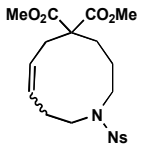
1.51-1.62 (m, 2H), 2.02-2.16 (m, 2H), 2.89 (dq, J = 6.6, 14.0 Hz, 2H), 3.28 (t, J = 7.6 Hz, 2H), 3.92 (d, J = 6.3 Hz, 2H), 5.12- 5.25 (m, 4H), 5.58-5.76 (m, 2H), 6.92-6.97 (m, 2H), 7.19-7.24 (m, 1H), 7.28-7.43 (m, 7H), 7.60-7.71 (m, 3H), 8.01-8.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 28.2, 34.1, 39.0, 46.7, 49.8, 53.8, 118.9, 119.1, 121.3, 124.2, 125.8, 126.4, 127.1, 128.6, 129.4, 130.9, 131.6, 132.8, 133.1, 133.4, 133.7, 141.5, 147.9, 150.8, 173.9; IR (neat) 2935, 1747, 1543, 1371, 1352, 1161, 1124 cm^{-1}; HRMS calcd for $C_{30}H_{32}N_2O_6SNa$ (M^+ + Na) 571.1878, found 571.1880.



(Z)-Dimethyl 1-(2-nitrophenylsulfonyl)-1,2,3,8-tetrahydroazocine-4,4(5H)-dicarboxylate (195). According to the procedure for Table 1, entry 14, the reaction of **183** (0.0689 g, 0.157 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0049 g, 0.0080 mmol, 0.05 equiv) in DCE (53 mL = 0.003 M) at 80 °C for 2.5 h (needle was inserted every 15-30 min) afforded after chromatography (1/7-1/1 EtOAc/hexanes) the title compound as white solid (Mp = 158 °C; R_f = 0.43, 1/1 EtOAc/hexanes). Yield 90% (0.0583 g, 0.142 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (m, 2H), 3.03 (d, J = 7.6 Hz, 2H), 3.55 (m, 2H), 3.76 (s, 6H), 4.00 (d, J = 4.1 Hz, 2H), 5.72-5.86 (m, 2H), 7.62-7.75 (m, 3H), 7.98-8.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 31.1, 45.3, 46.8, 52.9, 57.5, 124.2, 127.6, 129.2, 131.1, 131.7, 132.6, 133.6, 148.0, 171.2; IR (neat) 2954, 1732, 1541, 1373, 1346, 1221, 1163, 1130 cm^{-1}; HRMS calcd for $C_{17}H_{20}N_2O_8SNa$ (M^+ + Na) 435.0838, found 435.0833.

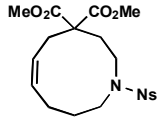


(Z)-Dimethyl 1-(2-nitrophenylsulfonyl)-2,3,8,9-tetrahydro-1H-azonine-4,4(5H)-dicarboxylate (196. According to the procedure for **195**, the reaction of **184** (0.0663 g, 0.146 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0046 g, 0.0073 mmol, 0.05 equiv) in DCE (50 mL = 0.003 M) at 80 °C for 2.5 h (needle was inserted every 15-30 min) afforded after chromatography (1/7-1/1 EtOAc/hexanes) the title compound as yellowish foam (R_f = 0.47, 1/1 EtOAc/hexanes). Yield 94% (0.0586 g, 0.138 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (t, *J* = 5.7 Hz, 2H), 2.52 (s, 2H), 3.04 (d, *J* = 8.4 Hz, 2H), 3.25 (s, 2H), 3.34 (s, 2H), 3.80 (s, 6H), 5.47-5.56 (m, 1H), 5.84-5.92 (m, 1H), 7.58-7.62 (m, 1H), 7.67-7.75 (m, 2H), 7.88-7.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 29.8, 31.9, 46.1, 49.2, 52.9, 56.6, 124.0, 128.3, 130.7, 131.1, 131.4, 131.4, 133.6, 148.7, 171.2; IR (neat) 2952, 1733, 1542, 1456, 1437, 1373, 1350, 1221, 1167 cm^{-1}; HRMS calcd for $C_{18}H_{23}N_2O_8S$ (M^+ + H) 427.1175, found 427.1173.



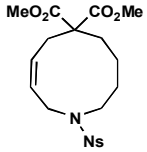
Dimethyl 1-(2-nitrophenylsulfonyl)-1,2,3,4,9,10-hexahydroazecine-5,5(6H)-dicarboxylate (197). According to the procedure for **195**, the reaction of **186** (0.0578 g, 0.123 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0039 g, 0.0062 mmol, 0.05 equiv) in DCE (42 mL = 0.003 M) at 80 °C for 2 h afforded after

chromatography (1/7-1/1 EtOAc/hexanes) the title compound (5:1 mixture of Z/E isomers) as oil (R_f = 0.43, 1/1 EtOAc/hexanes). Yield 90% (0.0495 g, 0.110 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of Z/E isomers) δ 1.45-1.80 (m, 2.7H), 1.90-2.50 (m, 3.9H), 2.62 (s, 1.3H), 3.00 (m, 4.5H), 3.75 (s, 8.2H), 3.93 (s, 1.1H), 5.42-5.51 (m, 1H, Z isomer), 5.50-5.61 (m, 1H, E isomer), 5.65-5.70 (m, 1H, E isomer), 5.71-5.79 (m, 1H, Z isomer), 7.58-7.64 (m, 1.07H), 7.65-7.73 (m, 2.36H), 7.86-7.93 (m, 1.18H); ^{13}C NMR (100 MHz, $CDCl_3$) (Z isomer) δ 22.9, 25.6, 28.4, 28.7, 49.1, 49.8, 52.6, 55.7, 124.1, 125.7, 127.8, 130.2, 131.1, 131.5, 133.4, 148.3, 171.8; IR (neat) 2952, 1730, 1543, 1437, 1373, 1344, 1273, 1257, 1209, 1141 cm^{-1}; HRMS calcd for $C_{19}H_{25}N_2O_8S$ (M^+ + H) 441.1332, found 441.1334.

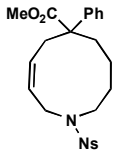


(Z)-Dimethyl 1-(2-nitrophenylsulfonyl)-2,3,5,8,9,10-hexahydroazecine-4,4(1H)-dicarboxylate (198). A 100 ml round-bottom flask charged with olefin **185** (0.0587 g, 0.125 mmol, 1.0 equiv) and DCE (62 mL, c = 0.003 M) was heated to 80 °C for 15 min open to air. Hoveyda-Grubbs 2 catalyst (0.0039 g, 0.0063 mmol, 0.05 equiv) was added in DCE (0.5 mL) at 80 °C. After stirring for 1.5 h at 80 °C, the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (1/7-1/4-/1/2 EtOAc/Hexanes) afforded the title compound as oil (R_f = 0.47, 1/1 EtOAc/hexanes). Yield 92% (0.0508 g, 0.116 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-2.40 (m, 4.6H), 2.50-2.85 (m, 2H), 3.10 (m, 3.5H), 3.25-3.65 (m,

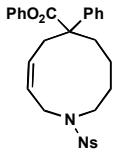
1.9H), 3.80 (s, 6H), 5.27-5.35 (m, 1H), 5.54-5.63 (m, 1H), 7.56-7.61 (m, 1H), 7.67-7.76 (m, 2H), 7.89-7.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 27.1, 27.1, 30.0, 44.5, 46.7, 52.9, 56.5, 123.9, 126.0, 130.0, 131.0, 131.2, 132.2, 133.8, 148.9, 171.3; IR (neat) 2952, 1732, 1545, 1460, 1373, 1357, 1222, 1172, 1126 cm^{-1}; HRMS calcd for $C_{19}H_{24}N_2O_8SNa$ (M^+ + Na) 463.1151, found 463.1147.



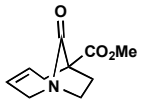
(Z)-Dimethyl 1-(2-nitrophenylsulfonyl)-1,2,7,8,9,10-hexahydroazecine-6,6(5H)-dicarboxylate (199). According to the procedure for **195**, the reaction of **188** (0.0587 g, 0.125 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0039 g, 0.0063 mmol, 0.05 equiv) in DCE (42 mL = 0.003 M) at 80 °C for 3 h afforded after chromatography (1/7-1/3-1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.71, 1/1 EtOAc/hexanes). Yield 79% (0.0435 g, 0.099 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.76 (s, 1H), 1.92 (s, 1H), 2.03 (s, 1H), 2.57 (m, 1H), 3.17 (m, 1H), 3.30 (m, 1H), 3.52 (m, 1H), 3.76 (s, 6H), 4.05 (m, 1H), 2.29 (m, 1H), 5.53-5.69 (m, 2H), 7.64-7.75 (m, 3H), 8.06-8.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 27.6, 28.6, 28.7, 41.6, 44.9, 52.8, 55.8, 124.3, 127.2, 131.2, 131.3, 131.7, 133.2, 133.5, 148.0, 171.2, 171.7; IR (neat) 2952, 1730, 1543, 1437, 1371, 1340, 1161 cm^{-1}; HRMS calcd for $C_{19}H_{24}N_2O_8SNa$ (M^+ + Na) 463.1151, found 463.1141.



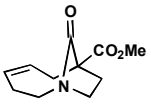
(Z)-Methyl 1-(2-nitrophenylsulfonyl)-6-phenyl-1,2,3,4,5,6,7,10-octahydroazecine-6-carboxylate (200). According to the procedure for **195**, the reaction of **193** (0.0678 g, 0.148 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0046 g, 0.0074 mmol, 0.05 equiv) in DCE (60 mL = 0.003 M) at 80 °C for 5 h afforded after chromatography (1/7-1/3 EtOAc/hexanes) the title compound as oil (R_f = 0.68, 1/1 EtOAc/hexanes). Yield 76% (0.0482 g, 0.112 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.21 (m, 0.9H), 1.36 (m, 0.5H), 1.43-1.66 (m, 1.1H), 1.78-2.06 (m, 2.1H), 2.15-2.33 (m, 1.1H), 2.50 (dd, *J* = 3.4, 14.0 Hz, 0.6H), 2.94-3.02 (m, 0.4H), 3.17 (t, *J* = 12.5 Hz, 0.5H), 3.31-3.44 (m, 1.6H), 3.48-3.70 (m, 1.2H), 3.67 (s, 3H), 3.94-4.10 (m, 1H), 4.31-4.42 (m, 1H), 5.34 (dt, *J* = 4.6, 11.8 Hz, 0.6H), 5.47 (dt, *J* = 4.6, 11.6 Hz, 0.6H), 5.60 (dt, *J* = 4.7, 11.6 Hz, 0.4H), 5.81 (dt, *J* = 4.6, 12.1 Hz, 0.4H), 7.25-7.40 (m, 6H), 7.64-7.75 (m, 3H), 8.06-8.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 18.9, 19.6, 28.8, 29.1, 29.3, 30.0, 30.4, 33.0, 41.9, 45.2, 52.1, 52.2, 52.3, 52.5, 124.3, 126.0, 126.1, 126.3, 126.3, 127.2, 128.6, 131.3, 131.6, 132.6, 133.2, 133.3, 133.5, 140.8, 142.2, 148.0, 175.6, 175.7; IR (neat) 2951, 1726, 1543, 1371, 1354, 1340, 1219, 1161 cm^{-1}; HRMS calcd for $C_{23}H_{26}N_2O_6SNa$ (M^+ + Na) 481.1409, found 481.1408.



(Z)-Phenyl 1-(2-nitrophenylsulfonyl)-6-phenyl-1,2,3,4,5,6,7,10-octahydroazecine-6-carboxylate (201). According to the procedure for **198**, the reaction of **194** (0.0397 g, 0.0723 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0023 g, 0.0036 mmol, 0.05 equiv) in DCE (61 mL = 0.0012 M) at 80 °C for 13 h afforded after chromatography (1/7-1/41/2 EtOAc/hexanes) the title compound as oil (R_f = 0.50, 1/2 EtOAc/hexanes). Yield 60% (0.0227 g, 0.044 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.25-1.45 (m, 1H), 1.55 (m, 1H), 1.70-1.95 (m, 2H), 2.09 (m, 1H), 2.39 (m, 1H), 2.57 (dd, *J* = 3.6, 13.7 Hz, 0.6H), 3.11-319 (m, 0.4H), 3.26-3.49 (m, 2H), 3.52-3.58 (m, 0.4H), 3.62-3.70 (m, 0.6H), 3.99 (dd, *J* = 4.8, 14.2 Hz, 0.6H), 4.06-4.13 (m, 0.4H), 4,40 (m, 1H), 5.40 (dd, *J* = 4.8, 12.0 Hz, 0.6H), 5.52 (dd, *J* = 4.9, 11.4 Hz, 0.6H), 5.69 (dd, *J* = 4.6, 11.2 Hz, 0.4H), 5.95-6.03 (m, 0.4H), 6.93 (t, *J* = 8.2 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.30-7.52 (m, 7H), 7.64-7.76 (m, 3H), 8.08-8.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 18.9, 19.7, 28.7, 29.1, 29.3, 29.7, 30.0, 30.4, 33.0, 41.9, 42.0, 45.2, 52.4, 52.6, 121.3, 124.3, 125.9, 126.1, 126.3, 126.8, 127.4, 128.8, 129.4, 131.3, 131.7, 132.4, 132.9, 133.1, 133.5, 140.3, 141.7, 148.0, 150.8, 173.7; IR (neat) 2916, 1745, 1542, 1371, 1340, 1194, 1163 cm^{-1}; HRMS calcd for $C_{28}H_{28}N_2O_6SNa$ (M^+ + Na) 543.1565, found 543.1565.

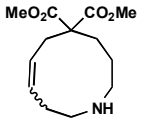


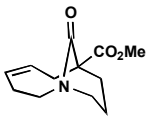
Methyl 9-oxo-1-azabicyclo[4.2.1]non-3-ene-6-carboxylate (202). According to the procedure for **178**, the reaction of **195** (0.0190 g, 0.046 mmol, 1.0 equiv), Cs_2CO_3 (0.15 g, 0.46 mmol, 10 equiv), PhSH (0.0254 g, 0.23 mmol, 5.0 equiv) in CH_3CN (5 mL) at 60 °C for 2 h afforded the title compound in 92 % yield (^{1}H NMR, vs. 2-nitrophenylphenylsulfide) and in 75% yield (0.0067 g, 0.034 mmol) after purification by PTLC (1:1 EtOAc/hexanes) (R_f = 0.57, 1/1 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (dd, *J* = 7.9, 12.5 Hz, 1H), 2.16-2.24 (m, 1H), 2.60-2.70 (m, 1H), 2.92-3.01 (m, 1H), 3.08-3.18 (m, 1H), 3.32-3.39 (m, 1H), 3.53 (t, *J* = 9.4 Hz, 1H), 3.81 (s, 3H), 4.24-4.33 (m, 1H), 5.38 (dp, *J* = 3.0, 12.7 Hz, 1H), 5.63-5.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 32.1, 46.8, 52.1, 52.7, 57.1, 122.6, 127.6, 171.1, 183.8; IR (neat) 2952, 1739, 1720, 1437, 1242, 1197, 1134 cm^{-1}; HRMS calcd for $C_{10}H_{13}NO_3Na$ (M^+ + Na) 218.0793, found 218.0785.



Methyl 10-oxo-1-azabicyclo[5.2.1]dec-4-ene-7-carboxylate (203). According to the procedure for **178**, the reaction of **196** (0.0213 g, 0.050 mmol, 1.0 equiv), Cs_2CO_3 (0.16 g, 0.50 mmol, 10 equiv), PhSH (0.0275 g, 0.25 mmol, 5.0 equiv) in CH_3CN (5 mL) at 60 °C for 13 h afforded the title compound after chromatography (1/2-1/1 EtOAc/hexanes) as oil (R_f = 0.39, 1/1 EtOAc/hexanes).

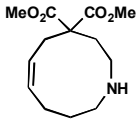
Yield 85% (0.00890 g, 0.043 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94-2.02 (m, 1H), 2,12 (ddd, *J* = 2.4, 8.0, 10.5 Hz, 1H), 2.50-2.77 (m, 3H), 2.96 (dd, *J* = 6.0, 14.3 Hz, 1H), 3.04-3.14 (m, 1H), 3.57-3.67 (m, 2H), 3.73-3.81 (m, 4H), 5.77-5.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 26.5, 33.8, 43.4, 49.8, 52.6, 60.1, 129.1, 132.7, 171.3, 180.2; IR (neat) 2949, 1737, 1697, 1456, 1400, 1251, 1194 cm^{-1}; HRMS calcd for $C_{11}H_{16}NO_3$ (M^+ + H) 210.1130, found 210.1128.

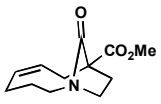




Dimethyl 1,2,3,4,9,10-hexahydroazecine-5,5(6H)-dicarboxylate (204A). According to the procedure for **178**, the reaction of **197** (0.104 g, 0.24 mmol, 1.0 equiv), Cs_2CO_3 (0.78 g, 2.4 mmol, 10 equiv), PhSH (0.13 g, 1.2 mmol, 5.0 equiv) in CH_3CN (12 mL) at 60 °C for 30 min afforded the title compound (5:1 mixture of Z/E isomers) after chromatography (0/0/100-1/4/95-1/9/90 NH_4OH/MeOH/DCM) as oil (R_f = 0.19, 1/9/90 NH_4OH/MeOH/DCM). Yield 99% (0.0614 g, 0.24 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (5:1 mixture of Z/E isomers) δ 1.50 (m, 2H), 2.00 (m, 2H), 2.11 (s, 1H), 2.52-2.59 (m, 1H), 2.80 (m, 4H), 2.97-3.19 (m, 2H), 3.76 (s, 6H), 5.38-5.48 (m, 1H, Z isomer), 5.56-5.65 (m, 1H), 5.75 (dt, *J* = 7.3, 21.5 Hz, 1H, E isomer); ^{13}C NMR (100 MHz, $CDCl_3$) (Z isomer) δ 23.9, 25.4, 27.8, 29.7, 46.3, 46.9, 52.6, 56.4, 126.7, 131.4, 171.9; IR (neat) 2951, 1732, 1437, 1269, 1248, 1205, 1180, 1138 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_4Na$ (M^+ + Na) 278.1368, found 278.1369.

Methyl 11-oxo-1-azabicyclo[5.3.1]undec-4-ene-7-carboxylate (204). 10 mL MW vial (Biotage) was charged with amine **204A** (0.0198 g, 0.078 mmol, 1.0 equiv), toluene (3.0 mL), and DBU (0.12 g, 0.78 mmol, 10 equiv). The vial was sealed with metal septum, placed in an oil bath preheated to 200 °C and stirred for 3 h. The reaction was cooled to rt, solvent was removed under vacuum and the residue was purified by chromatography (1/1 EtOAc/hexanes) to afford the title compound as oil (R_f = 0.67, 1/1 EtOAc/hexanes). Yield 65% (0.0093 g, 0.042 mmol out of possible 0.065 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-1.96 (m, 3H), 2.04-2.12 (m, 1H), 2.21-2.26 (m, 1H), 2.50-2.66 (m, 2H), 2.75-2.86 (m, 2H), 3.24-3.31 (m, 1H), 3.54-3.61 (m, 1H), 3.78 (s, 3H), 4.05 (dt, *J* = 4.6, 13.4 Hz, 1H), 5.80-5.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 24.5, 29.9, 36.4, 46.9, 50.4, 52.3, 60.7, 129.8, 132.3, 173.1, 177.3; IR (neat) 2928, 1739, 1653, 1452, 1329, 1248, 1192, 1118 cm^{-1}; HRMS calcd for $C_{12}H_{18}NO_3$ (M^+ + H) 224.1287, found 224.1279. In addition, decarboxylated amide was isolated in 22% yield.

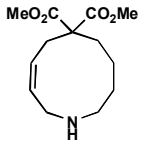




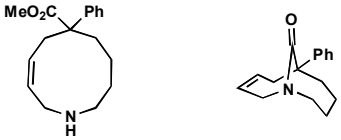
(Z)-Dimethyl 2,3,5,8,9,10-hexahydroazecine-4,4(1H)-dicarboxylate (205A). According to the procedure for **204A**, the reaction of **198** (0.0329 g, 0.075 mmol, 1.0 equiv), Cs_2CO_3 (0.24 g, 0.75 mmol, 10 equiv), PhSH (0.041 g, 0.37 mmol, 5.0 equiv) in CH_3CN (6 mL) at 60 °C for 1 h afforded the title compound after chromatography (0/0/100-1/4/95-1/9/90 NH_4OH/MeOH/DCM) as oil (R_f = 0.64,

1/9/90 NH_4OH/MeOH/DCM). Yield 98% (0.0187 g, 0.073 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.35-1.60 (m, 2H), 1.72-1.88 (m, 2H), 2.23 (t, *J* = 12.5, 1H), 2.44 (m, 2H), 2.56-2.68 (m, 2H), 2.77 (m, 2H), 3.75 (s, 6H), 3.98 (t, *J* = 13.4 Hz, 1H), 5.19-5.26 (m, 1H), 5.41-5.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 26.2, 27.2, 31.4, 41.7, 44.9, 52.5, 58.1, 126.2, 131.2, 172.1, 172.7; IR (neat) 3352, 2918, 1732, 1437, 1228, 1182, 1126 cm^{-1}; HRMS calcd for $C_{13}H_{22}NO_4$ (M^+ + H) 256.1549, found 256.1545.

Methyl 11-oxo-1-azabicyclo[6.2.1]undec-5-ene-8-carboxylate (205). According to the procedure for **204**, the reaction of **205A** (0.0100 g, 0.0392 mmol, 1.0 equiv) and DBU (0.12 g, 0.78 mmol, 20 equiv) in toluene (3.0 mL) at 180 °C for 12 h afforded the title compound after chromatography (1/1 EtOAc/hexanes) as oil (R_f = 0.33, 1/1 EtOAc/hexanes). Yield 44% (0.0038 g, 0.017 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.81-2.03 (m, 3H), 2.11 (ddd, *J* = 1.4, 8.6, 13.1 Hz, 1H), 2.18-2.31 (m, 1H), 2.45-2.55 (m, 1H), 2.61-2.69 (m, 1H), 2.85-2.92 (m, 2H), 3.22 (dt, *J* = 1.4, 9.2 Hz, 1H), 3.50 (q, *J* = 8.6 Hz, 1H), 3.79 (s, 3H), 3.22 (dt, *J* = 6.1, 13.6 Hz, 1H), 5.57-5.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 24.4, 29.0, 32.5, 41.8, 45.7, 52.7, 55.4, 122.2, 138.6, 172.4, 177.1; IR (neat) 2925, 1735, 1685, 1456, 1431, 1257, 1205, 1116, 1077 cm^{-1}; HRMS calcd for $C_{12}H_{18}NO_3$ (M^+ + H) 224.1287, found 224.1288.



(Z)-Dimethyl 1,2,7,8,9,10-hexahydroazecine-6,6(5H)-dicarboxylate (206A). According to the procedure for **204A**, the reaction of **199** (0.0444 g, 0.10 mmol, 1.0 equiv), Cs_2CO_3 (0.32 g, 1.0 mmol, 10 equiv), PhSH (0.056 g, 0.50 mmol, 5.0 equiv) in CH_3CN (6 mL) at 60 °C for 45 min afforded the title compound after chromatography (0/0/100-1/4/95-1/9/90 NH_4OH/MeOH/DCM) as oil (R_f = 0.44, 1/9/90 NH_4OH/MeOH/DCM). Yield 99% (0.027 g, 0.10 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.33-1.58 (m, 3H), 1.64 (m, 1H), 1.96 (m, 3H), 2.50 (s, 1H), 2.71 (s, 1H), 2.95 (s, 1H), 3.18-3.42 (m, 2H), 3.76 (s, 6H), 3.84 (m, 1H), 5.40-5.48 (m, 1H), 5.60-5.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 26.7, 29.1, 29.3, 40.3, 44.7, 52.5, 56.4, 127.8, 132.2, 172.1; IR (neat) 2951, 1732, 1456, 1435, 1286, 1203, 1178 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_4Na$ (M^+ + Na) 278.1368, found 278.1363. Note: attempted heating of **206A** with various bases at temperatures ranging from 110-220 °C led only to decomposition products.



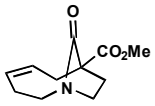
(Z)-Methyl 6-phenyl-1,2,3,4,5,6,7,10-octahydroazecine-6-carboxylate (207A). According to the procedure for **204A**, the reaction of **200** (0.0277 g, 0.064 mmol, 1.0 equiv), Cs_2CO_3 (0.21 g, 0.64 mmol, 10 equiv), PhSH (0.0354 g, 0.32

mmol, 5.0 equiv) in CH_3CN (6 mL) at 60 °C for 1 h afforded the title compound after chromatography (0/0/100-1/4/95-1/9/90 NH_4OH/MeOH/DCM) as oil (R_f = 0.46, 1/9/90 NH_4OH/MeOH/DCM). Yield 98% (0.0154 g, 0.063 mmol). ^1H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.22-1.42 (m, 1H), 1.45-1.82 (m, 3H), 1.98-2.22 (m, 3H), 2.42 (dd, *J* = 4.0, 14.0 Hz, 0.5H), 2.64-2.78 (m, 1H), 2.86 (m, 0.5H), 3.05 (q, *J* = 11.5 Hz, 1H), 3.22-3.38 (m, 1.5H), 3.47 (t, *J* = 13.4, 0.6H), 3.67 (s, 3H), 3.91 (t, *J* = 10.7 Hz, 0.9H), 5.06-5.19 (m, 0.6H), 5.48-5.72 (m, 1.4H), 7.23-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 19.9, 20.7, 28.0, 29.5, 29.7, 29.9, 30.4, 33.4, 40.5, 45.0, 52.1, 52.3, 52.8, 125.9, 126.2, 126.4, 126.8, 128.2, 128.4, 129.0, 129.7, 131.2, 131.6, 141.7, 142.9, 176.2; IR (neat) 2945, 2917, 1727, 1446, 1433, 1221, 1180, 1138 cm^{-1}; HRMS calcd for $C_{17}H_{24}NO_2$ (M^+ + H) 274.1807, found 274.1816.

6-Phenyl-1-azabicyclo[4.4.1]undec-3-en-11-one (207). From 207A. According to the procedure for **204**, the reaction of **207A** (0.0042 g, 0.0171 mmol, 1.0 equiv) and DBU (0.052 g, 0.34 mmol, 20 equiv) in toluene (3.0 mL) at 220 °C for 10 h afforded the title compound after chromatography (1/2 EtOAc/hexanes) as a white film (R_f = 0.39, 1/1 EtOAc/hexanes). Yield 34% (0.0014 g, 0.0058 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.75-1.89 (m, 2H), 1.92-2.03 (m, 3H), 2.16 (dd, *J* = 7.7, 14.4 Hz, 1H), 2.22-2.29 (m, 1H), 2.76-2.85 (m, 1H), 3.02-3.11 (m, 1H), 3.66-3.71 (m, 1H), 3.85-3.99 (m, 2H), 5.88-5.96 (m, 1H), 6.12-6.22 (m, 1H), 7.21-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 25.2, 33.3, 39.4, 49.7, 51.7, 63.8, 126.4, 126.9, 128.0, 128.3, 133.0, 146.0, 186.2; IR (neat) 2924, 2854, 1653, 1444, 1290, 1236,

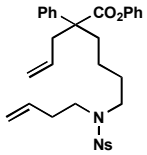
1186, 1149 cm^{-1}; HRMS calcd for $C_{16}H_{20}NO$ (M^+ + H) 242.1545, found 242.1546. Note: no conversion was observed at temperatures lower than 220 °C.

6-Phenyl-1-azabicyclo[4.4.1]undec-3-en-11-one (207). From 3k. To a solution of **201** (0.0187 g, 0.0359 mmol, 1.0 equiv) and Cs_2CO_3 (0.12 g, 0.35 mmol, 10 equiv) in CH_3CN (6 mL), thiophenol (0.0197 g, 0.18 mmol, 5 equiv) was added, and the resulting mixture was heated at 60 °C for 2 h. Solvent was removed under reduced pressure, the residue was taken in toluene (10 mL), and DBU (0.10 mL, 0.70 mmol, 20 equiv) was added. The reaction mixture was heated at 110 °C for 16 h, solvent was removed under reduced pressure, and the residue was purified by chromatography (1/6-1/4 EtOAc/hexanes) to give the title compound. Yield 86% (0.0074 g, 0.031 mmol).

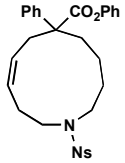


Lactam 204. One-pot RCM/Deprotection/Cyclization. A 100 ml round-bottom flask charged with olefin **186** (0.0418 g, 0.092 mmol, 1.0 equiv) and DCE (46 mL, c = 0.002 M) was heated to 80 °C for 15 min open to air. Hoveyda-Grubbs 2 catalyst (0.0029 g, 0.0046 mmol, 0.05 equiv) was added in DCE (1 mL) at 80 °C. After stirring for 1.5 h at 80 °C, the solvent was removed under reduced pressure. The residue was taken in CH_3CN (12 mL), Cs_2CO_3 (0.47 g, 1.4 mmol, 15 equiv) followed by PhSH (0.10 g, 0.92 mmol, 10 equiv) was added, and the resulting mixture was heated at 80 °C for 3 h. Solvent was removed under reduced pressure, the residue was

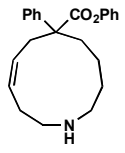
purified by chromatography to give **204** (0.0128 g, 0.061 mmol) in 67% yield. Spectroscopic properties matched those previously described.



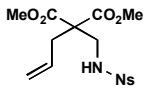
Phenyl 2-allyl-6-(N-(but-3-enyl)-2-nitrophenylsulfonamido)-2-phenyl hexanoate (208). According to the procedure described earlier, the reaction of N-(but-3-enyl)-2-nitrobenzenesulfonamide (0.128 g, 0.50 mmol, 1.0 equiv), K_2CO_3 (0.54 g, 1.1 mmol, 2.2 equiv), NaI (0.38 g, 2.5 mmol, 5 equiv) and chloride **192** (0.43 g, 1.25 mmol, 2.5 equiv) in DMF (15 mL) at 80 $^{\circ}$C for 14 h afforded after chromatography (1/5-1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.45, 1/1 EtOAc/hexanes). The compound was contaminated with ~5% of nosylamine. Yield (corrected for impurity) 54% (0.151 g, 0.27 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.22 (m, 2H), 1.47-1.62 (m, 2H), 2.03-2.17 (m, 2H), 2.26-2.34 (m, 2H), 2.81-2.99 (m, 2H), 3.24-3.38 (m, 4H), 5.02-5.21 (m, 4H), 5.60-5.75 (m, 2H), 6.93-6.98 (m, 2H), 7.18-7.43 (m, 8H), 7.58-7.69 (m, 3H), 7.96-8.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 28.5, 32.7, 34.2, 39.0, 46.5, 47.1, 53.8, 117.4, 118.9, 121.3, 124.2, 125.8, 126.4, 127.1, 128.6, 129.4, 130.7, 131.5, 133.1, 133.4, 133.7, 134.2, 141.5, 148.0, 150.8, 173.8; IR (neat) 2941, 1747, 1542, 1371, 1346, 1161, 1124 cm^{-1}; HRMS calcd for $C_{31}H_{34}N_2O_6SNa$ (M^+ + Na) 585.2035, found 585.2045.



(Z)-Phenyl 1-(2-nitrophenylsulfonyl)-6-phenylazacycloundec-8-ene-6-carboxylate (209). According to the procedure for **198**, the reaction of **208** (0.0447 g, 0.079 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0025 g, 0.0040 mmol, 0.05 equiv) in DCE (52 mL = 0.0015 M) at 80 °C for 2.5 h afforded after chromatography (1/7-1/4-1/3-1/2 EtOAc/hexanes) the title compound as oil (R_f = 0.23, 1/2 EtOAc/hexanes). Yield 79% (0.0329 g, 0.062 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.55-2.07 (m, 3.4H), 2.12-2.85 (m, 5H), 2.92-3.11 (m, 1.8H), 3.12-3.28 (m, 2H), 3.38-3.67 (m, 1.8H), 4.86-4.99 (m, 0.4H), 5.46-5.73 (m, 1.3H), 6.04-6.14 (m, 0.3H), 6.96 (d, *J* = 7.6 Hz, 1.4H), 7.05 (d, *J* = 7.6 Hz, 0.6H), 7.18-7.25 (m, 1H), 7.26-7.47 (m, 7H), 7.52-7.77 (m, 3H), 7.94-8.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 20.9, 22.4, 27.7, 28.3, 28.7, 29.7, 31.7, 33.0, 34.1, 36.1, 45.1, 50.9, 51.5, 52.9, 53.5, 55.7, 121.3, 121.6, 123.8, 123.9, 125.6, 125.7, 125.8, 126.3, 126.8, 127.0, 127.0, 128.6, 128.7, 128.7, 129.3, 129.4, 130.8, 130.9, 131.3, 131.3, 131.7, 131.9, 133.4, 133.6, 148.7, 149.0, 150.9, 173.3, 174.2; IR (neat) 2924, 1747, 1545, 1492, 1373, 1348, 1167 cm^{-1}; HRMS calcd for $C_{29}H_{30}N_2O_6SNa$ (M^+ + Na) 557.1722, found 557.1733.



(Z)-phenyl 6-phenylazacycloundec-8-ene-6-carboxylate (210A). According to the procedure for **204A**, the reaction of **209** (0.0115 g, 0.21 mmol, 1.0 equiv), Cs_2CO_3 (0.069 g, 0.21 mmol, 10 equiv), PhSH (0.012 g, 0.11 mmol, 5.0 equiv) in CH_3CN (6 mL) at 60 °C for 60 min afforded the title compound after chromatography (0/0/100-1/4/95-1/9/90 NH_4OH/MeOH/DCM) as oil (R_f = 0.30, 1/9/90 NH_4OH/MeOH/DCM). Yield 80% (0.0059 g, 0.017 mmol). Note: due to small quantity of the material, and the unproductive cyclization pathway, the compound was characterized only by ^1H NMR and HRMS. ^1H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.38-1.85 (m, 3.8H), 1.88-2.42 (m, 3.6H), 2.48-3.18 (m, 7H), 3.42 (m, 0.6H), 4.90 (m, 0.4H), 5.43-5.78 (m, 1.4H), 5.92-6.02 (m, 0.2H), 6.95 (m, 1.5H), 7.02 (d, J = 7.8 Hz, 0.5H), 7.20 (m, 1H), 7.28-7.52 (m, 7H); HRMS calcd for $C_{23}H_{28}NO_2$ (M^+ + H) 350.2120, found 350.2118. Note: attempted heating of **210A** with various amounts of DBU at temperatures ranging from 110-220 °C led to no conversion to the desired lactam.

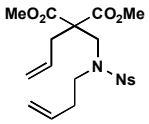


Dimethyl 2-allyl-2-((2-nitrophenylsulfonamido)methyl)malonate (210). According to the procedure by Fuller *et al.*,[398] the reaction of dimethyl 2-allylmalonate (1.0 g, 5.8 mmol, 1.0 equiv), NaH (60% dispersion in mineral oil, 0.26 g, 6.4 mmol, 1.1 equiv), and N-bromomethylphthalimide (1.44 g, 5.8 mmol, 1.0 equiv) in THF (15 mL) for 5 h afforded after aqueous work-up the crude dimethyl 2-

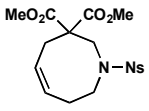
allyl-2-((1,3-dioxoisoindolin-2-yl)methyl)malonate as a white solid that was used in the next step without further purification. Yield 94% (1.81 g, 5.5 mmol).

In a 25 ml round bottom flask, hydrazine (0.154 g, 3.0 mmol, 1.1 equiv) was added to a solution of the crude phthalimide (0.91 g, 2.74 mmol, 1.0 equiv) in EtOH (10 mL). The reaction mixture was heated to reflux for 21 h, cooled to rt, quenched with 0.90 mL conc. HCl, filtered through a pad of celite, and concentrated under reduced pressure providing crude amine which was used without further purification.

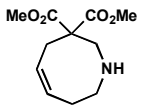
The crude amine was taken in 20 mL of DCM, pyridine (2.2 mL, 27.4 mmol, 10.0 equiv), followed by NsCl (0.94 g, 4.1 mmol, 1.5 equiv) was added, and the resulting reaction mixture was stirred at rt for 12 h. The reaction was quenched with water (30 mL), extracted with ether (3 x 50 mL), dried over Na_2SO_4, and concentrated. Chromatography (1/4=1/2 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.70, 1/1 EtOAc/hexanes). Yield 13% (0.133 g, 0.36 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (d, *J* = 7.4 Hz, 2H), 3.50 (d, *J* = 6.1 Hz, 2H), 3.77 (s, 6H), 5.13-5.24 (m, 2H), 5.62-5.73 (m, 1H), 6.02 (s, 1H), 7.73-7.80 (m, 2H), 7.86-7.92 (m, 1H), 8.11-8.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 45.8, 53.0, 58.0, 120.5, 125.5, 131.0, 131.2, 132.9, 133.5, 133.7, 148.1, 169.9; IR (neat) 3329, 2954, 1732, 1541, 1440, 1359, 1228, 1170 cm^{-1}; HRMS calcd for $C_{15}H_{19}N_2O_8S$ (M^+ + H) 387.0862, found 387.0864. Note: ethylmethylmalonate was obtained as the major product in the above reaction (in 3.3 to 1.0 ratio of the major product to **210**), most likely resulting from transesterification with EtOH during hydrazine deprotection. No attempt was made to optimize the above reaction sequence.



Dimethyl 2-allyl-2-((N-(but-3-enyl)-2-nitrophenylsulfonamido)methyl) malonate (211). To a round bottom flask charged with amine **210** (0.0272 g, 0.070 mmol, 1.0 equiv), K_2CO_3 (0.049 g, 0.35 mmol, 5.0 equiv), and DMF (6 mL), 4-bromobut-1-ene (0.10 g, 0.70 mmol, 10 equiv) was added, and the reaction mixture was heated at 80 $^{\circ}$C for 16 h. The reaction was cooled to room temperature, diluted with ether (20 mL), quenched with water (10 mL), and extracted with ether (3 x 50 mL). The organic layer was washed with water (4 x 50 mL), and brine (1 x 50 mL), dried (Na_2SO_4), and concentrated. Preparative thin-layer chromatography (1/2 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.44, 1/2 EtOAc/hexanes). Yield 38% (0.0116 g, 0.026 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13-2.22 (m, 2H), 2.76 (d, J = 7.3 Hz, 2H), 3.31 (m, 2H), 3.76 (s, 6H), 4.04 (s, 2H), 4.91-4.98 (m, 2H), 5.08-5.18 (m, 2H), 5.48-5.60 (m, 1H), 5.74-5.86 (m, 1H), 7.64-7.76 (m, 3H), 8.03-8.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 37.3, 47.3, 50.1, 52.8, 58.7, 117.3, 119.4, 124.3, 131.2, 131.7, 132.1, 133.3, 133.8, 133.8, 148.2, 170.3; IR (neat) 2924, 1732, 1545, 1439, 1371, 1167 cm^{-1}; HRMS calcd for $C_{19}H_{25}N_2O_8SNa$ (M^+ + Na) 463.1151, found 463.1160.



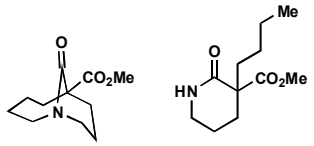
(Z)-Dimethyl 1-(2-nitrophenylsulfonyl)-1,2,7,8-tetrahydroazocine-3,3(4H)-dicarboxylate (212). According to the procedure for **209**, the reaction of **211** (0.0085 g, 0.0193 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0006 g, 0.0010 mmol, 0.05 equiv) in DCE (13 mL = 0.0015 M) at 80 °C for 1 h afforded after purification by preparative thin-layer chromatography (1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.66, 1/1 EtOAc/hexanes). Yield 77% (0.0061 g, 0.015 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (m, 2H), 2.92 (d, *J* = 8.5 Hz, 2H), 3.22-3.45 (m, 2H), 3.81 (s, 6H), 3.87 (m, 2H), 5.53 (q, *J* = 8.6 Hz, 1H), 5.90-5.98 (m, 1H), 7.62-7.65 (m, 1H), 7.68-7.76 (m, 2H), 7.94-7.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 29.0, 53.0, 53.0, 53.7, 60.1, 124.2, 127.4, 131.1, 131.5, 131.8, 131.9, 133.8, 148.5, 170.2; IR (neat) 2920, 1732, 1545, 1452, 1439, 1354, 1242, 1165 cm^{-1}; HRMS calcd for $C_{17}H_{20}N_2O_8SNa$ (M^+ + Na) 435.0838, found 435.0843.



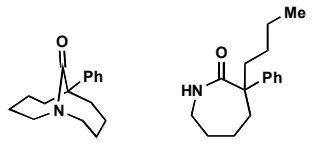
(Z)-Dimethyl 1,2,7,8-tetrahydroazocine-3,3(4H)-dicarboxylate (212A). According to the procedure for **204A**, the reaction of **212** (0.0055 g, 0.0133 mmol, 1.0 equiv), Cs_2CO_3 (0.044 g, 0.13 mmol, 10 equiv), PhSH (0.0075 g, 0.067 mmol, 5.0 equiv) in CH_3CN (5 mL) at 60 °C for 30 min afforded the title compound after chromatography (0/0/100-1/4/95-1/9/90 NH_4OH/MeOH/DCM) as oil (R_f = 0.46, 1/9/90 NH_4OH/MeOH/DCM). Yield 93% (0.0028 g, 0.0123 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (q, *J* = 7.2 Hz, 2H), 2.83 (m, 4H), 3.26 (m, 2H), 3.75 (2, 6H),

5.62-5.71 (m, 1H), 5.88-5.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.3, 30.2, 50.2, 51.9, 52.5, 61.7, 127.4, 132.9, 171.5; IR (neat) 2925, 1730, 1554, 1450, 1437, 1242, 1099 cm^{-1}; HRMS calcd for $C_{11}H_{18}NO_4SNa$ (M^+ + Na) 228.1236, found 228.1237. Note: attempted heating of **212A** with various amounts of DBU at temperatures ranging from 110-220 °C led only to decomposition products.

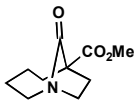
General procedure for hydrogenation of bridged amides: To a solution of twisted amides in MeOH (5 mL), Pd/C (5%), ca. 30-40 mg was added, and the reaction was stirred under H_2 balloon at rt. Filtration through cotton or celite pad, followed by chromatography afforded the products.



Methyl 10-oxo-1-azabicyclo[4.3.1]decane-6-carboxylate (179) and Methyl 3-butyl-2-oxopiperidine-3-carboxylate (180). According to the general procedure, the reaction of **178** (0.0042 g, 0.0020 mmol, 1.0 equiv) and Pd/C (5%) (ca. 25 mg) in MeOH (4 mL) for 22 h at rt afforded 1:3 mixture of **179** and **180** (0.0040 g, 0.0190 mmol). Yield 95%. Spectroscopic properties matched those previously described.

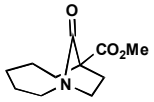


6-Phenyl-1-azabicyclo[4.4.1]undecan-11-one (214) and 3-Butyl-3-phenylazepan-2-one (213). According to the general procedure, the reaction of **207** (0.0105 g, 0.0044 mmol, 1.0 equiv) and Pd/C (5%) (ca. 40 mg) in MeOH (6 mL) for 18 h at rt afforded 1.1:1.0 mixture of **214** and **213** (0.0057 g, 0.0240 mmol). Yield 54%. Further purification by PTLC (1/1 EtOAc/hexanes) afforded analytical samples of **214** and **213**. Compound **214**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73-1.93 (m, 8H), 1.95-2.04 (m, 2H), 2.17-2.25 (m, 2H), 3.10-3.18 (m, 2H), 3.54 (ddd, *J* = 3.8, 6.4, 10.0 Hz, 2H), 7.21-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 25.5, 35.5, 50.3, 59.9, 126.1, 127.3, 127.9, 145.0, 186.3; IR (neat) 2951, 2910, 1643, 1492, 1437, 1413, 1302, 1219 cm^{-1}; HRMS calcd for $C_{16}H_{21}NONa$ (M^+ + Na) 266.1521, found 266.1523. Compound **213**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.3 Hz, 3H), 1.03-1.13 (m, 1H), 1.17-1.32 (m, 3H), 1.36-1.46 (m, 1H), 1.62-1.98 (m, 6H), 2.31 (dt, *J* = 2.5, 14.0 Hz, 1H), 2.62-2.72 (m, 1H), 2.80-2.88 (m, 1H), 5.93 (s, 1H), 7.21-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 23.3, 24.8, 27.4, 29.0, 33.0, 41.8, 44.9, 53.9, 126.2, 127.2, 128.4, 141.2, 179.4; IR (neat) 3284, 3219, 2929, 2858, 1654, 1465, 1446, 1363, 1280 cm^{-1}; HRMS calcd for $C_{16}H_{24}NO$ (M^+ + H) 246.1858, found 246.1852.

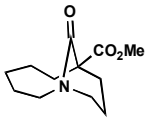


Methyl 9-oxo-1-azabicyclo[4.2.1]nonane-6-carboxylate (215). According to the general procedure, the reaction of **202** (0.0042 g, 0.022 mmol, 1.0 equiv) and

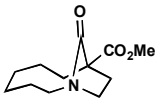
Pd/C (5%) (ca. 30 mg) in MeOH (5 mL) for 18 h at rt afforded **215** (0.0031 g, 0.016 mmol). Yield 74%. (R_f = 0.39, 1/1 EtOAc/hexanes) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.92 (m, 4H), 2.02 (ddd, *J* = 1.3, 8.6, 9.9 Hz, 1H), 2.34 (m, 1H), 2.57-2.67 (m, 1H), 2.77-2.85 (m, 1H), 3.17-3.26 (m, 1H), 3.58 (t, *J* = 9.6 Hz, 1H), 3.68-3.78 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 24.3, 28.6, 32.4, 47.1, 48.6, 52.6, 57.1, 171.7, 183.4; IR (neat) 2924, 1739, 1716, 1458, 1437, 1282, 1186, 1123 cm^{-1}; HRMS calcd for $C_{10}H_{16}NO_3$ (M^+ + H) 198.1130, found 198.1126.



Methyl 10-oxo-1-azabicyclo[5.2.1]decane-7-carboxylate (216). According to the general procedure, the reaction of **203** (0.0070 g, 0.033 mmol, 1.0 equiv) and Pd/C (5%) (ca. 40 mg) in MeOH (5 mL) for 18 h at rt afforded **216** (0.0050 g, 0.024 mmol). Yield 72%. (R_f = 0.39, 1/1 EtOAc/hexanes) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36-1.55 (m, 2H), 1.68-1.84 (m, 2H), 1.96-2.15 (m, 4H), 2.42-2.52 (m, 1H), 2.62-2.71 (m, 1H), 2.93 (dd, *J* = 5.4, 13.8 Hz, 1H), 3.44 (dt, *J* = 1.6, 10.3 Hz, 1H), 3.66 (q, *J* = 9.0 Hz, 1H), 3.78 (s, 3H), 4.18 (dt, *J* = 4.8, 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 24.5, 26.3, 31.8, 41.7, 44.0, 44.9, 52.5, 54.8, 172.4, 180.1; IR (neat) 2931, 1739, 1693, 1435, 1418, 1271, 1248, 1195 cm^{-1}; HRMS calcd for $C_{11}H_{18}NO_3$ (M^+ + H) 212.1287, found 212.1288.

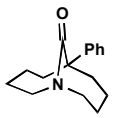


Methyl 11-oxo-1-azabicyclo[5.3.1]undecane-7-carboxylate (217). According to the general procedure, the reaction of **204** (0.0089 g, 0.040 mmol, 1.0 equiv) and Pd/C (5%) (ca. 50 mg) in MeOH (5 mL) for 24 h at rt afforded **217** (0.0071 g, 0.032 mmol). Yield 79%. (R_f = 0.32, 1/1 EtOAc/hexanes) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.59 (m, 2H), 1.70-1.83 (m, 3H), 1.88-2.16 (m, 6H), 2.43 (t, *J* = 12.4 Hz, 1H), 2.75 (dd, *J* = 4.8, 13.6 Hz, 1H), 3.27-3.33 (m, 1H), 3.68 (dt, *J* = 3.2, 11.7 Hz, 1H), 3.75 (s, 3H), 4.62 (dt, *J* = 4.0, 13.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 23.2, 24.8, 31.0, 32.4, 43.7, 48.2, 49.3, 52.2, 54.5, 174.1, 176.6; IR (neat) 2929, 1743, 1647, 1491, 1444, 1244, 1192, 1122 cm^{-1}; HRMS calcd for $C_{12}H_{20}NO_3$ (M^+ + H) 226.1443, found 226.1440.



Methyl 11-oxo-1-azabicyclo[6.2.1]undecane-8-carboxylate (218). According to the general procedure, the reaction of **205** (0.0056 g, 0.025 mmol, 1.0 equiv) and Pd/C (5%) (ca. 40 mg) in MeOH (5 mL) for 16 h at rt afforded **218** (0.0050 g, 0.022 mmol). Yield 89%. (R_f = 0.33, 1/1 EtOAc/hexanes) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.21 (m, 1H), 1.26-1.38 (m, 1H), 1.42-1.52 (m, 1H), 1.71-1.90 (m, 6H), 2.02 (ddd, *J* = 2.1, 9.1, 13.3 Hz, 1H), 2.20 (t, *J* = 11.5 Hz, 1H), 2.67-2.77 (m, 1H), 2.86-2.93 (m, 1H), 3.45 (dt, *J* = 2.0, 10.6 Hz, 1H), 3.74 (q, *J* = 9.2 Hz, 1H),

3.78 (s, 3H), 3.94-4.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.6, 25.9, 26.0, 27.5, 36.4, 43.3, 46.2, 52.5, 55.3, 172.9, 173.4; IR (neat) 2924, 1737, 1685, 1458, 1437, 1255, 1120 cm^{-1}; HRMS calcd for $C_{12}H_{20}NO_3$ (M^+ + H) 226.1443, found 226.1439.



Lactam 214. Hydrogenation in the presence of Willkinson's catalyst. To a solution of **207** (0.0074 g, 0.031 mmol, 1.0 equiv) in THF (5 mL), $Rh(PPh_3)_3Cl$ (0.0284 g, 0.031 mmol, 1.0 equiv) was added under nitrogen. H_2 atmosphere was established, H_2 was bubbled through the solution for ca. 30 s, and the reaction was stirred under H_2 balloon for 19 h. Solvent was removed under reduced pressure, and the residue was purified by chromatography to give the title compound **214** (0.0065 g, 0.027 mmol) in 86% yield. Spectroscopic properties matched those previously described.

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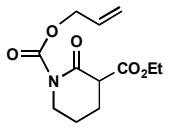
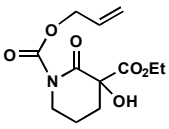
Oxidative cyclization approach

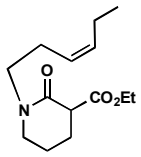


1-Allyl 3-ethyl 2-oxopiperidine-1,3-dicarboxylate (220). Prepared from Ethyl 2-oxo-3-piperidine carboxylate and allyl chloroformate. A solution of piperidone (0.0496 g, 0.29 mmol, 1.0 equiv) and allyl chloroformate (0.15 mL, 1.45 mmol, 5.0 equiv) in toluene (10 mL) was heated at 105 °C for 6 h. Solvent removal, followed by chromatography (1/4 EtOAc/hexanes) afforded the title compound as film (R_f = 0.65, 1/1 EtOAc/hexanes). Yield 87% (0.0645 g, 0.25 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 1.81-1.91 (m, 1H), 1.96-2.06 (m, 1H), 2.09-2.18 (m, 1H), 2.19-2.28 (m, 1H), 3.53-3.58 (m, 1H), 3.77-3.82 (m, 2H), 4.20-4.29 (m, 2H), 4.77 (dt, *J* = 1.3, 5.6 Hz, 2H), 5.26-5.32 (m, 1H), 5.42-5.48 (m, 1H), 5.91-6.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.9, 24.1, 46.1, 51.5, 61.7, 67.7, 118.9, 131.4, 153.9, 167.5, 169.7; IR (neat) 2980, 2916, 1777, 1716, 1373, 1250, 1157 cm^{-1}; HRMS calcd for $C_{12}H_{18}NO_5$ (M^+ + H) 256.1185, found 256.1192.



1-Allyl 3-ethyl 3-hydroxy-2-oxopiperidine-1,3-dicarboxylate (221). To a solution of **220** (0.0311 g, 0.12 mmol, 1.0 equiv) in CH_3CN (12 mL, degassed by passing argon for 1 h), $Mn(OAc)_3$ (0.10 g, 0.36 mmol, 3.0 equiv) was added as a

powder at rt, and the resulting mixture was stirred at 80 °C for 24 h. The reaction was cooled to rt, divided between water (20 mL) and ether (20 mL), extracted with ether (3 x 50 mL), washed with brine (20 mL), dried and concentrated. Analysis of the crude reaction mixture by NMR did not indicate the presence of the desired lactam. Chromatography (1/1 EtOAc/hexanes) afforded the title product as oil (R_f = 0.55, 1/1 EtOAc/hexanes) contaminated with ~15% of unidentified inseparable impurity. Yield 37% (0.012 g, 0.044 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 1.98-2.08 (m, 3H), 2.41-2.53 (m, 1H), 3.70-3.77 (m, 1H), 3.91-3.98 (m, 1H), 4.21 (s, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.78 (d, *J* = 5.4 Hz, 2H), 5.27-5.35 (m, 1H), 5.40-5.48 (m, 1H), 5.88-6.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.3, 31.4, 46.5, 62.8, 68.0, 76.9, 119.1, 131.2, 153.6, 170.1, 170.8; IR (neat) 3450, 2917, 2949, 1775, 1731, 1540, 1385, 1260, 1025 cm^{-1}; HRMS calcd for $C_{12}H_{18}NO_6$ (M^+ + H) 272.1134, found 272.1138. Note: prolonged reaction time or alternative conditions for cyclization led to decomposition of the product.

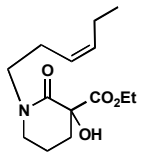


(*Z*)-Ethyl 1-(hex-3-enyl)-2-oxopiperidine-3-carboxylate (222). Prepared by a sequential N-alkylation and C-acylation. To a suspension of NaH (60% in mineral oil, 0.70 g, 17.4 mmol, 1.5 equiv) in THF/HMPA (30 mL/ 3.05 mL, 17.4 mmol, 1.5 equiv), 2-piperidinone (1.08 mL, 11.6 mmol, 1.0 equiv) was added at 0 °C, and the resulting mixture was stirred at rt for 30 min. (*Z*)-1-iodo-3-hexane (3.18 g, 15.1

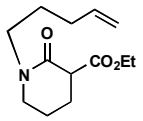
mmol, 1.3 mmol) was added at rt, and the resulting solution was heated to reflux for 24 h. The reaction was quenched with sat. NH_4Cl (20 mL), extracted with 1:1 ether/EtOAc (3 x 100 mL), washed with brine (1 x 20 mL), dried and concentrated. Chromatography (1/2 EtOAc/hexanes) afforded the alkylated 2-piperidone as oil (R_f = 0.42, EtOAc). Yield 18% (0.37 g, 2.0 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.5 Hz, 3H), 1.72-1.83 (m, 4H), 2.01-2.11 (m, 2H), 2.26-2.42 (m, 4H), 3.25-3.41 (m, 4H), 5.26-5.36 (m, 1H), 5.41-5.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 20.6, 21.4, 23.3, 25.2, 32.6, 47.2, 48.3, 125.3, 133.9, 169.6; IR (neat) 2957, 2934, 1626, 1497, 1354, 1179 cm^{-1}; HRMS calcd for $C_{11}H_{19}NONa$ (M^+ + Na) 204.1364, found 204.1369.

To a stirred solution of the alkylated lactam (0.37 g, 2.04 mmol, 1.0 equiv) in THF (15 mL), LHMDS (1.0 M in THF, 9.0 mL, 9.0 mmol, 4.4 equiv) was added at -78 °C. After 1 h ethyl chloroformate (0.37 g, 3.3 mmol, 1.6 equiv) was added at -78 °C in THF (5 mL). The resulting solution was stirred at -78 °C for 4 h, warmed slowly to rt and quenched with sat. NH_4Cl (10 mL) after the next 3 h. The reaction was extracted with 1:1 ether/EtOAc (3 x 50 mL), washed with brine (1 x 30 mL), dried and concentrated. Chromatography (1/3-1/2 EtOAc/hexanes) afforded the title product as oil (R_f = 0.72, EtOAc). Yield 44% (0.23 g, 0.91 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92-1.00 (m, 3H), 1.24-1.32 (m, 3H), 1.71-1.82 (m, 1H), 1.91-2.20 (m, 5H), 2.27-2.38 (m, 2H), 3.26-3.47 (m, 5H), 4.15-4.26 (m, 2H), 5.26-5.36 (m, 1H), 5.42-5.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.3, 20.6, 21.2, 25.1, 25.1,

47.5, 48.1, 49.2, 61.2, 125.0, 134.1, 165.6, 171.2; IR (neat) 2916, 1736, 1648, 1466, 1256, 1158 cm^{-1}; HRMS calcd for $C_{14}H_{24}NO_3$ (M^+ + H) 254.1756, found 254.1774.



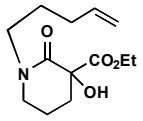
(*Z*)-Ethyl 1-(hex-3-enyl)-3-hydroxy-2-oxopiperidine-3-carboxylate (223). According to the procedure described earlier, the reaction of **222** (0.0261 g, 0.10 mmol, 1.0 equiv) and $Mn(OAc)_3$ (0.0855 g, 0.31 mmol, 3.0 equiv) in degassed CH_3CN (10 mL) at 80 °C for 24 h, afforded after chromatography (1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.7, EtOAc). Yield 57% (0.0154 g, 0.057 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (td, *J* = 0.7, 7.5 Hz, 3H), 1.31 (td, *J* = 0.8, 8.0 Hz, 3H), 1.95-2.15 (m, 5H), 2.29-3.38 (m, 3H), 3.31-3.51 (m, 4H), 4.09 (s, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 5.28-5.37 (m, 1H), 5.44-5.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.3, 19.1, 20.6, 24.9, 31.7, 47.8, 48.3, 62.3, 74.9, 124.7, 134.3, 168.1, 172.3; IR (neat) 3381, 2961, 2932, 2919, 1734, 1648, 1254, 1131, 1029 cm^{-1}; HRMS calcd for $C_{14}H_{23}NO_4Na$ (M^+ + Na) 292.1525, found 292.1520. Note: use of EtOAc instead of CH_3CN led to 50% conversion after 24 h at reflux, use of AcOH instead of CH_3CN afforded the title compound in 65% yield after 24 h at 80 °C, use of $Cu(OAc)_2$ as an additive (1.0 equiv) in AcOH for 24 at 80 °C afforded the title compound in 39% yield. Analysis of crude reaction mixtures did not indicate the formation of the desired amides.



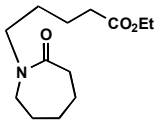
Ethyl 2-oxo-1-(pent-4-enyl)piperidine-3-carboxylate (224). Prepared in a sequence analogous to **222**. To a solution of NaHMDS (1.0 M in THF, 10.0 mL, 10.0 mmol, 1.0 equiv) in THF (5 mL), 2-piperidinone (1.02 g, 10.0 mmol, 1.0 equiv) was added at rt. The resulting solution was stirred at rt for 30 min, and 5-bromo-1-pentene (1.14 mL, 9.1 mmol, 0.91 equiv) was added at rt. The resulting mixture was stirred at 60 °C for 18 h, cooled to rt and quenched with sat. NH_4Cl/conc. HCl mixture (10 mL/ 0.5 mL) The organic layer was washed with aq. HCl (1.0 M, 10 mL), the aq. Layers were extracted with EtOAc (2 x 25 mL), washed with brine (1 x 20 mL), dried and concentrated. Chromatography (EtOAc) afforded the title compound as oil (R_f = 0.56, EtOAc). Yield 84% (1.28 g, 7.7 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48-1.59 (m, 2H), 1.63-1.74 (m, 4H), 1.92-1.99 (m, 2H), 2.22-2.28 (m, 2H), 3.14-3.20 (m, 2H), 3.22-3.28 (m, 2H), 4.82-4.96 (m, 2H), 5.65-5.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 23.2, 26.1, 31.0, 32.3, 46.6, 47.8, 114.7, 137.8, 169.4; IR (neat) 2938, 1620, 1499, 1356, 1292, 1191 cm^{-1}; HRMS calcd for $C_{10}H_{17}NONa$ (M^+ + Na) 190.1208, found 190.1203. Note: these conditions were found to be superior to the alkylation method used for the synthesis of **222**.

According to the procedure described for the preparation of **222**, the reaction of alkylated 2-piperidone (0.49 g. 2.94 mmol, 1.0 equiv), LHMDS (1.0 M in THF, 12.9 mL, 12.9 mmol, 4.4 equiv) and ethyl chloroformate (0.53 g, 4.7 mmol, 1.6 equiv), after chromatography (40% EtOAc/hexanes) afforded the title product as oil

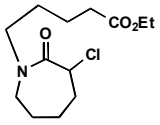
(R_f = 0.19, 1/2 EtOAc/hexanes). Yield 62% (0.43 g, 1.8 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.61-1.69 (m, 2H), 1.71-1.82 (m, 1H), 1.89-2.16 (m, 5H), 3.22-3.44 (m, 5H), 4.11-4.25 (m, 2H), 4.91-5.03 (m, 2H), 5.74-5.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.1, 25.1, 26.1, 30.9, 47.0, 47.7, 49.2, 61.2, 114.9, 137.9, 165.6, 171.2; IR (neat) 2918, 2849, 1736, 1642, 1493, 1372, 1179, 1162 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_3Na$ (M^+ + Na) 262.1419, found 262.1400.



Ethyl 3-hydroxy-2-oxo-1-(pent-4-enyl)piperidine-3-carboxylate (225). According to the procedure described earlier, the reaction of **224** (0.0489 g, 0.20 mmol, 1.0 equiv) and $Mn(OAc)_3$ (0.17 g, 0.61 mmol, 3.0 equiv) in degassed CH_3CN (20 mL) at 80 °C for 24 h, afforded the title compound as oil (R_f = 0.32, 1/1 EtOAc/hexanes). Yield 78% (0.0398 g, 0.16 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-1.33 (m, 3H), 1.61-1.73 (m, 2H), 1.93-2.15 (m, 6H), 2.25-2.36 (m, 1H), 3.22-3.47 (m, 3H), 3.49-3.59 (m, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.94-5.08 (m, 2H), 5.75-5.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 29.1, 26.0, 30.8, 31.8, 47.3, 47.9, 62.2, 75.0, 115.2, 137.6, 168.3, 172.3; IR (neat) 3466, 2930, 2866, 1734, 1638, 1449, 1254, 1200, 1026 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_4Na$ (M^+ + Na) 278.1368, found 278.1349. Note: the bridged lactam was not detected in the crude reaction mixture.

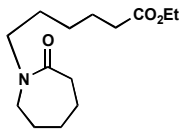


Ethyl 5-(2-oxoazepan-1-yl)pentanoate (226). According to the procedure described for alkylation of 2-piperidone,[399] the reaction of ε-caprolactam (1.17 g, 10.0 mmol, 1.0 equiv), NaHMDS (1.0 M in THF, 10.0 mL, 1.0 equiv) and ethylbromovalerate (1.49 mL, 9.1 mmol, 9.1 equiv) in THF (5 mL) at 60 °C for 18 h, afforded after chromatography (1/2 EtOAc/hexanes) the title compound as oil (R_f = 0.51, EtOAc). Yield 73% (1.60 g, 6.6 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.48-1.76 (m, 10H), 2.32 (t, *J* = 7.0 Hz, 2H), 2.47-2.52 (m, 2H), 3.29-3.34 (m, 2H), 3.36 (t, *J* = 7.2 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.2, 23.4, 27.5, 28.7, 30.0, 33.9, 37.3, 47.7, 49.6, 60.3, 173.5, 175.7; IR (neat) 2930, 2859, 1732, 1644, 1634, 1445, 1372, 1198 cm^{-1}; HRMS calcd for $C_{13}H_{24}NO_3$ (M^+ + H) 242.1756, found 242.1762.



Ethyl 5-(3-chloro-2-oxoazepan-1-yl)pentanoate (227). To a solution of amide **226** (0.115 g, 0.48 mmol, 1.0 equiv) in THF (9.6 mL), LDA (0.63 M in THF, 1.65 mL, 1.05 mmol, 2.2 equiv, freshly prepared from 1.1 equiv of DIPA and 1.0 equiv of *n*BuLi) was added at -78 °C as rapidly as possible. After 5 min $CuCl_2$ (0.2 M in DMF, 5.25 mL, 2.2 equiv) was added at -78 °C as rapidly as possible. After 5 min, the dry ice-acetone bath was removed and the reaction was stirred for an additional 45

min. The reaction was quenched with sat. NH_4Cl (10 mL), extracted with EtOAc (3 x 50 mL), washed with brine (1x 50 mL), dried and concentrated. The analysis of the crude reaction mixture by NMR indicated complex mixture of products, including **227** and **226** in ca. 1:1 ratio as major products. The bridged lactam was not detected. Chromatography (1/1 EtOAc/hexanes) afforded the title product as oil. Yield 19% (0.0209 g, 0.076 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H), 1.58-1.78 (m, 8H), 1.88-2.09 (m, 2H), 2.47-2.57 (m, 2H), 3.29-3.51 (m, 4H), 4.24 (q, J = 7.2 Hz, 2H), 4.35 (dd, J = 5.6, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 23.4, 24.6, 28.7, 30.0, 32.0, 37.3, 47.0, 49.5, 57.2, 62.1, 169.6, 175.9; IR (neat) 2930, 2855, 1742, 1636, 1445, 1180 cm^{-1}; HRMS calcd for $C_{13}H_{22}ClNO_3Na$ (M^+ + Na) 298.1186, found 298.1186. Note: attempted Dieckmann condensation of **226** according to procedure by Arata *et al.* for an analogous amido-ester[146] using 1.5 equiv of NaH in refluxing xylenes afforded the corresponding amido-acid in 14% yield. The bridged lactam was not detected in the crude reaction mixture.



Ethyl 6-(2-oxoazepan-1-yl)hexanoate (228). According to the procedure described above, the reaction of ε-caprolactam (1.17 g, 10.0 mmol, 1.0 equiv), NaHMDS (1.0 M in THF, 10.0 mL, 1.0 equiv) and ethyl 6-bromohexanoate (1.63 mL, 9.1 mmol, 9.1 equiv) in THF (10 mL) at 60 °C for 18 h, afforded after chromatography (EtOAc) the title compound as oil (R_f = 0.52, EtOAc). Yield 58%

(1.35 g, 5.3 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.1 Hz, 3H), 1.22-1.32 (m, 2H), 1.41-1.52 (m, 2H), 1.54-1.71 (m, 8H), 2.23 (t, *J* = 7.5 Hz, 2H), 2.42-2.48 (m, 2H), 3.24-3.34 (m, 4H), 4.07 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 23.4, 24.7, 26.4, 27.8, 28.7, 30.0, 34.2, 37.3, 47.9, 49.5, 60.1, 173.6, 175.5; IR (neat) 2930, 2859, 1732, 1636, 1447, 1374, 1198 cm^{-1}; HRMS calcd for $C_{14}H_{26}NO_3$ (M^+ + H) 256.1913, found 256.1935. Note: attempted oxidative cyclization according to the procedure described for **226** afforded a complex mixture of products. The bridged lactam was not detected in the crude reaction mixture.

Hydrolytic stability of one-carbon bridged amides

General Procedure for Extraction Studies of Lactam 229 (Table 20). Lactam **229** was dissolved in a specified amount of CH_3CN at room temperature. After addition of water, aqueous HCl, or aqueous NaOH the reaction mixture was vigorously stirred under conditions specified in Table 1 and Schemes B1-B6. Reactions were cooled to room temperature (if necessary) and extracted with EtOAc (4 x 10 mL). Combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4), and concentrated to afford the title compound. For entries 4-6 (Table 20) the reactions were neutralized with saturated $NaHCO_3$ before extraction with EtOAc.

Recovery of Lactam 229 from H_2O/CH_3CN Mixture. According to the general procedure, lactam **229** (40.0 mg, 0.116 mmol) was dissolved in 6.0 mL of CH_3CN and 1.5 mL of H_2O was added. After stirring at room temperature for 20 h the reaction mixture was extracted with EtOAc (4 x 10 mL), combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4), and concentrated to afford 34.9 mg (0.101 mmol) of the title compound. Yield 87%.

Recovery of Lactam 229 from aq NaOH/CH_3CN Mixture. According to the general procedure, lactam **229** (40.3 mg, 0.116 mmol) was dissolved in 6.0 mL of CH_3CN. 0.5 mL of H_2O was added, followed by 0.25 mL of 1.0 *N* NaOH. After stirring at room temperature for 20 h the reaction mixture was extracted with EtOAc (4 x 10 mL), combined organic layers were washed with water (1 x 10 mL), brine (1

x 10 mL), dried (Na_2SO_4), and concentrated to afford 37.8 mg (0.109 mmol) of the title compound. Yield 94%.

Recovery of Lactam 229 from aq NaOH/CH_3CN Mixture under Reflux. According to the general procedure, lactam **229** (25.6 mg, 0.074 mmol) was dissolved in 6.0 mL of CH_3CN, and 0.25 mL of 1.0 *N* NaOH was added. After stirring at room temperature for 30 min, the reaction was refluxed for 22 h. The reaction was cooled to room temperature, extracted with EtOAc (4 x 10 mL), combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4), and concentrated to afford 20.6 mg (0.060 mmol) of the title compound. Yield 81%.

Recovery of Lactam 229 from aq HCl/CH_3CN Mixture. According to the general procedure, lactam **229** (41.7 mg, 0.121 mmol) was dissolved in 6.0 mL of CH_3CN, and 0.5 mL of H_2O was added followed by 0.25 mL of 1.0 *N* HCl. After stirring at room temperature for 20 h, reaction mixture was basified with saturated $NaHCO_3$, extracted with EtOAc (4 x 10 mL), combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4), and concentrated to afford 34.3 mg (0.099 mmol) of the title compound. Yield 82%. Note: it was also found that the title compound could be recovered from acidic solutions by simple extraction with EtOAc, without prior basification with $NaHCO_3$.

Recovery of Lactam 229 from aq HCl/CH_3CN Mixture, 8 Days. According to the general procedure, lactam **229** (27.0 mg, 0.078 mmol) was dissolved in 5.0 mL of CH_3CN. 0.5 mL of H_2O was added followed by 0.20 mL of 1.0 *N* HCl. After stirring at room temperature for 8 days (187 h), the reaction mixture was basified with

saturated $NaHCO_3$, extracted with EtOAc (4 x 10 mL), combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4), and concentrated to afford 23.5 mg (0.068 mmol) of the title compound. Yield 87%.

Conversion of Lactam 229 to Compound 232. According to the general procedure, lactam **229** (19.2 mg, 0.056 mmol) was dissolved in 6.0 mL of CH_3CN, and 0.25 mL of 1.0 *N* HCl was added. After stirring at room temperature for 30 min, the reaction was refluxed for 23 h. The reaction was cooled to room temperature, basified with saturated $NaHCO_3$, extracted with EtOAc (4 x 10 mL), combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (1/4 EtOAc/hexanes) afforded compound **232** as a colorless film, yield 95% (19.1 mg, 0.53 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.53 (m, 2H), 1.65-1.77 (m, 2H), 1.81-2.05 (m, 3H), 2.21-2.36 (br, 1H), 2.52 (dd, *J* = 4.8, 11.9 Hz, 1H), 2.79-2.84 (m, 1H), 3.06 (dd, *J* = 1.4, 10.0 Hz, 1H), 3.16 (dt, *J* = 3.6, 12.1 Hz, 1H), 3.24-3.29 (m, 1H), 3.51-3.58 (m, 1H), 3.60-3.67 (m, 1H), 5.56-5.59 (m, 1H), 6.04-6.09 (m, 1H), 6.26-6.34 (br, 1H), 7.01 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 29.1, 29.8, 33.7, 36.5, 40.4, 44.3, 46.1, 48.8, 119.6, 128.7, 128.9, 130.5, 130.6, 141.4, 171.3; IR (neat) 3223, 3135, 2995, 2890, 1630, 1455, 795, 705 cm^{-1}; HRMS calcd for $C_{18}H_{23}BrNO2$ (M^+ + H) 364.0912, found 364.0910.

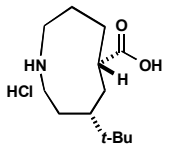
General Procedure for NMR Studies of Lactam 229. An NMR tube was charged with a solution of lactam **229** in THF-d_8. To this was added D_2O, DCl (1.0 *N*

in D_2O) or NaOD (1.0 *N* in D_2O) in one portion. The tube was well shaken and transferred to the probe of NMR spectrometer operating at ambient temperature.

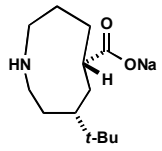
NMR Study of Lactam 229 Dissolved in 1:1 D_2O/THF-d_8. According to the general procedure, lactam **229** (10.0 mg, 0.029 mmol) was dissolved in 0.30 mL of THF-d_8 and transferred to an NMR tube. To this 0.30 mL of D_2O was added, the tube was well shaken and NMR spectra were recorded. The tube was left at ambient temperature for seven days and the spectra were taken again.

NMR Study of Lactam 229 Dissolved 1:6 DCl (1.0 *N* in D_2O)/THF-d_8. According to the general procedure, lactam **229** (10.0 mg, 0.029 mmol) was dissolved in 0.50 mL of THF-d_8 and transferred to an NMR tube. To this 0.080 mL of DCl (1.0 *N* in D_2O) was added, the tube was well shaken and NMR spectra were recorded. The tube was left at ambient temperature for seven days and the spectra were taken again.

NMR Study of Lactam 229 Dissolved 1:6 NaOD (1.0 *N* in D_2O)/THF-d_8. According to the general procedure, lactam **229** (10.0 mg, 0.029 mmol) was dissolved in 0.50 mL of THF-d_8 and transferred to an NMR tube. To this 0.080 mL of NaOD (1.0 *N* in D_2O) was added, the tube was well shaken and NMR spectra were recorded. The tube was left at ambient temperature for seven days and the spectra were taken again.



Synthesis of Amino Acid 237 under Acidic Conditions. 10 mL round bottom flask was charged with lactam **3** (20.0 mg, 0.096 mmol, 1.0 equiv) and HCl (1.0 *N* in H_2O) (1.0 mL, 1.0 mmol, 11.1 equiv). The flask was gently stirred for 15 min. The solvent was evaporated and the flask was left under vacuum overnight to give the title compound as a white solid. Recrystallization from water afforded crystals suitable for x-ray analysis. Yield: quantitative (25.0 mg, 0.095 mmol). Mp = 156-158 °C; ^{1}H NMR (400 MHz, D_2O) δ 0.90 (s, 9H), 1.32-1.36 (m, 1H), 1.42-1.53 (m, 2H), 1.76-2.12 (complex, 6H), 2.51-2.62 (m, 1H), 3.07-3.17 (m, 2H), 3.26-3.36 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 17.3, 22.2, 26.0, 26.3, 26.5, 33.7, 40.5, 41.8, 43.8, 46.2, 180.3; IR (KBr) 3430, 3120, 3030, 2950, 1715, 1575, 1155 cm^{-1}; HRMS calcd for $C_{13}H_{26}NO_2$ (M^+ + H) 228.1963, found 228.1955.



Synthesis of Amino Acid 237 under Basic Conditions. 10 mL round bottom flask was charged with lactam **3** (20.0 mg, 0.096 mmol, 1.0 equiv) and NaOH (1.0 *N* in H_2O) (0.10 mL, 0.096 mmol, 1.0 equiv). The flask was stirred for 3 h. The solvent was evaporated and the flask was left under vacuum overnight to give the title compound as a white solid. Yield: quantitative (24.0 mg, 0.096 mmol). Mp > 300 °C; ^{1}H NMR (400 MHz, D_2O) δ 0.87 (s, 9H), 1.18-1.42 (m, 3H), 1.46-1.57 (m, 1H), 1.64-1.92 (m, 5H), 2.22-2.35 (m, 1H), 2.66-2.79 (m, 2H), 2.81-2.96 (m, 2H); ^{13}C NMR

(100 MHz, D_2O) δ 20.2, 24.9, 26.6, 27.7, 28.7, 33.5, 41.2, 42.0, 46.6, 48.2, 186.3; IR (KBr) 3370, 2880, 1525, 1375 cm^{-1}; HRMS calcd for $C_{13}H_{26}NO_2$ (M^+ + H) 228.1963, found 228.1958.

Procedure for Determining Stability of Compound 3 in 1:1 D_2O/THF-*d_8* Mixture. Lactam **3** (20.0 mg, 0.096 mmol) was dissolved in 0.30 mL of THF-*d_8* and transferred to NMR tube. To this 0.30 mL of D_2O was added in one portion, the tube was well shaken and transferred to the probe of NMR spectrometer operating at ambient temperature. The ratio of **3** to the product amino acid **237** was determined by the integral values of ^1H NMR spectra.

General Procedure for Extraction Studies of Bicyclic Lactams (Table 23). Bicyclic lactam was dissolved in a specified amount of CH_3CN at room temperature or placed in a round bottom flask (10 mL). To this buffer (pH 4.0, Fluka 82566 or pH 10.0, Fluka 82575) was added, and the reaction mixture was vigorously stirred under conditions specified in Table 23. Reactions were extracted with EtOAc (4 x 10 mL). Combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4), and concentrated to afford the title compounds.

Stability of Compound 35 in 1:1 D_2O/THF-*d_8* Mixture. Lactam **35** was dissolved in 0.30 mL of THF-*d_8* and transferred to NMR tube. To this 0.30 mL of D_2O was added in one portion, the tube was well shaken and transferred to the probe of NMR spectrometer operating at ambient temperature. The amino acid was not observed by ^1H NMR.

Recovery of Lactam 34 from Buffer (pH 4)/CH_3CN Mixture. According to the general procedure, lactam **34** (11.5 mg, 0.040 mmol) was dissolved in 0.20 mL of CH_3CN. 2.0 mL of buffer (pH 4) was added, and the reaction mixture was vigorously stirred for 2 h. The reaction mixture was extracted with EtOAc (4 x 10 mL), combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4), and concentrated to afford the 10.7 mg (0.038 mmol) of the title compound. Yield 93%.

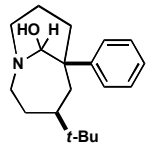
Recovery of Lactam 34 from Buffer (pH 10)/CH_3CN Mixture. According to the general procedure, lactam **34** (12.2 mg, 0.043 mmol) was dissolved in 0.20 mL of CH_3CN. 2.0 mL of buffer (pH 10) was added, and the reaction mixture was vigorously stirred for 2 h. The reaction mixture was extracted with EtOAc (4 x 10 mL), combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4), and concentrated to afford the 12.1 mg (0.043 mmol) of the title compound. Yield 99%.

Recovery of Lactam 58 from Buffer (pH 4). According to the general procedure, lactam **58** (11.1 mg, 0.056 mmol) was dissolved in 2.0 mL of buffer (pH 4), and the reaction mixture was vigorously stirred for 2 h. The reaction mixture was extracted with EtOAc (4 x 10 mL), combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4), and concentrated to afford the 11.0 mg (0.055 mmol) of the title compound. Yield 99%.

Recovery of Lactam 58 from Buffer (pH 10). According to the general procedure, lactam **58** (10.8 mg, 0.054 mmol) was dissolved in 2.0 mL of buffer (pH

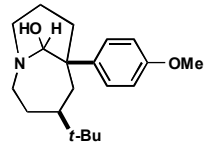
10), and the reaction mixture was vigorously stirred for 2 h. The reaction mixture was extracted with EtOAc (4 x 10 mL), combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4), and concentrated to afford the 10.4 mg (0.052 mmol) of the title compound. Yield 96%.

General procedure for reduction with $NaBH_4$: To a solution of amide (1.0 equiv) in EtOH, $NaBH_4$ (3.0 equiv) was added at rt, and the reaction mixture was stirred at rt for 20-24 h. The reaction was quenched with sat. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 50 mL), washed with brine (1 x 10 ml) and dried. Chromatography ($MeOH/CH_2Cl_2$) afforded the final products.



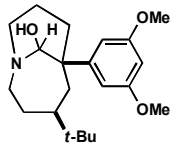
(4R,6R)-4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-ol (238). According to the general procedure, the reaction of amide **34** (0.0250 g, 0.088 mmol, 1.0 equiv) and $NaBH_4$ (0.010 g, 0.26 mmol, 3.0 equiv) in EtOH (5.0 mL) for 21 h at rt afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title compound as oil (R_f = 0.43, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$). Yield 90% (0.02228 g, 0.079 mmol), 80:20 mixture of inseparable diastereoisomers. ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 0.87 (s, 9H), 1.38-1.61 (m, 3H), 1.73-1.92 (m, 3H), 1.99-2.21 (m, 2H), 2.43-2.53 (m, 2H), 2.65 (dt, *J* = 5.0, 13.4 Hz, 1H), 3.48 (dt, *J* = 3.9, 13.5 Hz, 1H), 3.63-3.70 (m, 1H), 5.13 (s, 1H), 7.16-7.42 (m, 5H); (minor isomer, diagnostic peaks) δ 0.95 (s, 9H), 2.93 (d, *J* = 7.9 Hz, 1H), 4.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 21.3, 27.5, 29.9, 30.8, 33.8, 42.8, 45.2, 47.1, 47.5, 53.1, 83.5, 125.4, 125.5, 128.2, 150.6; (minor isomer, diagnostic peaks) δ 21.4,

27.8, 29.4, 34.0, 38.0, 38.1, 43.4, 46.2, 50.2, 51.9, 88.3, 126.0, 128.0, 151.2; IR (neat) 3400, 2057, 2957, 2941, 2866, 1468, 1445, 1366, 733, 696 cm^{-1}; HRMS calcd for $C_{19}H_{30}NO$ (M^+ + H) 288.2327, found 288.2330.

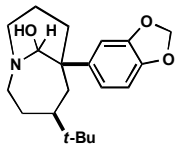


(4R,6R)-4-*tert*-Butyl-6-(4-methoxyphenyl)-1-azabicyclo[4.3.1]decan-10-ol (239). According to the general procedure, the reaction of amide **35** (0.0335 g, 0.11 mmol, 1.0 equiv) and $NaBH_4$ (0.0121 g, 0.32 mmol, 3.0 equiv) in EtOH (5.0 mL) for 20 h at rt afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.40, 1/10/90 NH_4OH/MeOH/CH_2Cl_2). Yield 91% (0.0318 g, 0.10 mmol), 77:23 mixture of inseparable diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$) (major isomer) δ 0.86 (s, 9H), 1.38-1.58 (m, 3H), 1.73-1.95 (m, 3H), 1.98-2.21 (m, 2H), 2.37-2.53 (m, 2H), 2.64 (dt, *J* = 5.0, 12.8 Hz, 1H), 3.47 (dt, *J* = 4.1, 13.8 Hz, 1H), 3.62-3.73 (m, 1H), 3.81 (s, 3H), 5.08 s, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 8.9 Hz, 2H); (minor isomer, diagnostic peaks) δ 0.94 (s, 9H), 2.93 (d, *J* = 7.1 Hz, 1H), 4.91 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 21.2, 27.5, 30.0, 30.7, 33.8, 42.2, 45.1, 47.2, 47.5, 53.1, 55.2, 83.5, 113.3, 126.4, 142.7, 157.2; (minor isomer, diagnostic peaks) δ 27.8, 34.0, 38.1, 38.3, 42.8, 46.2, 50.4, 51.9, 88.6, 113.3, 127.1, 142.7; IR (neat) 3440, 2955, 2988, 1610,

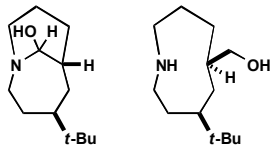
1512, 1250, 1186, 825, 731 cm^{-1}; HRMS calcd for $C_{20}H_{32}NO_2$ (M^+ + H) 318.2433, found 318.2429.



(4R,6R)-4-*tert*-Butyl-6-(3,5-dimethoxyphenyl)-1-azabicyclo[4.3.1]decan-10-ol (240). According to the general procedure, the reaction of amide **40** (0.0571 g, 0.17 mmol, 1.0 equiv) and $NaBH_4$ (0.0188 g, 0.50 mmol, 3.0 equiv) in EtOH (5.0 mL) for 18 h at rt afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title compound as oil (R_f = 0.53, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$). Yield 95% (0.0561 g, 0.16 mmol), 77:23 mixture of inseparable diastereoisomers. ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 0.86 (s, 9H), 1.38-1.60 (m, 3H), 1.71-1.91 (m, 3H), 1.93-2.22 (m, 2H), 2.36-2.52 (m, 2H), 2.64 (dt, *J* = 5.0, 12.6 Hz, 1H), 3.48 (dt, *J* = 4.1, 13.8 Hz, 1H), 3.59-3.69 (m, 1H), 3.82 (s, 9H), 5.05 (s, 1H), 6.32 (t, *J* = 2.0 Hz, 1H), 6.54 (d, *J* = 2.2 Hz, 2H); (minor isomer, diagnostic peaks) δ 0.94 (s, 9H), 1.66 (m, 2H), 2.92 (d, *J* = 7.2 Hz, 2H), 4.90 (s, 1H), 6.81 (d, *J* = 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 21.3, 27.5, 30.0, 30.7, 33.8, 43.0, 45.0, 46.7, 47.4, 52.9, 55.2, 83.5, 96.8, 104.5, 153.3, 160.5; (minor isomer, diagnostic peaks) δ 21.3, 27.8, 29.2, 34.0, 38.0, 43.7, 46.1, 50.3, 51.8, 55.2, 88.2, 97.0, 105.1, 153.9, 160.3; IR (neat) 3400, 3088, 2955, 2868, 1595, 1456, 1308, 1204, 1151, 1069, 910, 733 cm^{-1}; HRMS calcd for $C_{21}H_{34}NO_3$ (M^+ + H) 348.2539, found 348.2538.

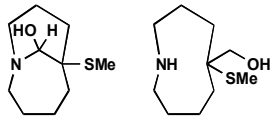


(4R,6R)-6-(Benzo[d][1,3]dioxol-5-yl)-4-*tert*-butyl-1-azabicyclo[4.3.1] decan-10-ol (241). According to the general procedure, the reaction of amide **39** (0.0335 g, 0.10 mmol, 1.0 equiv) and $NaBH_4$ (0.0116 g, 0.30 mmol, 3.0 equiv) in EtOH (5.0 mL) for 18 h at rt afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title compound as oil (R_f = 0.79, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$). Yield 94% (0.0313 g, 0.094 mmol), 78:22 mixture of inseparable diastereoisomers. ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 0.86 (s, 9H), 1.37-1.50 (m, 2H), 1.51-1.59 (m, 1H), 1.71-1.81 (m, 2H), 1.86 (d, *J* = 11.8 Hz, 1H), 1.93-2.22 (m, 2H), 2.38 (dt, *J* = 6.5, 12.6 Hz, 1H), 2.49 (dd, *J* = 4.8, 14.1 Hz, 1H), 2.64 (dt, *J* = 4.9, 13.2 Hz, 1H), 3.46 (dt, *J* = 4.0, 13.7 Hz, 1H), 3.61-3.69 (m, 1H), 5.03 (s, 1H), 5.94 (s, 2H), 6.73-6.84 (m, 2H), 6.90 (s, 1H); (minor isomer, diagnostic peaks) δ 0.94 (s, 9H), 2.92 (d, *J* = 7.5 Hz, 1H), 4.86 (s, 1H), 5.93 (s, 2H), 7.06 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 21.2, 27.5, 30.3, 30.7, 33.8, 42.7, 45.0, 47.2, 47.4, 53.0, 83.5, 100.8, 106.4, 107.9, 118.2, 144.9, 145.1, 147.5; (minor isomer, diagnostic peaks) δ 21.3, 27.8, 30.4, 38.2, 38.5, 43.4, 46.1, 50.3, 51.8, 88.5, 100.7, 107.3, 107.6, 118.9, 144.9, 145.4, 147.2; IR (neat) 3400, 2959, 2941, 2868, 1504, 1489, 1234, 1042, 912, 733 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO_3$ (M^+ + H) 332.2226, found 332.2225.



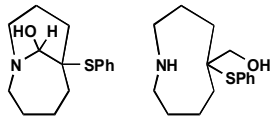
(4R,6R)-4-*tert*-Butyl-1-azabicyclo[4.3.1]decan-10-ol (242) and ((7R)-7-*tert*-Butylazonan-5-yl)methanol (243). According to the general procedure, the reaction of amide **3** (0.100 g, 0.47 mmol, 1.0 equiv) and $NaBH_4$ (0.0545 g, 1.44 mmol, 3.0 equiv) in EtOH (20 mL) for 18 h at rt afforded after chromatography (1/20/80 $NH_4OH/MeOH/CH_2Cl_2$) **242** as oil (R_f = 0.52, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$), yield 24% (0.0240 g, 0.11 mmol), 80:20 mixture of inseparable diastereoisomers, and **243** as oil (R_f = 0.24, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$), yield 52% (0.0522 g, 0.25 mmol), isolated as 77:23 mixture with the ammonium salt. Analysis of the crude reaction mixture by ^1H NMR indicated 30:70 mixture of **242** to **243**. Compound **242**: ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 0.89 (s, 9H), 0.99 (td, *J* = 3.5, 14.0 Hz, 1H), 1.21-1.55 (m, 4H), 1.70-1.88 (m, 2H), 2.05-2.16 (m, 1H), 2.16-2.24 (m, 2H), 2.57 (dd, *J* = 4.7, 14.4 Hz, 1H), 2.85 (td, *J* = 2.8, 14.7 Hz, 1H), 3.03 (dt, *J* = 3.4, 14.5 Hz, 1H), 3.44 (td, *J* = 4.0, 13.8 Hz, 1H), 4.66 (s, 1H); (minor isomer, diagnostic peaks) δ 0.90 (s, 9H), 2.38-2.46 (m, 2H), 2.48-2.54 (m, 1H), 4.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 19.4, 24.3, 27.6, 30.5, 31.9, 33.7, 33.9, 44.7, 45.8, 54.8, 81.4; (minor isomer, diagnostic peaks) δ 19.3, 24.8, 27.6, 29.8, 33.5, 34.7, 35.3, 45.3, 48.1, 51.4, 81.2; IR (neat) 3400, 3125, 2937, 1468, 1450, 1366, 1053, 986 cm^{-1}; HRMS calcd for $C_{13}H_{26}NO$ (M^+ + H) 212.2014, found 212.2009. Compound **243**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 9H), 1.18-1.80 (m, 9H), 1.81-1.92 (m,

1H), 2.03 (br, 2H), 2.53 (td, *J* = 3.9, 13.1 Hz, 1H), 2.64-2.78 (m, 2H), 2.82-2.92 (m, 1H), 3.38-3.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 26.7, 27.7, 28.5, 32.9, 34.2, 34.8, 40.6, 42.9, 49.5, 67.5; IR (neat) 3350, 2939, 2866, 1477, 1364, 1140, 1030 cm^{-1}; HRMS calcd for $C_{13}H_{28}NO$ (M^+ + H) 214.2171, found 214.2170.



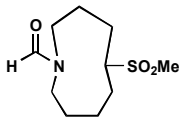
6-(Methylthio)-1-azabicyclo[4.3.1]decan-10-ol (244) and (5-(Methylthio)azonan-5-yl)methanol (245). According to the general procedure, the reaction of amide **58** (0.0322 g, 0.16 mmol, 1.0 equiv) and $NaBH_4$ (0.018 g, 0.48 mmol, 3.0 equiv) in EtOH (10 mL) for 18 h at rt afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) **244** as oil (R_f = 0.65, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 40% (0.0129 g, 0.064 mmol), and **245** as oil (R_f = 0.17, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 48% (0.0161 g, 0.079 mmol). Compound **244**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43-1.73 (m, 5H), 1.74-2.05 (m, 5H), 2.12 (s, 3H), 2.34-2.42 (m, 1H), 2.58 (dd, *J* = 4.8, 14.2 Hz, 1H), 2.94-3.08 (m, 2H), 3.34-3.45 (m, 1H), 4.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1, 22.6, 25.9, 31.7, 32.0, 38.6, 43.7, 50.9, 55.1, 80.9; IR (neat) 2400, 2920, 2856, 1450, 1163, 1155, 1113 cm^{-1}; HRMS calcd for $C_{10}H_{20}NOS$ (M^+ + H) 202.1266, found 202.1263. Compound **245**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.55 (m, 4H), 1.58-1.78 (m, 5H), 1.78-1.95 (m, 3H), 1.91 (s, 3H), 2.07-2.85 (m, 4H), 3.33 (q, *J* = 11.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.5, 17.5, 20.5, 25.6, 26.1, 28.4, 41.9, 47.7, 56.7, 63.6; IR

(neat) 3400, 2920, 2862, 1480, 1157, 1123, 748 cm^{-1}; HRMS calcd for $C_{10}H_{22}NOS$ (M^+ + H) 204.1422, found 204.1420.

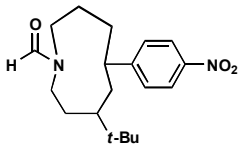


6-(Phenylthio)-1-azabicyclo[4.3.1]decan-10-ol (246) and (5-(Phenylthio)azonan-5-yl)methanol (247). According to the general procedure, the reaction of amide **73** (0.0245 g, 0.093 mmol, 1.0 equiv) and $NaBH_4$ (0.011 g, 0.28 mmol, 3.0 equiv) in EtOH (5 mL) for 18 h at rt afforded after chromatography (1/5/95 $NH_4OH/MeOH/CH_2Cl_2$) **246** as oil (R_f = 0.50, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$), yield 62% (0.0151 g, 0.057 mmol), 83:17 mixture of diastereoisomers, and **247** as oil (R_f = 0.31, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$), yield 34% (0.0083 g, 0.031 mmol). Analysis of the crude reaction mixture by ^1H NMR indicated 63:37 mixture of **246** to **247**. Compound **246**: ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 1.02-1.16 (m, 1H), 1.48-1.65 (m, 5H), 1.78-1.91 (m, 3H), 2.18 (td, *J* = 4.6, 12.4 Hz, 1H), 2.34 (ddd, *J* = 3.4, 6.2, 15.8 Hz, 1H), 2.55 (dd, *J* = 4.9, 14.1 Hz, 1H), 2.86-2.99 (m, 2H), 3,44 (td, *J* = 3.5, 13.7 Hz, 1H), 4.50 (s, 1H), 7.30-7.42 (m, 3H), 7.60 (dd, *J* = 1.8, 7.9 Hz, 2H); (minor isomer, diagnostic peaks) δ 2.68-2.75 (m, 1H), 4.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 22.9, 24.8, 31.2, 32.4, 38.1, 43.5, 54.5, 55.8, 81.9, 128.8, 129.0, 130.9, 136.7; IR (neat) 3450, 3071, 3057, 2924, 2855, 1450, 1437, 1350, 1150, 750 cm^{-1}; HRMS calcd for $C_{15}H_{22}NOS$ (M^+ + H) 264.1422, found 264.1422. Compound **247**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.39-1.65 (m, 6H), 1.65-

2.16 (m, 6H), 2.63-2.71 (m, 1H), 2.73-2.87 (m, 3H), 3.24 (q, J = 11.6 Hz, 2H), 7.33-7.43 (m, 3H), 7.51 (dd, J = 1.4, 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 20.7, 25.9, 26.3, 28.5, 41.5, 47.6, 62.3, 64.3, 128.9, 129.1, 130.0, 137.3; IR (neat) 3400, 3057, 2918, 2849, 1474, 1437, 1410, 1050, 750 cm^{-1}; HRMS calcd for $C_{15}H_{24}NOS$ (M^+ + H) 266.1579, found 266.1577.



5-(Methylsulfonyl)azonane-1-carbaldehyde (248). According to the general procedure, the reaction of amide **84** (0.0110 g, 0.048 mmol, 1.0 equiv) and $NaBH_4$ (0.0054 g, 0.14 mmol, 3.0 equiv) in EtOH (4 mL) for 18 h at rt afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) **248** as oil (R_f = 0.35, 1/10/90 NH_4OH/MeOH/CH_2Cl_2). Yield 98% (0.0110 g, 0.047 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 1.61-1.99 (m, 7H), 2.06-2.37 (m, 3H), 2.84 (s, 3H, minor rotamer), 2.85 (s, 3H, major rotamer), 2.89-3.02 (m, 1H), 3.08-3.37 (m, 2H), 3.42-3.56 (m, 1H), 3.68-3.77 (m, 1H), 8.15 (s, 1H, major rotamer), 8.20 (s, 1H, minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 23.5, 23.8, 24.3, 24.4, 25.3, 25.4, 25.6, 26.0, 26.6, 26.8, 37.7, 37.9, 45.1, 45.7, 49.6, 50.4, 62.1, 62.2, 163.9, 164.3; IR (neat) 1651, 1283, 1128 cm^{-1}; HRMS calcd for $C_{10}H_{20}NO_3S$ (M^+ + H) 234.1164, found 234.1167.



4-*tert*-Butyl-6-(4-nitrophenyl)azonane-1-carbaldehyde (249). According to the general procedure, the reaction of amide **36** (0.0221 g, 0.067 mmol, 1.0 equiv) and $NaBH_4$ (0.008 g, 0.20 mmol, 3.0 equiv) in EtOH (10 mL) for 20 h at rt afforded **249** as 42:68 mixture of diastereoisomers (determined by ^1H NMR of the crude reaction mixture). PTLC (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) afforded minor diastereoisomer **249a** as oil (R_f = 0.54, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$), yield 36% (0.0081 g, 0.024 mmol), and major diastereoisomer **249b** as oil (R_f = 0.46, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$), yield 46% (0.0103 g, 0.031 mmol). Compound **249a**: ^1H NMR (400 MHz, $CDCl_3$) (64:36 mixture of rotamers) δ 0.91 (s, 9H, major rotamer), 0.94 (s, 9H, minor rotamer), 1.58-2.8 (m, 10H), 3.21-3.69 (m, 4H), 7.62-7.68 (m, 2H), 8.16-8.22 (m, 2H), 8.32 (s, 1H, minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 21.8, 21.9, 27.6, 30.2, 33.4, 34.6, 34.7, 36.8, 37.7, 39.1, 40.8, 42.5, 44.1, 45.8, 48.9, 50.1, 75.6, 76.2, 123.6, 123.6, 125.5, 125.7, 146.8, 157.6, 164.0, 164.1; IR (neat) 2959, 2870, 1661, 1518, 1348, 733 cm^{-1}; HRMS calcd for $C_{19}H_{29}N_2O_3$ (M^+ + H) 333.2178, found 333.2159. Compound **249b**: ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 0.45 (s, 9H, minor rotamer), 0.55 (s, 9H, major rotamer), 0.96-1.02 (m, 1H), 1.48-2.44 (m, 9H), 3.26-3.43 (m, 2H), 3.46-3.58 (m, 1H), 3.61-3.71 (m, 1H, minor rotamer), 3.83 (td, J = 4.3, 13.8 Hz, 1H, major rotamer), 7.66-7.73 (m, 2H), 8.16-8.20 (m, 2H), 8.22 (s, 1H, minor rotamer), 8.29 (s, 1H, major rotamer); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 20.2, 20.8,

27.3, 27.5, 29.7, 31.2, 32.0, 33.2, 34.1, 34.3, 39.4, 39.6, 40.9, 42.6, 42.9, 43.7, 47.7, 48.8, 123.3, 126.7, 127.0, 146.9, 155.9, 156.0, 163.9, 164.5; IR (neat) 2961, 2872, 1659, 1518, 1349, 1076, 912, 856, 733 cm^{-1}; HRMS calcd for $C_{19}H_{28}N_2O_3Na$ (M^+ + Na) 355.1997, found 355.2019.

Reduction of Lactam 34. Representative entries from Table 15. Entry 2: According to the general procedure amide **34** (0.0205 g, 0.065 mmol, 1.0 equiv) was reacted with $NaBH_4$ (0.0074 g, 0.20 mmol, 3.0 equiv) in MeOH (3 mL) for 20 h at rt. Analysis of the reaction mixture by ^1H NMR indicated 32% conversion to the aminal **238**, dr = 86:14.

Entry 3: To a solution of amide **34** (0.0150 g, 0.053 mmol, 1.0 equiv) in EtOH (10 mL), $CeCl_3$ (0.019 g, 0.053 mmol, 1.0 equiv) was added, followed by $NaBH_4$ (0.006 g, 0.16 mmol, 3.0 equiv), and the resulting mixture was stirred at rt for 24 h. Analysis of the crude reaction mixture by ^1H NMR indicated 31% conversion to the aminal **238**, dr = 81:19.

Entry 4: According to the general procedure amide **34** (0.0150 g, 0.053 mmol, 1.0 equiv) was reacted with $LiBH_4$ (0.0037 g, 0.16 mmol, 3.0 equiv) in EOH (10 mL) for 20 h at rt, to afford aminal **238**, yield 94% (0.0143 g, 0.050 mmol), dr = 82:18.

Entry 5: To a solution of amide **34** (0.0150 g, 0.053 mmol, 1.0 equiv) in THF (5 mL), $LiAl(O\mathit{t}Bu)_3H$ (0.068 g, 0.26 mmol, 5.0 equiv) was added at rt, and the reaction mixture was stirred at rt for 24 h. After aqueous work-up, analysis of the crude reaction mixture indicated only the presence of the starting material.

Entry 6: To a solution of amide **34** (0.0150 g, 0.053 mmol, 1.0 equiv) in THF (5 mL), L-Selectride (1.0 M in THF, 0.26 mL 0.26 mmol, 5.0 equiv) was added at rt, and the reaction mixture was stirred at rt for 24 h. After aqueous work-up, analysis of the crude reaction mixture indicated only the presence of the starting material.

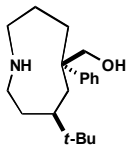
Entry 7: To a solution of amide **34** (0.0150 g, 0.053 mmol, 1.0 equiv) in Et_2O (5 mL), $LiAlH_4$ (1.0 M in Et_2O, 0.16 mL, 0.16 mmol, 3.0 equiv) was added at 0 °C, and the reaction mixture was stirred at rt for 5 h. Fieser and Fieser work-up, followed by chromatography afforded **238**, yield 99% (0.0150 g, 0.052 mmol), dr = 82:18.

Entry 8: To a solution of amide **34** (0.0181 g, 0.064 mmol, 1.0 equiv) in toluene (5 mL), Red-Al (65% in toluene, 0.10 mL, 0.31 mmol, 5.0 equiv) was added at rt, and the reaction mixture was heated to reflux for 2 h. Fieser and Fieser work-up, followed by chromatography afforded **238**, yield 96% (0.0177 g, 0.062 mmol), dr = 80:20.

Entry 9: To a solution of amide **34** (0.0150 g, 0.053 mmol, 1.0 equiv) in toluene (5 mL), DIBAL-H (1.0 M in toluene, 0.26 mL, 0.26 mmol, 5.0 equiv) was added at rt, and the reaction mixture was heated to reflux for 2 h. Fieser and Fieser work-up, followed by chromatography afforded **238**, yield 97% (0.0147 g, 0.051 mmol), dr = 81:19.

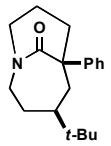
Entry 10: To a solution of amide **34** (0.040 g, 0.14 mmol, 1.0 equiv) in THF (10 mL), BH_3•Me_2S (2.0 M in THF, 0.35 mL, 0.70 mmol, 5.0 equiv) was added at rt, and the reaction mixture was heated to reflux for 24 h. The reaction was quenched with water, extracted with CH_2Cl_2, washed with brine, dried and concentrated.

Chromatography afforded **238**, yield 47% (0.0187 g, 0.065 mmol), dr = 74:26. The remaining mass balance consisted of an unidentified compound (0.0209 g, possibly polymer, R_f = 0.83, 1/4 EtOAc/hexanes).

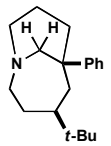


((7R)-7-*tert*-Butyl-5-phenylazonan-5-yl)methanol (250). To a solution of amide **34** (0.0150 g, 0.05 mmol, 1.0 equiv) in THF (10 mL), LiEt3BH (1.0 M in THF, 0.26 mL, 0.26 mmol, 5.0 equiv) was added dropwise at rt, and the resulting mixture was stirred for 3 h at rt. Aqueous work-up (quench with water, extraction with CH_2Cl_2), followed by chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) afforded aminal **238** (R_f = 0.45, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 38% (0.0055 g, 0.019 mmol), and alcohol **250** (R_f = 0.13, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 54% (0.0078 g, 0.027 mmol). Compound **250**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.40 (s, 9H), 1.25-1.99 (m, 10H), 2.56 (d, *J* = 13.9 Hz, 1H), 2.65-2.90 (m, 4H), 3.54 (d, *J* = 11.4 Hz, 1H), 3.78 (dd, *J* = 1.4, 11.3 Hz, 1H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.27 (t, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 23.3, 27.2, 34.2, 34.6, 37.7, 38.8, 47.2, 47.4, 47.8, 68.4, 126.3, 127.5, 128.6, 145.4; IR (neat) 3350, 2947, 2870, 1557, 1487, 1445, 1366, 1034, 911 cm^{-1}; HRMS calcd for $C_{19}H_{32}NO$ (M^+ + H) 290.2484, found 290.2462. Note: a number of other reductants were also tried with lactam **34** (Bu_3SnH/SiO_2, Ph_3SiH, $NaBH_4/BF_3$, $NaBH_4/TiCl_4$, $NaCNBH_3$), however no reaction or complex reactions mixtures were obtained.

Attempted reduction of lactam 93. According to the general procedure, amide **93** (0.0383 g, 0.18 mmol, 1.0 equiv) was reacted with $NaBH_4$ (0.0205 g, 0.54 mmol, 3.0 equiv) in EtOH (10 mL) at rt for 18 h. Analysis of the crude reaction by NMR indicated only the presence of the starting material.

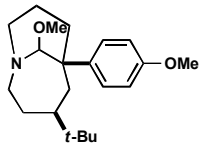


Lactam 34 by Oxidation of 238. To a solution of alcohol **238** (0.0150 g, 0.052 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) containing some MS 4Å, NMO (0.0122 g, 0.104 mmol, 2.0 equiv) and TPAP (0.004 g, 0.01 mmol, 0.2 equiv) were added, and the resulting mixture was stirred at rt for 2 h. After solvent removal, chromatography (1/4 EtOAc/hexanes) afforded the title lactam. Yield 91% (0.0135 g, 0.047 mmol). Spectroscopic properties matched those previously described.



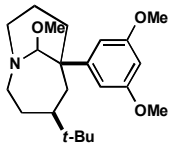
(4R,6R)-4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decane (251). To a solution of aminal **238** (0.0252 g, 0.088 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) TFA (1.0 mL, excess) was added at rt, followed by Et_3SiH (0.014 mL, 10 equiv) after 15 min. The reaction mixture was warmed stirred at rt for 12 days. Quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (1 x 20 mL), dried,

and concentrated. Chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) afforded the title product as oil (R_f = 0.33, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 73% (0.0174 g, 0.064 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.25-1.36 (m, 1H), 1.42-1.61 (m, 2H), 1.70 (t, *J* = 12.4 Hz, 1H), 1.78-2.01 (m, 3H), 2.04-2.16 (m, 1H), 2.30 (d, *J* = 13.0 Hz, 1H), 2.61 (td, *J* = 3.6, 13.4 Hz, 1H), 2.91 (d, *J* = 7.2 Hz, 2H), 3.04 (d, *J* = 14.2 Hz, 1H), 3.61-3.72 (m, 2H), 7.18-7.24 (m, 1H), 7.31-7.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 27.5, 30.0, 33.8, 36.1, 37.4, 46.8, 48.3, 53.3, 54.1, 54.2, 124.6, 125.8, 128.3, 151.9; IR (neat) 3056, 2944, 2917, 2849, 1576, 1540, 1470, 1366, 1100, 1036, 992 cm^{-1}; HRMS calcd for $C_{19}H_{30}N$ (M^+ + H) 272.2378, found 272.2373.



(4R,6R)-4-*tert*-Butyl-10-methoxy-6-(4-methoxyphenyl)-1-azabicyclo[4.3.1] decane (252). To a solution of aminal **239** (0.0280 g, 0.088 mmol, 1.0 equiv) in MeOH (5 mL), *p*TsOH (0.020 g, 0.11 mmol, 1.2 equiv) was added and the reaction mixture was stirred at rt. After 5 h 1.2 equiv of *p*TsOH was added, and the reaction was stirred for the next 19 h. The reaction was quenched with sat. $NaHCO_3$, solvent was removed under reduced pressure, the aqueous layer was extracted with Et_2O (3 x 30 mL), dried and concentrated. Chromatography (100% EtOAc) afforded the title product as oil (R_f = 0.90, EtOAc, R_f = 0.63, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 76% (0.0221 g, 0.067 mmol). Single diastereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ

0.86 (s, 9H), 1.24-1.44 (m, 2H), 1.46-1.52 (m, 1H), 1.73-1.88 (m, 3H), 2.02-2.17 (m, 2H), 2.26-2.36 (m, 1H), 2.50 (dd, *J* = 4.7, 15.0 Hz, 1H), 2.73 (td, *J* = 5.6, 13.0 Hz, 1H), 3.12-3.24 (m, 1H), 3.19 (s, 3H), 3.67 (dd, *J* = 5.2, 13.6 Hz, 1H), 3.81 (s, 3H), 4.41 (s, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 27.6, 31.1, 31.4, 33.7, 42.1, 45.2, 47.4, 48.1, 53.9, 54.0, 55.2, 90.7, 113.3, 126.0, 143.6, 156.8; IR (neat) 2914, 2866, 1512, 1251, 1186, 1086 cm^{-1}; HRMS calcd for $C_{21}H_{34}NO_2$ (M^+ + H) 332.2590, found 332.2585.

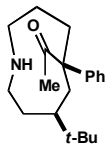


(4R,6R)-4-*tert*-Butyl-6-(3,5-dimethoxyphenyl)-10-methoxy-1-azabicyclo [4.3.1] decane (253). According to the procedure described above, the reaction of the corresponding aminal **240** (0.0416 g, 0.12 mmol, 1.0 equiv) and pTsOH (0.0227 g, 0.12 mmol, 1.0 equiv) in MeOH (10 mL) at rt for 36 h, afforded after chromatography (EtOAc) the title product as oil (R_f = 0.72, EtOAc, R_f = 0.78, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$), yield 67% (0.0290 g, 0.080 mmol). Single diastereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 9H), 1.26-1.51 (m, 3H), 1.74-1.88 (m, 3H), 1.99-2.13 (m, 2H), 2.24-2.35 (m, 1H), 2.49 (dd, *J* = 5.0, 14.4 Hz, 1H), 2.71 (td, *J* = 5.7, 13.4 Hz, 1H), 3.18 (td, *J* = 4.2, 13.3 Hz, 1H), 3.20 (s, 3H), 3.62-3.69 (m, 1H), 3.82 (s, 6H), 6.31 (t, J = 2.0 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 27.6, 31.1, 31.4, 33.8, 42.9, 45.1, 47.4, 47.6, 53.9, 54.0,

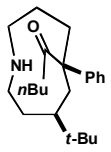
55.2, 90.7, 96.4, 104.2, 154.0, 160.2; IR (neat) 2941, 2866, 1595, 1456, 1204, 1151, 1084 cm^{-1}; HRMS calcd for $C_{22}H_{36}NO_3$ (M^+ + H) 362.2695, found 362.2694.

Epimerization of aminal 238. A reference spectrum of **238** in DMSO-d_6 indicated dr = 76:24 favoring the same diastereoisomer as in $CDCl_3$. A vial was charged with **238** (0.010 g, 0.025 mmol), DMSO-d_6 (0.30 mL), and DCl (1.0 *N* in D_2O, 0.3 mL). The vial was heated with a heat gun until a clear solution was obtained (~10-15 s). ^1H NMR indicated dr = 36:64 favoring the opposite epimer. The NMR tube was heated with heat gun for ~5 min. NMR indicated no change in dr. DCl (1.0 *N* in D_2O, 0.1 mL) was added directly to the NMR tube, and the reaction was heated with a heat gun for ~ 1 min. NMR indicated no change in the dr. Note: a similar change in dr (from 71:29 to 38:62) was observed when CD_3CN was used as a solvent.

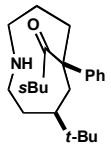
General procedure for Organometallic Addition to Bridged Amides: To a solution of bridged amide (1.0 equiv) in Et_2O at -78 °C, organometallic reagent (3.0 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h, allowed to warm slowly to rt, quenched after next 2 h with water (10 mL) (overall 3 h reaction time), extracted with ether (3 x 50 mL), washed with brine (1 x 10 ml) and dried. Chromatography ($MeOH/CH_2Cl_2$) afforded the final products.



1-((5R,7R)-7-*tert*-Butyl-5-phenylazonan-5-yl)ethanone (254). According to the general procedure, the reaction of **34** (0.0100 g, 0.035 mmol, 1.0 equiv) and MeLi (1.6 M in Et_2O, 0.070 mL, 0.11 mmol, 3.0 equiv) in Et_2O (5.0 mL), afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.31-0.62, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 89% (0.0094 g, 0.031 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38 (s, (9H), 1.38-1.99 (m, 9H), 1.91 (s, 3H), 2.18 (dd, *J* = 3.8, 12.7 Hz, 1H), 2.68-2.96 (m, 4H), 7.18-7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 24.0, 26.4, 27.4, 33.4, 33.8, 34.0, 37.6, 43.3, 46.4, 60.5, 126.8, 127.6, 128.5, 144.1, 211.7; IR (neat) 2947, 2868, 1701, 1477, 1364, 1169, 1144 cm^{-1}; HRMS calcd for $C_{20}H_{32}NO$ (M^+ + H) 302.2484, found 302.2474. Note: the reaction of **34** (0.0100 g, 0.035 mmol, 1.0 equiv) and MeLi•LiBr (1.5 M, Et_2O, 0.070 mL, 0.11 mmol, 3.0 equiv) in Et_2O (5 mL) afforded **254** in 85% yield (0.0090 g, 0.030 mmol). Resubmission of **254** (0.0094 g, 0.031 mmol) to the reaction with MeLi (1.6 M, Et_2O, 0.06 mL, 3.0 equiv) in Et_2O (10 mL) for 3 h led to quantitative recovery of **254**, suggesting that the further addition does not occur due to the steric hindrance around the ketone. Note: the reaction of **34** (0.010 g, 0.035 mmol, 1.0 equiv) and MeMgI (3.0 M in Et_2O, 0.035 mL, 0.11 mmol, 3.0 equiv) in Et_2O (10 mL) for 24 h, afforded **254** in 73% yield (0.0077 g, 0.026 mmol).

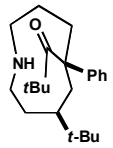


1-((5R,7R)-7-*tert*-Butyl-5-phenylazonan-5-yl)pentan-1-one (255). According to the general procedure, the reaction of **34** (0.0200 g, 0.070 mmol, 1.0 equiv) and *n*BuLi (2.3 M in hexanes, 0.090 mL, 0.21 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.73, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 83% (0.0200 g, 0.058 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.40 (s, 9H), 0.80 (t, *J* = 7.3 Hz, 3H), 1.09-1.22 (m, 2H), 1.26-1.35 (m, 1H), 1.37-1.58 (m, 5H),1.64 (d, *J* = 16.0 Hz, 1H), 1.72-1.84 (m, 1H), 1.98-2.10 (m, 1H), 2.11-28 (m, 4H), 2.69-2.95 (m, 5H), 7.18-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.3, 22.4, 24.0, 26.8, 27.3, 33.3, 34.0, 34.1, 37.5, 37.9, 43.4, 46.4, 60.3, 126.8, 127.7, 128.5, 144.1, 213.7; IR (neat) 3369, 2955, 2870, 1701, 1474, 1364, 1130, 702 cm^{-1}; HRMS calcd for $C_{23}H_{38}NO$ (M^+ + H) 344.2954, found 344.2944.

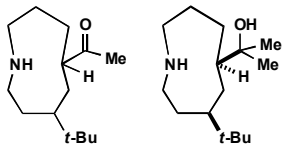


1-((5R,7R)-7-*tert*-Butyl-5-phenylazonan-5-yl)-2-methylbutan-1-one (256). According to the general procedure, the reaction of **34** (0.0200 g, 0.070 mmol, 1.0 equiv) and *sec*-BuLi (1.4 M in cyclohexane, 0.15 mL, 0.21 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.54, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 93% (0.0223 g, 0.065 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.44, 0.46 (s, 9H), 0.59 (t, *J* = 7.5 Hz, 1H), 0.78-0.85 (m, 3H), 0.99 (d, *J* = 6.7 Hz, 2H), 1.19-1.68 (m, 7H), 1.70-1.81 (m,

2H), 2.01-2.13 (m, 1H), 2.28-2.41 (m, 2H), 2.64-2.93 (m, 4H), 2.97-3.09 (m, 1H), 7.18-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 11.3, 11.4, 17.6, 18.5, 23.1, 23.9, 24.2, 27.3, 27.4, 27.5, 28.4, 34.2, 34.3, 35.6, 35.9, 37.5, 37.7, 42.7, 43.1, 46.3, 46.4, 47.4, 60.8, 60.9, 126.8, 126.8, 128.1, 128.2, 128.3, 128.3, 142.9, 143.1, 217.7, 217.8; IR (neat) 3373, 2961, 2873, 1699, 1464, 1366, 1148, 1013, 733, 702 cm^{-1}; HRMS calcd for $C_{23}H_{38}NO$ (M^+ + H) 344.2954, found 344.2939.

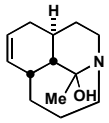


1-((5R,7R)-7-*tert*-Butyl-5-phenylazonan-5-yl)-2,2-dimethylpropan-1-one (257). According to the general procedure, the reaction of **34** (0.0200 g, 0.070 mmol, 1.0 equiv) and *tert*-BuLi (1.7 M in pentanes, 0.12 mL, 0.21 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.37, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 80% (0.0192 g, 0.056 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.39 (s, 9H), 0.98 (s, 9H), 1.24-1.44 (m, 2H), 1.45-1.66 (m, 3H), 1.77-1.88 (m, 1H), 2.21-2.34 (m, 1H), 2.36 (dd, *J* = 5.2, 15.8 Hz, 1H), 2.75-3.04 (m, 6H), 7.18-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.5, 27.2, 30.3, 33.7, 34.2, 37.2, 38.0, 45.0, 46.1, 46.5, 61.0, 126.8, 127.9, 128.3, 143.4, 217.4; IR (neat) 3377, 2959, 2870, 1680, 1479, 1364, 1146, 1090, 1005, 910, 735, 704 cm^{-1}; HRMS calcd for $C_{23}H_{38}NO$ (M^+ + H) 344.2954, found 344.2924.

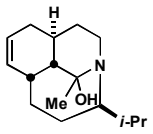


1-(7-*tert*-Butylazonan-5-yl)ethanone (258) and 2-((7R)-7-*tert*-Butylazonan-5-yl)propan-2-ol (259). According to the general procedure for addition of organometallic reagents, amide **3** (0.100 g, 0.48 mmol, 1.0 equiv) was reacted with MeLi (1.6 M in Et_2O, 0.90 mL, 1.44 mmol, 3.0 equiv) in Et_2O for 3 h, to afford after chromatography (1/5/95-1/10/90 NH_4OH/MeOH/CH_2Cl_2) ketone **258** (R_f = 0.25, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 81% (0.0875 g, 0.39 mmol), and alcohol **259** (R_f = 0.10, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 5% (0.0062 g, 0.026 mmol). Compound **258** exists as a mixture of ketone and enol tautomers stabilized by transannular interaction with the amine group. Compound **258**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (s, 9H), 1.03-1.75 (m, 9H), 1.82-1.95 (m, 1H), 2.04 (s, 3H), 2.41 (s, 1H), 2.55-2.92 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.8, 23.8, 27.6, 28.2, 28.6, 31.8, 32.2, 34.1, 34.3, 41.2, 43.8, 44.3, 45.0, 46.7, 48.7, 49.9, 53.1, 164.0, 164.6, 212.9; IR (neat) 3369, 2947, 2868, 1709, 1477, 1364, 1231, 1163, 1140, 926 cm^{-1}; HRMS calcd for $C_{14}H_{28}NO$ (M^+ + H) 226.2171, found 226.2177. Compound **259**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 9H), 0.88-0.97 (m, 1H), 1.12 (s, 6H), 1.21-1.48 (m, 4H), 1.48-1.81 (m, 6H), 2.57-2.71 (m, 2H), 2.72-2.78 (m, 1H), 2.78-2.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.1, 27.2, 27.5, 27.6, 27.6, 30.6, 32.1, 35.1, 47.0, 47.9, 49.5, 50.9, 75.1; IR (neat) 3400, 2959, 2918, 1475, 1366, 1140, 913 cm^{-1}; HRMS calcd for $C_{15}H_{32}NO$ (M^+ + H) 242.2484, found 242.2514. Note: performing

the reaction for 1 h at -78 °C (quenching at -78 °C) or for 24 h (-78 °C to rt) did not change the ratio of **258** to **259**.

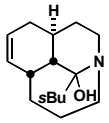


Aminal 261. According to the general procedure, the reaction of **230** (0.0189 g, 0.099 mmol, 1.0 equiv) and MeLi (1.6 M in Et_2O, 0.20 mL, 0.30 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as solid (Mp = 107-108 °C, R_f = 0.10, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 95% (0.0194 g, 0.094 mmol), dr > 10:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-1.41 (m, 2H), 1.52 (s, 3H), 1.64-1.82 (m, 3H), 1.84-1.95 (m, 2H), 1.96-2.11 (m, 2H), 2.35 (q, *J* = 14.4 Hz, 1H), 2.40-2.48 (m, 1H), 2.54-2.77 (m, 2H), 2.86 (s, 1H), 3.05 (t, *J* = 13.5 Hz, 1H), 3.34-3.50 (m, 1H), 5.65 (s, 1H), 5.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4, 25.8, 27.3, 31.4, 34.7, 34.9, 35.3, 49.4, 51.8, 52.6, 86.5, 127.6, 134.9; IR (neat) 3350, 3011, 2949, 2914, 2866, 1462, 1447, 1369, 1292, 1163, 1134, 1018, 924, 731, 708 cm^{-1} Note: ketone peak not detected; HRMS calcd for $C_{13}H_{22}NO$ (M^+ + H) 208.1701, found 208.1706.



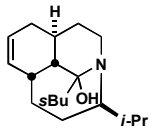
Aminal 262. According to the general procedure, the reaction of **260** (0.0200 g, 0.086 mmol, 1.0 equiv) and MeLi (1.6 M in Et_2O, 0.17 mL, 0.26 mmol, 3.0 equiv)

in Et_2O (10 mL), afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title compound as oil (R_f = 0.20, 1/10/90 $NH_3/MeOH/CH_2Cl_2$). Yield 92% (0.0196 g, 0.079 mmol), dr > 10:1.^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68-0.93 (m, 6H), 1.26 (d, *J* = 13.8 Hz, 1H), 1.31-1.42 (m, 1H), 1.49 (s, 3H), 1.57 (m, 4H), 1.71-1.83 (m, 2H), 1.86-1.92 (m, 1H), 1.97 (dt, *J* = 4.0, 16.9 Hz, 1H), 2.22-2.43 (m, 2H), 2.54-2.66 (m, 2H), 2.69-2.78 (m, 1H), 3.22-3.33 (m, 1H), 5.47 (s, 1H), 5.75 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 19.3, 24.9, 26.5, 28.5, 32.9, 34.5, 35.5, 35.8, 49.6, 50.2, 73.5, 86.1, 125.4, 135.6; IR (neat) 3589, 3460, 3011, 2951, 2914, 1968, 1713 (w), 1632, 1464, 1371, 1219, 1169, 1113, 1055, 943, 703 cm^{-1} Note: CO absorption < 1:10 of the expected intensity; HRMS calcd for $C_{16}H_{28}NO$ (M^+ + H) 250.2171, found 250.2164.

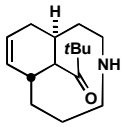


Aminal 263. According to the general procedure, the reaction of **230** (0.0164 g, 0.086 mmol, 1.0 equiv) and *sec*-BuLi (1.4 M in cyclohexane, 0.18 mL, 0.26 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title compound as oil (R_f = 0.57, 1/10/90 $NH_3/MeOH/CH_2Cl_2$). Yield 80% (0.0172 g, 0.069 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78-2.25 (m, 19H), 2.31-2.52 (m, 2H), 2.582-.67 (m, 2H), 2.702-.85 (m, 1H), 3.38-3.46 (m, 1H), 5.48-5.67 (m, 2H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.7, 11.4, 11.8, 13.6, 20.7, 23.7, 23.7, 24.4, 25.1, 25.2, 33.3, 33.4, 33.9, 34.3, 34.4, 37.5, 37.9,

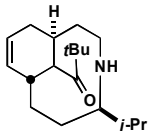
48.6, 48.7, 50.5, 50.6, 88.2, 88.4, 126.4, 134.1, 134.1 IR (neat) 3591, 3450, 3013, 2963, 2916, 2870, 1653, 1540, 1456, 1379, 1292, 1259, 1113, 1057, 1021, 912, 802, 744 cm^{-1} Note: ketone peak not detected; HRMS calcd for $C_{16}H_{28}NO$ (M^+ + H) 250.2171, found 250.2185.



Aminal 264. According to the general procedure, the reaction of **260** (0.0200 g, 0.086 mmol, 1.0 equiv) and *sec*-BuLi (1.4 M in cyclohexane, 0.18 mL, 0.26 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.26, 1/1 EtOAc/hexanes). Yield 88% (0.0219 g, 0.075 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 0.82-1.07 (m, 12H), 1.21-1.46 (m, 3H), 1.58-1.86 (m, 6H), 1.92-2.17 (m, 4H), 2.26-2.38 (m, 1H), 2.47 (q, *J* = 13.6 Hz, 1H), 2.53-2.62 (m, 1H), 2.68-2.82 (m, 2H), 3.06-3.19 (m, 1H), 5.51-5.58 (m, 1H), 5.84-5.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (mixture of rotamers) δ 13.2, 13.3, 14.1, 18.4, 18.5, 18.8, 19.0, 23.4, 24.2, 26.1, 26.3, 27.8, 28.1, 28.5, 32.8, 35.2, 35.3, 35.5, 35.6, 35.7, 44.3, 44.5, 45.8, 49.7, 49.8, 73.2, 88.2, 88.4, 125.3, 136.1; IR (neat) 3595, 3013, 3959, 3013, 2959, 2870, 2829, 1705 (vw), 1634, 1464, 1381, 1258, 1163, 1107, 1061, 1011, 808, 704 cm^{-1} Note: CO absorption < 1:10 of the expected intensity; HRMS calcd for $C_{19}H_{34}NO$ (M^+ + H) 292.2641, found 292.2642.

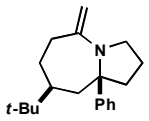


1-((1S,8R)-4-Azabicyclo[6.3.1]dodec-9-en-12-yl)-2,2-dimethylpropan-1-one (265). According to the general procedure, the reaction of **230** (0.0200 g, 0.105 mmol, 1.0 equiv) and *tert*-BuLi (1.7 M in pentanes, 0.18 mL, 0.31 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.14, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 90% (0.0235 g, 0.094 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 1.17-1.34 (m, 3H), 1.56-1.68 (m, 1H), 1.72-1.96 (m, 4H), 2.07-2.17 (m, 1H), 2.46 (s, 1H), 2.67-2.84 (m, 2H), 2.89-2.97 (m, 1H), 3.18-3.27 (m, 2H), 3.36-3.46 (m, 1H), 5.51-5.58 (m, 1H), 5.85-5.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of ketone and enol tautomers) δ 26.4, 28.8, 29.2, 29.6, 30.6, 38.6, 42.5, 45.6, 49.9, 50.8, 52.6, 130.7, 132.5, 218.5; IR (neat) 3391, 3015, 2951, 2918, 2868, 1705, 1541, 1477, 1441, 1389, 1364, 1317, 1099, 916, 735 cm^{-1}; HRMS calcd for $C_{16}H_{28}NO$ (M^+ + H) 250.2171, found 250.2175. Note: after chromatography partial closure to the hemiaminal occur (^{13}C NMR, δ 81.4 ppm).



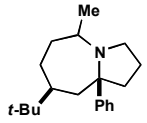
1-((1S,5R,8R)-5-Isopropyl-4-azabicyclo[6.3.1]dodec-9-en-12-yl)-2,2-dimethyl propan-1-one (266). According to the general procedure, the reaction of **260** (0.0200 g, 0.086 mmol, 1.0 equiv) and *tert*-BuLi (1.7 M in pentanes, 0.15 mL,

0.26 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title compound as oil (R_f = 0.27, 1/10/90 $NH_3/MeOH/CH_2Cl_2$). Yield 90% (0.0226 g, 0.078 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 0.88-0.98 (m, 6H), 1.13 (s, 9H), 1.21-1.37 (m, 3H), 1.52-1.81 (m, 3H), 1.86-2.29 (M, 5H), 2.31-2.80 (m, 4H), 3.16-3.32 (m, 1H), 5.57-5.71 (m, 1H), 5.82-5.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (mixture of slowly equilibrating ketone and enol tautomers) δ 19.9, 21.4, 21.7, 24.7, 26.0, 26.1, 26.4, 28.8, 29.7, 30.2, 30.9, 32.5, 34.0, 36.6, 37.2, 38.8, 40.9, 43.1, 43.2, 45.7, 46.0, 50.9, 52.8, 130.4, 131.2, 132.7, 132.9, 219.2, 220.5; IR (neat) 3597, 3375, 3013, 2955, 2924, 2868, 1697, 1626, 1466, 1387, 1366, 1261, 1099, 910, 804 cm^{-1}; HRMS calcd for $C_{19}H_{34}NO$ (M^+ + H) 292.2641, found 292.2636. Note: a similar keto-enol equilibration was observed in analogous 9-membered heterocycle **258**, in which α-position to the ketone is unsubstituted. We think that this effect arises from a transannular interaction of the amino group with the enol. Further investigation will be necessary to confirm this effect.



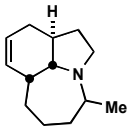
(8S,9aR)-8-*tert*-Butyl-5-methylene-9a-phenyloctahydro-1H-pyrrolo[1,2-a] azepine (268). According to the general procedure, the reaction of planar amide **267** (0.0200 g, 0.070 mmol, 1.0 equiv) and MeLi•LiBr (1.5 M in Et_2O, 0.14 mL, 0.21 mmol, 3.0 equiv) in Et_2O (5 mL) for 18 h, afforded after chromatography (1/15/85

$NH_4OH/MeOH/CH_2Cl_2$) the title product as oil (R_f = 0.28, $NH_4OH/MeOH/CH_2Cl_2$), yield 71% (0.0141 g, 0.050 mmol). ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (s, 9H), 1.12-1.78 (m, 7H), 1.85-2.35 (m, 5H), 2.84-3.61 (m, 3H), 7.02-7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 27.2, 27.7, 29.3, 31.7, 32.6, 39.8, 41.0, 43.3, 49.2, 69.1, 74.5, 125.1, 126.1, 126.7, 128.1, 150.6, 151.8; IR (neat) 2959, 2866, 1632, 1445, 1366, 731, 702 cm^{-1}; HRMS calcd for $C_{20}H_{30}N$ (M^+ + H) 283.2378, found 283.2373. Note: the reaction was much slower than with the bridged analogue of **268**. The structure of enamine was confirmed by reduction under acidic conditions (see below). The analogous reaction using *n*BuLi (3.0 equiv, 18 h) instead of MeLi led to a mixture of products, including starting material, ketone (as the major product), enamine, and alcohol.



(8S,9aR)-8-*tert*-Butyl-5-methyl-9a-phenyloctahydro-1H-pyrrolo[1,2-a] azepine (269). To a solution of enamine **268** (0.0121 g, 0.043 mmol, 1.0 equiv) in THF (5 mL), $NaBH_4$ (0.005 g, 0.13 mmol, 5.0 equiv), followed by AcOH (0.05 mL, 0.86 mmol, 20 equiv) was added at rt, and the resulting mixture was stirred at rt for 5 h. The reaction was diluted with ether (15 mL), quenched with sat. $NaHCO_3$, washed with brine, dried and concentrated. Chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) afforded the title product as oil (R_f = 0.65, $NH_4OH/MeOH/CH_2Cl_2$, R_f = 0. 32, 1/10 EtOAc/hexanes), yield 83% (0.0102 g,

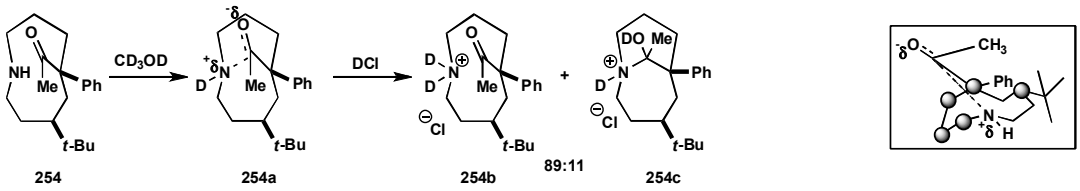
0.036 mmol). 4:1 mixture of diastereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$) (major isomer) δ 0.84 (s, 9H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.10-1.73 (m, 9H), 1.82 (dd, *J* = 6.4, 12.2 Hz, 1H), 1.96-2.09 (m, 1H), 2.42 (d, *J* = 14.4 Hz, 1H), 2.89-3.06 (m, 2H), 7.04-7.40 (m, 5H); ^{1}H NMR (400 MHz, $CDCl_3$) (minor isomer, diagnostic peaks) δ 0.86 (s, 9H), 7.50 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 23.2, 27.7, 29.7, 29.7, 31.5, 33.7, 40.6, 44.0, 45.2, 45.3, 50.7, 67.3, 125.3, 126.2, 127.7, 153.2; IR (neat) 2859, 2868, 1636, 1558, 1445, 1366, 910 cm^{-1}; HRMS calcd for $C_{20}H_{30}N$ (M^+ + H) 286.2535, found 286.2523.



Amine **274**. According to the general procedure, the planar tricyclic amide **270** (0.080 g, 0.43 mmol, 1.0 equiv) was reacted with MeLi•LiBr (1.5 M in Et_2O, 0.84 mL, 1.26 mmol, 3.0 equiv) in Et_2O (10 mL) for 18 h. Analysis of the crude reaction mixture indicated presence of enamine **271**, ketone **272** and alcohol **273** in 3:1:1 ratio as judged by ^{1}H NMR. Due to the very similar and high polarity the products could not be separated at this stage. Compound **271**: ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 26.4, 28.7, 29.9, 31.2, 37.1, 38.3, 47.4, 64.2, 74.7, 126.0, 131.5, 151.8; HRMS calcd for $C_{13}H_{20}N$ (M^+ + H) 190.1596, found 190.1597. Compounds **272** and **273**: ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.7, 29.0, 29.3, 29.9, 31.0, 32.2, 35.7, 38.0, 38.1, 44.0, 44.1, 44.8, 63.6, 63.7, 70.8, 126.8, 127.1, 130.5, 130.9, 209.0; HRMS calcd for $C_{13}H_{20}NO$ (M^+ + H) 208.1701, found 208.1734; HRMS calcd for

$C_{14}H_{26}NO$ (M^+ + H) 224.2014, found 224.2036. IR (neat) 3339, 3017, 2920, 2868, 1715, 1613, 1408, 1356, 1161 cm^{-1}. The above crude reaction mixture was subjected to the reduction under acidic conditions as described above for bicyclic enamine, using $NaBH_4$ (0.080 g, 2.1 mmol, 5.0 equiv), AcOH (0.48 mL, 8.4 mmol, 20 equiv) in THF (10 mL) for 5 h at rt. Chromatography (1/4 EtOAc/hexanes) afforded **274** as oil (R_f = 0.82, 1/4 EtOAc/hexanes), yield 34% (2 steps, 0.0271 g, 0.14 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.18-2.22 (m, 10 H, 1.35 (d, *J* = 6.8 Hz, 3H), 2.33 (dt, *J* = 4.5, 17.4 Hz, 1H), 2.65 (s, 1H), 2.86-3.08 (m, 2H), 3.14-3.26 (m, 1H), 3.87 (dd, *J* = 4.0, 13.2 Hz, 1H), 5.34-5.43 (m, 1H), 5.57-5.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 29.0, 30.7, 31.8, 32.8, 33.8, 35.3, 37.8, 54.9, 67.2, 79.2, 124.5, 132.8; IR (neat) 3019, 2920, 2851, 2352, 1450, 1383, 1196, 1163, 1084, 1013, 849 cm^{-1}; HRMS calcd for $C_{13}H_{22}N$ (M^+ + H) 192.1752, found 192.1763.

Transannular Interaction in Bicyclic System



254 254a 254b 254c

According to the general procedure for addition of organometallic reagents, amide **34** (0.0300 g, 0.105 mmol, 1.0 equiv) was reacted with MeLi•LiBr (1.5 M in Et_2O, 0.36 mL, 0.53 mmol, 5.0 equiv). After aqueous work-up, crude NMR ($CDCl_3$) indicated the presence of **254** as a single major product. Purification by chromatography (1/10/90 NH_3/MeOH/CH_2Cl_2) afforded **254** in 99% yield (0.0313 g,

0.104 mmol). ^{1}H NMR and ^{13}C NMR ($CDCl_3$, 0.75 mL, 1000 scans) were identical with the previously described for **254**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38 (s, (9H), 1.38-1.99 (m, 9H), 1.91 (s, 3H), 2.18 (dd, *J* = 3.8, 12.7 Hz, 1H), 2.68-2.96 (m, 4H), 7.18-7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 24.0, 26.4, 27.4, 33.4, 33.8, 34.0, 37.6, 43.3, 46.4, 60.5, 126.8, 127.6, 128.5, 144.1, 211.7; no change was observed in comparison with the crude spectra, indicating that purification on SiO_2 does not influence the interaction between the ketone and the amine groups.

The solvent was removed (rinsing with CH_2Cl_2), the sample dissolved in MeOD-*d*$_4$ (0.75 mL), and NMR spectra were recorded after ~3 min. Major changes were not observed in ^{1}H NMR, however ^{13}C NMR indicated significant broadening of 7 peaks; despite much longer acquisition time (23 700 scans) ketone peak was not detected. ^{1}H NMR (400 MHz, CD_3OD) δ 0.47 (s, 9H), 1.44 (s, 2H), 1.63 (d, *J* = 15.5 Hz, 3H), 1.78-1.92 (m, 1H), 1.83 (s, 3H), 2.20 (dd, *J* = 4.8, 15.6 Hz, 2H), 2.58 (d, *J* = 14.0 Hz, 1H), 2.71-2.84 (m, 2H), 2.84-3.02 (m, 2H), 7.19-7.38 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 20.3, 25.0 (br), 25.2, 26.5, 31.2, 33.5, 34.5 (br), 38.6 (br), 43.2 (br), 45.8, 58.7 (br), 126.6, 127.2, 128.3, 144.5 (br). 2D NMR correlations allowed for assignment of carbons corresponding to the broadened peaks, suggesting that the transannular interaction takes place over the western part of the amino ketone (box, shaded circles).

NMR tube was kept at rt. 24 h after dissolution of **254** in MeOD-*d*$_4$, ^{1}H NMR was identical to the described above, for t = 3 min. At this time, 0.75 mL of MeOD-*d*$_4$ was added to the NMR tube, and 1/2 of the resulting mixture was transferred to 5 mL

round bottom flask, evaporated to dryness, and dissolved in $CDCl_3$. NMR was identical to the described above for **254** in $CDCl_3$, indicating that the interaction is reversible. To the remaining part of **254a** in MeOD-d_4, 0.2 mL of 1.0 *N* DCl in D_2O was added, the NMR tube was wrapped in parafilm, and the reaction was mixed by turning the NMR tube upside down 5 times, followed by gentle shaking. NMR (recorded ~5 min after addition of acid) indicated 89:11 mixture of the protonated **254b** and hemiaminal **254c**. As expected, peaks were much sharper than in MeOD-d_4 indicating that this time the interaction does not occur; ^{13}C NMR (4000 scans) showed a sharp ketone peak at 213.4 ppm, and a hemiaminal peak at 94.0 ppm. The ratio of **254b** to **254c** did not change after the next 24 h.

Protonated **254b.** ^1H NMR (400 MHz, CD_3OD) δ 0.42 (s, 9H), 1.31 (s, 1H), 1.52-1.73 (m, 2H), 1.78 (d, *J* = 16.2, 1H), 1.92-2.05 (m, 1H), 1.98 (s, 3H), 2.14 (td, *J* = 5.1, 16.4 Hz, 1H), 2.40-2.49 (m, 2H), 3.19-3.41 (m, 5H), 7.20-7.42 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 17.7, 24.9, 25.6, 26.2, 28.6, 33.6, 33.8, 39.0, 42.3, 44.8, 59.9, 127.3, 127.4, 128.8, 142.3, 213.4. Aminal **254c.** ^1H NMR (400 MHz, CD_3OD) (diagnostic peaks) δ 0.89 (s, 9H), 1.87 (t, *J* = 11.5 Hz, 1H), 2.30-2.40 (m, 2H), 2.60-2.72 (m, 1H), 3.11-3.21 (m, 1H), 3.54 (td, *J* = 5.0, 14.1 Hz, 1H), 4.01-4.09 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 17.7, 24.4, 26.5, 27.0, 30.1, 33.5, 41.6, 45.2, 46.1, 50.0, 53.0, 94.1, 126.5, 127.3, 128.1, 147.1.

Note: a similar interaction does not occur upon dissolution of **254** in C_6D_6 and CD_3CN, however in DMSO-d_6 NMR showed formation of minor amounts of aminal

254c. Additionally, when more sterically hindered ketones **256** and **257** were treated with MeOD-d_4 the transannular interaction has not been observed.

Compound **254** in C_6D_6.^{1}H NMR (400 MHz, C_6D_6) δ 0.61 (s, 9H), 1.21 (s, 2H), 1.48 (s, 1H), 1.62-1.78 (m, 4H), 1.85 (s, 3H), 1.92 (d, J = 16.3 Hz, 1H), 2.38-2.72 (m, 5H), 3.10 (d, J = 11.6 Hz, 1H), 7.07-7.40 (m, 5H); ^{13}C NMR (100 MHz, C_6D_6) δ 21.4, 23.9, 25.9, 27.5, 33.7, 33.9, 34.5, 37.6, 43.3, 46.3, 60.5, 126.7, 144.8, 209.1.

Compound **254** in CD_3CN.^{1}H NMR (400 MHz, CD_3CN) δ 0.41 (s, 9H), 1.21-1.65 (m, 6H), 1.76 (s, 1H), 1.86 (s, 3H), 2.18-2.36 (m, 2H), 2.60-2.85 (m, 4H), 2.94-3.06 (m, 1H), 7.18-7.37 (m, 5H); ^{13}C NMR (100 MHz, CD_3CN) δ 21.4, 24.0, 25.6, 26.8, 33.4, 33.6, 34.3, 37.6, 43.7, 46.2, 60.4, 126.7, 127.6, 128.4, 144.5, 210.7.

Compound **254** in DMSO-d_6. Note: spectrum in DMSO-d_6 at rt showed 71:29 mixture of ketone to hemiaminal. ^{1}H NMR (400 MHz, DMSO-d_6) (diagnostic peaks) δ 0.34 (s, 9H), 1.41-1.52 (m, 2H), 1.84 (s, 3H), 2.06-2.14 (m, 1H), 2.93 (d, J = 12.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.5, 24.2, 26.5, 27.7, 34.1, 34.6, 37.6, 43.9, 45.7, 46.4, 60.4, 127.1, 127.7, 129.0, 144.4, 210.8. Aminal **254c**.^{1}H NMR (400 MHz, DMSO-d_6) (diagnostic peaks) δ 0.82 (s, 9H), 3.15 (t, J = 13.0 Hz, 1H), 3.67 (d, J = 12.6 Hz, 1H), 5.26 (s, 1H), 7.68 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (diagnostic peaks) δ 22.3, 27.9, 28.1, 31.4, 33.0, 33.5, 34.1, 41.7, 49.5, 51.6, 125.3, 127.7, 151.7.

Corey-Chaykovsky Reaction of Bridged Amides

Preparation of Spiro-epoxyamines. General procedure: Round-bottom flask was charged with NaH (60% dispersion in mineral oil) and DMSO was added dropwise at rt. After stirring for 20 min at rt, THF was added and the reaction mixture was cooled to 0 °C. Trimethylsulfonium iodide was added in DMSO, and after stirring for 10 min at 0 °C, twisted amide was added dropwise in THF/DMSO mixture at 0 °C. The reaction mixture was slowly warmed to rt over 4-6 h, and stirred at rt for the remaining time. The reaction was quenched with water (20 mL), extracted with EtOAc (3 x 50 mL), washed with brine (5 x 50 mL), dried, concentrated and chromatographed to afford the final products.

Concentration influence on the Corey-Chaykovsky reaction (Table 28). Entry 1: According to the general procedure, **34** (0.0200 g, 0.070 mmol, 1.0 equiv) was reacted with NaH (0.014 g, 0.35 mmol, 5.0 equiv), and sulfonium iodide (0.0295 g, 0.14 mmol, 2.0 equiv) in DMSO (3 mL, 1.5 mL and 2 mL) and THF (5 mL and 2 mL) (c_{total} = 0.005 M, c_{ylide} = 0.007 M, c_{amide} = 0.018 M) for 15 h. Analysis of the crude reaction mixture by ^{1}H NMR indicated 81% conversion.

Entry 2: According to the general procedure, the reaction of **34** (0.0200 g, 0.070 mmol, 1.0 equiv), NaH (0.0196 g, 0.49 mmol, 7.0 equiv), and sulfonium iodide (0.0368 g, 0.18 mmol, 2.5 equiv) in DMSO (3.0 mL, 2.0 mL, and 2.0 mL), and THF (5.0 mL and 3.0 mL) (c_{total} = 0.005 M, c_{ylide} = 0.007 M, c_{amide} = 0.014 M) for 17 h at

rt afforded after chromatography (1/3 EtOAc-hexanes) **275** in 75% yield (0.0157 g, 0.053 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated >95% conversion.

Entry 3. According to the general procedure, the reaction of **34** (0.0200 g, 0.070 mmol, 1.0 equiv), NaH (0.056 g, 1.40 mmol, 20.0 equiv), and sulfonium iodide (0.0736 g, 0.35 mmol, 5.0 equiv) in DMSO (3.0 mL, 1.5 mL, and 2.0 mL), and THF (5.0 mL and 2.0 mL) (c_{total} = 0.005 M, c_{ylide} = 0.007 M, c_{amide} = 0.018 M) for 24 h at rt afforded after chromatography (1/3 EtOAc-hexanes) **275** in 80% yield (0.0167 g, 0.056 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated >95% conversion.

Entry 4. According to the general procedure, **34** (0.0300 g, 0.105 mmol, 1.0 equiv) was reacted with NaH (0.0295 g, 0.74 mmol, 7.0 equiv), and sulfonium iodide (0.0552 g, 0.26 mmol, 2.5 equiv) in DMSO (3.0 mL, 2.0 mL, and 2.0 mL), and THF (5.0 mL and 3.0 mL) (c_{total} = 0.007 M, c_{ylide} = 0.011 M, c_{amide} = 0.021 M) for 18 h at rt. Analysis of the crude reaction mixture by ^{1}H NMR indicated only unidentified decomposition products.

Entry 5. According to the general procedure, **34** (0.0300 g, 0.105 mmol, 1.0 equiv) was reacted with NaH (0.0295 g, 0.74 mmol, 7.0 equiv), and sulfonium iodide (0.0552 g, 0.26 mmol, 2.5 equiv) in DMSO (5.0 mL, 2.5 mL, and 2.0 mL), and THF (10.0 mL and 3.0 mL) (c_{total} = 0.005 M, c_{ylide} = 0.006 M, c_{amide} = 0.021 M) for 18 h at rt to afford after chromatography (1/3 hexanes/EtOAc) **275** in 53% yield (0.0276 g,

0.092 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated >95% conversion.

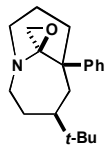
Entry 6. According to the general procedure, **34** (0.0300 g, 0.105 mmol, 1.0 equiv) was reacted with NaH (0.0295 g, 0.74 mmol, 7.0 equiv), and sulfonium iodide (0.0552 g, 0.26 mmol, 2.5 equiv) in DMSO (5.0 mL, 2.5 mL, and 2.0 mL), and THF (10.0 mL and 6.0 mL) (c_{total} = 0.004 M, c_{ylide} = 0.006 M, c_{amide} = 0.013 M) for 18 h at rt to afford after chromatography (1/3 hexanes/EtOAc) **275** in 73% yield (0.0230 g, 0.077 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated >95% conversion.

Entry 7. According to the general procedure, **34** (0.0500 g, 0.175 mmol, 1.0 equiv) was reacted with NaH (0.0491 g, 1.23 mmol, 7.0 equiv), and sulfonium iodide (0.0920 g, 0.44 mmol, 2.5 equiv) in DMSO (6.0 mL, 2.5 mL, and 2.0 mL), and THF (10.0 mL and 11.0 mL) (c_{total} = 0.0050 M, c_{ylide} = 0.0095 M, c_{amide} = 0.013 M) for 18 h at rt to afford after chromatography (1/3 hexanes/EtOAc) **275** in 78% yield (0.0408 g, 0.137 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated >95% conversion.

Entry 8. According to the general procedure, **34** (0.0300 g, 0.105 mmol, 1.0 equiv) was reacted with NaH (0.0295 g, 0.74 mmol, 7.0 equiv), and sulfonium iodide (0.0552 g, 0.26 mmol, 2.5 equiv) in DMSO (5.0 mL, 2.0 mL, and 2.0 mL), and THF (20.0 mL and 3.0 mL) (c_{total} = 0.003 M, c_{ylide} = 0.003 M, c_{amide} = 0.021 M) for 18 h at rt to afford after chromatography (1/3 hexanes/EtOAc) **275** in 88% yield (0.0276 g,

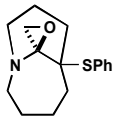
0.092 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated >95% conversion.

Reaction rate: According to the general procedure, **34** (0.0300 g, 0.105 mmol, 1.0 equiv) was reacted with NaH (0.0295 g, 0.74 mmol, 7.0 equiv), and sulfonium iodide (0.0552 g, 0.26 mmol, 2.5 equiv) in DMSO (5.0 mL, 2.5 mL, and 2.0 mL), and THF (10.0 mL and 6.0 mL) (c_{total} = 0.004 M, c_{ylide} = 0.006 M, c_{amide} = 0.013 M). 3.0 mL aliquots were taken, and analyzed by ^{1}H NMR after aqueous work-up, indicated as follows: 5.9% conversion 10 min after the start of the reaction, 7.1% conversion after 30 min, 12.4% conversion after 2 h, 63% conversion after 6.5 h, 87% conversion after 18 h.



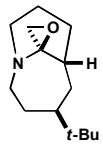
4-*tert*-Butyl-6-phenyl-1-azaspiro[bicyclo[4.3.1]decane-10,2'-oxirane] (275). According to the general procedure, the reaction of **34** (0.0300 g, 0.105 mmol, 1.0 equiv), NaH (0.0295 g, 0.74 mmol, 7.0 equiv) and sulfonium iodide (0.0552 g, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (20.0 mL and 3.0 mL) for 18 h afforded after chromatography (1/4-1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.39, 1/4 EtOAc/hexanes). Yield 88% (0.0276 g, 0.092 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 9H), 1.48-1.55 (m, 1H), 1.59-1.67 (m, 2H), 1.70 (d, *J* = 6.3 Hz, 1H), 1.73-1.80 (m, 2H), 1.88 (m, 1H), 2.00-2.10 (m, 1H), 2.13-2.19 (m, 2H), 2.32 (ddt, *J* = 2.1, 4.3, 13.2 Hz, 1H), 2.48-2.55 (m, 1H), 2.87-2.99 (m, 2H), 3.51 (dt, *J*

= 3.9, 13.0 Hz, 1H), 7.08-7.12 (m, 1H), 7.16-7.20 (m, 2H), 7.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 27.5, 29.2, 33.9, 36.8, 42.7, 44.1, 48.2, 52.1, 53.2, 53.8, 72.6, 126.0, 126.9, 127.6, 147.0; IR (neat) 3416, 2955, 2922, 2853, 1458, 1365, 1333, 1267. 1163, 1101 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO$ (M^+ + H) 300.2327, found 300.2327.

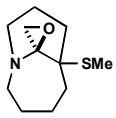


6-(Phenylthio)-1-azaspiro[bicyclo[4.3.1]decane-10,2'-oxirane] (276).

According to the general procedure, the reaction of **73** (0.0202 g, 0.077 mmol, 1.0 equiv), NaH (0.0217 g, 0.54 mmol, 7.0 equiv) and sulfonium iodide (0.0379 g, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (10.0 mL and 3.0 mL) for 17 h afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.37, 1/4 EtOAc/hexanes). Yield 81% (0.0171 g, 0.062 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.53 (m, 1H), 1.60-1.72 (m, 2H), 1.77-2.13 (m, 7H), 2.56 (d, *J* = 6.5 Hz, 1H), 2.76 (m, 1H), 2.96-3.12 (m, 2H), 3.20-3.27 (m, 1H), 3.63 (d, *J* = 6.5 Hz, 1H), 7.28-7.35 (m, 3H), 7.56-7.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 24.3, 27.9, 37.4, 40.4, 50.7, 52.6, 52.8, 53.6, 74.4, 128.3, 128.4, 132.4, 136.6; IR (neat) 3057, 2931, 2855, 1474, 1447, 1439, 1329, 1264, 1165, 1017 cm^{-1}; HRMS calcd for $C_{16}H_{22}NOS$ (M^+ + H) 276.1422, found 276.1419.

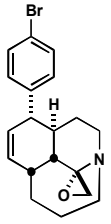


4-*tert*-Butyl-1-azaspiro[bicyclo[4.3.1]decane-10,2'-oxirane] (277). According to the general procedure, the reaction of **3** (0.0276 g, 0.132 mmol, 1.0 equiv), NaH (0.0370 g, 0.92 mmol, 7.0 equiv) and sulfonium iodide (0.0694 g, 2.5 equiv) in DMSO (6.0 mL and 2.5 mL and 2.0 mL) and THF (10.0 mL and 8.0 mL) for 18 h afforded after chromatography (5% MeOH/EtOAc) the title compound as oil (R_f = 0.55, 10% MeOH/EtOAc). Yield 41% (0.0121 g, 0.054 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.26-1.84 (m, 9H), 1.94-2.04 (m, 1H), 2.45 (d, *J* = 6.2 Hz, 1H), 2.50 (dt, *J* = 3.4, 12.9 Hz, 1H); 2.64 (d, *J* = 6.2 Hz, 1H), 2.90-3.05 (m, 2H), 3.45 (dt, *J* = 3.5, 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 27.6, 28.9, 31.5, 33.1, 33.6, 36.1, 48.7, 522.4, 54.4, 55.3, 71.7; IR (neat) 2939, 2863, 1468, 1448, 1364, 1337, 1263, 1227, 1186, 1149, 1119, 1082 cm^{-1}; HRMS calcd for $C_{14}H_{24}NO$ (M^+ + H) 224.2014, found 224.2004.



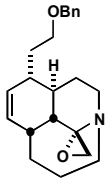
6-(Methylthio)-1-azaspiro[bicyclo[4.3.1]decane-10,2'-oxirane] (278). To a solution of sulfonium iodide (0.26 g, 1.23 mmol, 10.0 equiv) in THF (15 mL), *n*BuLi (2.5 M in hexanes, 0.38 mL, 0.96 mmol, 8.0 equiv) was added dropwise at 0 °C. After 5 min at 0 °C, amide **58** (0.0245 g, 0.12 mmol, 1.0 equiv) was added in THF (3.0 mL) dropwise at 0 °C. The reaction mixture was warmed slowly to rt over 3 h,

and stirred at rt for additional 2 h. The reaction mixture was quenched with water (20 mL), extracted with EtOAc (3 x 50 mL), washed with brine (1 x 20 mL), dried, concentrated and purified by chromatography (1/3 EtOAc/hexanes) to afford the title compound as oil (R_f = 0.19, 1/4 EtOAc/hexanes). Yield 89% (0.0233 g, 0.11 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.49 (m, 1H), 1.64-1.92 (m, 8H), 1.94 (s, 3H), 2.00-2.08 (m, 1H), 2.24 (d, *J* = 6.8 Hz, 1H), 2,68-2.75 (m, 1H), 2.95-3.11 (m, 2H), 3.20-3.27 (m, 1H), 3.47 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 22.2, 25.4, 29.6, 38.4, 39.1, 48.4, 51.1, 52.4, 53.9, 75.6; IR (neat) 3066, 2919, 2852, 1448, 1330, 1263, 1217, 1164 cm^{-1}; HRMS calcd for $C_{11}H_{20}NOS$ (M^+ + H) 214.1266, found 214.1262. Note: the compound is unstable at rt. The reaction of **58** under general conditions led to formation of unidentified polymerized material.



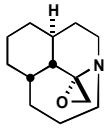
Epoxide 281. According to the general procedure, the reaction of **229** (0.0250 g, 0.072 mmol, 1.0 equiv), NaH (0.0202 g, 0.51 mmol, 7.0 equiv) and sulfonium iodide (0.0375 g, 0.18 mmol, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (10.0 mL and 3.0 mL) for 18 h afforded after chromatography (1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.31, 1/1 EtOAc/hexanes). Yield 70% (0.0183 g, 0.051 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-1.43 (m, 1H), 1.46-1.53 (m, 1H), 1.60-1.74 (m, 2H), 1.86 (dd, *J* = 4.1, 10.8 Hz, 1H), 2.01-2.11 (m, 1H), 2.16-

2.29 (m, 2H), 2.50 (d, J = 6.1 Hz, 1H), 2.49-2.56 (m, 1H), 2.59-2.69 (m, 2H), 2.73 (d, J = 6.1 Hz, 1H), 3.11 (d, J = 10.6 Hz, 1H), 3.38 (dd, J = 8.1, 13.5 Hz, 1H), 3.50 (dd, J = 4.2, 12.0 Hz, 1H), 5.51 (d, J = 9.8 Hz, 1H), 5.98-6.04 (m, 1H), 7.06 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 24.6, 35.0, 35.3, 37.6, 48.1, 50.7, 52.7, 54.7, 58.7, 70.4, 120.3, 129.7, 129.8, 131.5, 134.7, 142.8; IR (neat) 3013, 2916, 2860, 1483, 1441, 1385, 1337, 1298, 1246, 1137, 1071, 1011 cm^{-1}; HRMS calcd for $C_{19}H_{23}BrNO$ (M^+ + H) 360.0963, found 360.0960.

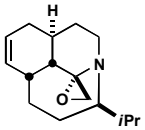


Epoxide 282. According to the general procedure, the reaction of **279** (0.0272 g, 0.084 mmol, 1.0 equiv), NaH (0.0234 g, 0.59 mmol, 7.0 equiv) and sulfonium iodide (0.0437 g, 0.21 mmol, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (10.0 mL and 5.0 mL) for 19 h afforded after chromatography (0-2.5% MeOH/EtOAc) the title compound as oil (R_f = 0.27, EtOAc). Yield 73% (0.0209 g, 0.062 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27-1.67 (m, 5H), 1.84-1.97 (m, 3H), 2.04-2.26 (m, 3H), 2.32-2.44 (m, 1H), 2.44 (d, J = 6.1 Hz, 1H), 2.64 (t, J = 11.4 Hz, 1H), 2.72 (d, J = 6.1 Hz, 1H), 2.72-2.84 (m, 1H), 3.42-3.52 (m, 2H), 2.55-3.63 (m, 2H), 4.53 (s, 2H), 5.51 (d, J = 9.9 Hz, 1H), 5.82-5.87 (m, 1H), 7.29-7.38 (m 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 24.7, 32.2, 34.4, 34.8, 35.3, 41.0, 48.3, 53.0, 54.7, 58.8, 68.0, 70.5, 73.1, 127.6, 127.6, 128.4, 130.0, 133.7, 138.5; IR (neat) 3009, 2914,

2860, 1481, 1453, 1385, 1364, 1294, 1258, 1142, 1102, 1053 cm^{-1}; HRMS calcd for $C_{22}H_{30}NO_2$ (M^+ + H) 340.2277, found 340.2256.



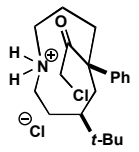
Epoxide 283. According to the general procedure, the reaction of **280** (0.0090 g, 0.047 mmol, 1.0 equiv), NaH (0.0130 g, 0.33 mmol, 7.0 equiv) and sulfonium iodide (0.0240 g, 0.12 mmol, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (10.0 mL and 3.0 mL) for 18 h afforded after chromatography (10% MeOH/EtOAc) the title compound as oil (R_f = 0.36, 10% MeOH/EtOAc). Yield 77% (0.0075 g, 0.036 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01-1.14 (m, 1H), 1.32-1.78 (m, 10H), 1.85-2.05 (m, 2H), 2.14-2.25 (m, 2H), 2.43 (dd, *J* = 2.3, 6.1 Hz, 1H), 2.69 (dd, *J* = 1.9, 6.2 Hz, 1H), 2.76-2.85 (m, 2H), 3.35 (dd, *J* = 8.4, 13.4 Hz, 1H), 3.49-3.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 25.0, 28.2, 30.9, 31.0, 32.0, 33.2, 33.8, 52.1, 52.8, 54.6, 58.7, 71.0; IR (neat) 2918, 2859, 1484, 1453, 1443, 1383, 1321, 1285, 1242, 1152 cm^{-1}; HRMS calcd for $C_{13}H_{22}NO$ (M^+ + H) 208.1701, found 208.1694.



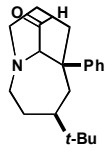
Epoxide 284. According to the general procedure, the reaction of **260** (0.0258 g, 0.11 mmol, 1.0 equiv), NaH (0.0310 g, 0.78 mmol, 7.0 equiv) and sulfonium iodide

(0.0572 g, 0.28 mmol, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (10.0 mL and 6.0 mL) for 18 h afforded after chromatography (2.5% EtOAc/hexanes) the title compound as oil (R_f = 0.84, 1/10 EtOAc/hexanes). Yield 70% (0.0190 g, 0.077 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (dd, *J* = 2.6, 6.8 Hz, 6H), 1.37-1.61 (m, 5H), 1.65-1.72 (m, 1H), 1.80-1.89 (m, 1H), 1.97 (dd, *J* = 2.0, 13.3 Hz, 1H), 2.01-2.17 (m, 3H), 2.35-2.43 (m, 1H), 2.41 (d, *J* = 6.6 Hz, 1H), 2.62 (dd, *J* = 1.8, 11.2 Hz, 1H), 2.68 (d, *J* = 6.6 Hz, 1H), 2.74-2.84 (m, 1H), 3.41 (dd, *J* = 8.0, 13.3 Hz, 1H), 5.55-5.63 (m, 1H), 5.77-5.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 18.3, 25.6, 27.9, 29.9, 33.5, 33.7, 34.8, 36.1, 48.6, 53.4, 54.8, 69.9, 74.7, 126.0, 133.8; IR (neat) 3015, 2954, 2927, 2669, 1463, 1451, 1393, 1378, 1341, 1291, 1260, 1064 cm^{-1}; HRMS calcd for $C_{16}H_{26}NO$ (M^+ + H) 248.2014, found 248.2015.

Attempted epoxidation of 93, [5.3.1] ring system. According to the general procedure, **93** (0.0228 g, 0.11 mmol, 1.0 equiv) was reacted with NaH (0.0300 g, 0.75 mmol, 7.0 equiv) and sulfonium iodide (0.0563 g, 0.27 mmol, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (10.0 mL and 6.0 mL) for 17 h. Analysis of the crude reaction mixture by NMR indicated only presence of the starting material.

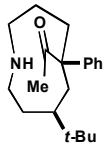


4-*tert*-Butyl-6-(2-chloroacetyl)-6-phenylazonanium chloride (285). To a 10 ml round bottom flask charged with epoxide **275** (0.0041 g, 0.014 mmol, 1.0 equiv) and MeOH (5.0 mL), HCl (4.0 M, dioxane, 0.40 mL, 1.6 mmol, 100 equiv) was added dropwise at rt, and the resulting reaction mixture was stirred at rt. After 19 h the solvent was removed to provide the title compound as a white solid (m.p. = 230-5 °C). Yield 99% (0.0050 g, 0.0135 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.34 (s, 9H), 1.28-1.48 (m, 3H), 1.60 (m, 1H), 1.83 (m, 1H), 1.95 (m, 1H), 2.05 (m, 1H), 2.17 (m, 1H), 2.57 (m, 1H), 3.00 (m, 2H), 3.14 (m, 2H), 4.12 (d, *J* = 16.0 Hz, 1H), 4.48 (d, *J* = 16.0 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.1 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 8.76 (br, 1H), 9.51 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.9, 24.6, 27.2, 29.1, 33.9, 34.3, 37.9, 41.7, 44.6, 57.1, 59.6, 127.9, 128.0, 129.3, 142.1, 204.6; IR (KBr) 3423, 2931, 1725, 1574, 1466, 1290, 1124, 1075 cm^{-1}; HRMS calcd for $C_{20}H_{31}ClNO$ (M^+) 336.2094, found 336.2093. Note: the reaction of **275** (0.0163 g, 0.055 mmol) and HCl (4.0 M, dioxane, 4.0 mL), w/o MeOH, afforded **285** in 97% yield.



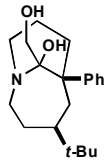
4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decane-10-carbaldehyde (286). To a solution of epoxide **275** (0.0232 g, 0.078 mmol, 1.0 equiv) in MeOH (10.0 mL), NaOMe (0.0882 g, 1.6 mmol, 20.0 equiv) was added, and the resulting mixture was refluxed for 48 h. The reaction mixture was cooled to rt, ether (10 mL) was added,

followed by water (10 mL), and the reaction mixture was extracted with EtOAc (3 x 30 mL), washed with brine (1 x 20 mL), dried, concentrated and analyzed by NMR. Yield 38% (vs. nitromethane as the internal standard), dr = 84:16. Note: the compound is very unstable, it decomposes rapidly over time, attempted purification led only to decomposition products. (R_f = ~0.50, 1/1 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) (major diastereomer) δ 0.88 (s, 9H), 1.53 (m, 3H), 1.80 (m, 2H), 1.86-1.96 (m, 1H), 2.02-2.20 (m, 2H), 2.35-2.44 (m, 1H), 2.72 (dt, *J* = 4.7, 13.5 Hz, 2H), 2.93 (dt, *J* = 3.9, 13.4 Hz, 1H), 3.77 (ddd, *J* = 1.8, 5.2, 13.6 Hz, 1H), 4.09 (s, 1H), 7.17-7.55 (m, 5H), 9.44 (s, 1H); (minor diastereomer, diagnostic peaks) δ 4.20 (s, 1H), 9.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereomer) δ 21.6, 27.5, 30.4, 32.5, 33.8, 38.9, 48.2, 49.3, 49.7, 56.3, 66.9, 125.1, 125.6, 128.4, 150.1, 199.7; IR (neat) 2956, 2943, 2706, 1726, 1444, 1365, 1224, 1155, 1099 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO$ (M^+ + H) 300.2327, found 300.2301. Note: the reaction of **275** with other bases, including sodium salt of dimethylmalonate, ethylmagnesium bromide, also afforded the aldehyde **286**.

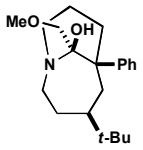


7-*tert*-Butyl-5-phenylazonan-5-yl)ethanone (287). To a solution of epoxide **275** (0.0157 g, 0.053 mmol, 1.0 equiv) in Et_2O (10 mL), $LiAlH_4$ (1.0 M, Et_2O, 0.26 mL, 0.26 mmol, 5.0 equiv) was added at rt. After stirring for 20 h at rt, the reaction was quenched at 0 °C by sequential addition of H_2O, 15% NaOH, H_2O and Na_2SO_4

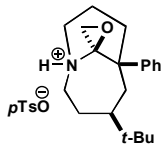
according to the procedure by Fieser and Fieser. Purification by chromatography (1/10/90 NH_3/MeOH/CH_2Cl_2) afforded the title compound as oil (R_f = 0.31-0.62, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 91% (0.0144 g, 0.048 mmol). Spectroscopic properties matched those previously described.



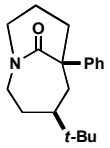
4-*tert*-Butyl-10-(hydroxymethyl)-6-phenyl-1-azabicyclo[4.3.1]decan-10-ol (288). To a 10 ml round bottom flask charged with epoxide **275** (0.0050 g, 0.017 mmol, 1.0 equiv) and CH_2Cl_2 (2.0 mL), H_2O (0.030 g, 1.7 mmol, 100 equiv) and TFA (2.0 mL) were added at rt. After the reaction mixture was stirred at rt for 18 h, the solvent was removed and the reaction was analyzed by NMR. Yield 76% (vs. nitromethane as the internal standard). Note: the compound is unstable, it decomposes at rt over time; attempted purification led only to products with diminished purity. (R_f = 0.65, 1/1 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.75 (m, 1H), 1.87 (d, *J* = 14.0 Hz, 1H), 2.04-2.21 (m, 5H), 2.37-2.47 (m, 2H), 2.59-2.66 (m, 1H), 2.97-3.09 (m, 1H), 3.32 (d, *J* = 3.8 Hz, 1H), 3.50 (m, 2H), 4.20 (d, *J* = 13.6 Hz, 1H), 7.24-7.58 (m, 5H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 26.7, 27.3, 33.6, 34.1, 42.2, 43.1, 47.5, 50.3, 54.5, 55.3, 74.3, 127.7, 128.3, 128.6, 142.6; IR (neat) 3400, 2962, 1673, 1464, 1201 cm^{-1}; HRMS calcd for $C_{20}H_{32}NO_2$ (M^+ + H) 318.2433, found 318.2415.



4-*tert*-Butyl-10-(methoxymethyl)-6-phenyl-1-azabicyclo[4.3.1]decan-10-ol (289). To a solution of epoxide **275** (0.0154 g, 0.052 mmol, 1.0 equiv) in MeOH (10 mL), 2 drops of H_2SO_4 were added, and the reaction mixture was heated to reflux for 5 h. The reaction was cooled to rt, quenched with sat. $NaHCO_3$ (10 mL), extracted with EtOAc (3 x 20 mL), washed with brine (1 x 20 mL), dried, concentrated and purified by chromatography (20% MeOH/EtOAc) to afford the title compound as oil (R_f = 0.27, 20% MeOH/EtOAc). Yield ca. 50% (0.0081 g, 0.025 mmol). Note: the title compound was obtained as 2:1 mixture with an unidentified by-product. Attempts to (1) separate the by-product using different solvent systems on silica gel or PTLC, (2) change the reaction time (1 h - partial conversion was observed and 17 h), (3) resubmitting the final product to the reaction conditions or (4) use of other acids (*p*TsOH, HNO_3, HCl_{aq}) always afforded the unidentified by-product in ratio ca. 1:2.5 to **2z**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 9H), 1.43 (m 1H), 1.54-2.14 (m, 6H), 2.18-2.56 (m, 4H), 2.71-2.81 (m, 1H), 2.83 (m, 1H), 3.12-3.28 (m, 1H), 3.37 (s, 3H), 3.57-3.66 (m, 1H), 7.16-7.70 (m, 5H); diagnostic peaks of the unidentified impurity δ 0.94 (s, 9H), 5.48 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 27.9, 30.7, 33.7, 33.9, 44.0, 45.1, 46.3, 50.6, 51.0, 53.2, 62.2, 92.6, 125.8, 127.6, 128,7, 147.6; IR (neat) 3379, 2960, 1470, 1366, 1138, 1032 cm^{-1}; HRMS calcd for $C_{21}H_{34}NO_2$ (M^+ + H) 332.2590, found 332.2590.

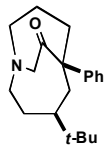


Salt 290. To a solution of epoxide **275** (0.0146 g, 0.049 mmol, 1.0 equiv) in acetone (2.0 mL), *p*TsOH (0.0093 g, 0.049 mmol, 1.0 equiv) was added in acetone (0.5 mL). Et_2O (2.5 mL) wad added and the reaction mixture was kept for 5 days at -20 °C. The solvent was removed to afford the title compound as white foam. Yield 99% (0.0238 g, 0.049 mmol). Note: the compound is unstable. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 9H), 1.72 (m, 1H), 1.84 (d, *J* = 14.0 Hz, 1H), 2.06-2.21 (m, 5H), 2.32-2.45 (m, 2H), 2.34 (s, 3H), 2.62 (m, 1H), 3.05 (m, 1H), 3.47 (d, *J* = 3.9 Hz, 1H), 3.63 (d, *J* = 7.7 Hz, 2H), 4.21-4.29 (m, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 2.27-7.38 (m, 3H), 7.45 (m, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 11.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 21.4, 26.7, 27.3, 33.6, 34.0, 42.1, 43.2, 47.4, 50.5, 55.0, 55.4, 74.4, 126.0, 126.0, 127.6, 128.6, 128.9, 140.4, 141.3, 142.7; IR (neat) 3352, 2954, 2918, 2848, 1718, 1458, 1365, 1273, 1226, 1165, 1120 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO$ (M^+) 300.2327, found 300.2337.

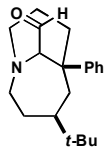


Lactam 34. A solution of epoxide **275** (0.0106 g, 0.035 mmol, 1.0 equiv), KCN (0.0455 g, 0.70 mmol, 20.0 equiv) in DMF (10 mL) was heated at 110 °C for 24 h. The reaction mixture was cooled to rt, diluted with EtOAc (50 mL), washed with

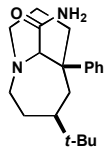
water (4 x 20 mL), brine (1 x 20 mL), dried, concentrated and purified by chromatography (1/2 EtOAc/hexanes) the title compound. Yield 86% (0.0086 g, 0.030 mmol). Spectroscopic properties matched those previously described. Note: the reaction of **275** (0.0252 g, 0.084 mmol) with KCN (0.0279 g, 0.42 mmol, 5.0 equiv) and $LiClO_4$ (0.0447 g, 0.42 mmol, 5.0 equiv) in CH_3CN (10 mL) at 70 °C for 80 h afforded **34** in 45% yield at 70% conversion.



4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.2]undecan-11-one (291). According to the procedure for **34**, the reaction of **275** (0.0170 g, 0.057 mmol, 1.0 equiv) and NaI (0.17 g, 1.1 mmol, 20.0 equiv) in DMF (10 mL) at 110 °C for 16 h, afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.22, 1/4 EtOAc/hexanes). Yield 51% (0.0087 g, 0.029 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.32-1.49 (m, 2H), 1.78-2.-2 (m, 3H), 2.14 (dd, *J* = 2.0, 13.0 Hz, 1H), 2.33 (tt, *J* = 2.6, 13.4 Hz, 1H), 2.41-2.52 (m, 1H), 2.59 (dd, *J* = 3.7, 13.1 Hz, 1H), 2.76 (dt, *J* = 4.0, 13.2 Hz, 1H), 3.14-3.31 (m, 2H), 3.59 (dt, *J* = 3.0, 14.5 Hz, 1H), 3.73 (q, *J* = 16.9 Hz, 2H), 7.13-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 28.4, 31.5, 35.2, 40.9, 42.0, 46.6, 56.9, 57.1, 58.6, 65.5, 126.0, 126.2, 128.1, 151.6, 203.1; IR (neat) 2960, 2918, 2870, 1697, 1444, 1365, 1163, 1116 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO$ (M^+ + H) 300.2327, found 300.2304.



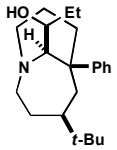
4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decane-10-carbaldehyde (286). 10 mL MW vial (Biotage) was charged with epoxide **275** (0.0046 g, 0.015 mmol, 1.0 equiv) and toluene (3.0 mL, 0.005 M), the vial was sealed and heated to 200 °C for 10 h. The solvent was removed and the reaction was analyzed by NMR. Yield 81% (vs. nitromethane as the internal standard), dr = 86:14. Note: the compound is very unstable, it decomposes rapidly over time, attempted purification led only to decomposition products. Spectroscopic properties matched those previously described. Note: the reaction carried out in DMF (120 °C, 14 h) resulted in decomposition; in MeOH (150 °C, 2 h) (MW) a complex mixture was formed (27% yield of **3f**); in $PhCH_3$ (110 °C, 15 h) <5% conversion; in $PhCH_3$ (150 °C, 14 h) 23% conversion; in $PhCH_3$ (180 °C, 5 h) 38% conversion. All reactions at c = 0.005 M.



4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decane-10-carboxamide (292). A solution of epoxide **275** (0.0221 g, 0.074 mmol, 1.0 equiv), NaN_3 (0.21 g, 3.3 mmol, 50 equiv) and DMF (10 mL) was heated at 110 °C for 21 h. The reaction mixture was cooled to rt, diluted with EtOAc (50 mL), washed with water (4 x 20 mL), brine (1 x 20 mL), dried, concentrated and purified by chromatography (1/10/90

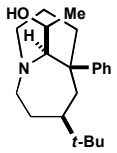
NH_3/MeOH/CH_2Cl_2) to afford the title compound as oil (R_f = 0.40, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 62% (0.0143 g, 0.045 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 9H), 1.46-1.76 (m, 6H), 1.91 (dd, *J* = 6.9, 15.0 Hz, 1H), 2.11-2.29 (m, 2H), 2.34 (d, *J* = 14.6 Hz, 1H), 2.57-2.72 (m, 2H), 2.04 (d, *J* = 15.0 Hz, 1H), 3.83 (dt, *J* = 2.8, 15.2 Hz, 1H), 4.40 (dd, *J* = 4.8, 13.7 Hz, 1H), 4.29 (s, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 26.2, 28.4, 34.0, 35.9, 39.3, 44.8, 48.9, 49.8, 51.1, 59.9, 126.1, 126.9, 128.5, 149.7, 177.5; IR (neat) 3387, 2959, 2926, 1661, 1480, 1430, 1366, 1220, 1156, 1100 cm^{-1}; HRMS calcd for $C_{20}H_{31}N_2O$ (M^+ + H) 315.24361, found 315.2430.

Reactions of 275 under Lewis acidic conditions. General procedure: To a round-bottom flask charged with epoxide **275** and CH_2Cl_2, Lewis acid was added at rt, unless indicated otherwise. If an additive was used, it was added before the Lewis acid. After the reaction mixture was stirred for a specified time, the reaction was quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, dried, concentrated and chromatographed to afford the final products. Stereochemistry (migration with retention of configuration) was determined by 2D NMR correlations.



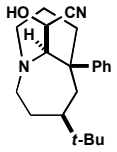
4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-yl)propan-1-ol (293). According to the general procedure, the reaction of **275** (0.0147 g, 0.049 mmol, 1.0

equiv) and Et_2AlCl (1.8 M, toluene, 0.055 mL, 0.10 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) for 15 h at rt, afforded after chromatography (1/10/90 NH_3/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.33, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 92% (0.0149 g, 0.045 mmol), dr = 59:41. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 0.40 (t, *J* = 6.9 Hz, 3H, minor isomer), 0.65 (t, *J* = 7.3 Hz, 3H, major isomer), 0.89 (s, 9H), 1.53-2.05 (m, 16H), 2.08-2.31 (m, 4H), 2.48 (dt, *J* = 4.1, 13.6 Hz, 1H), 2.59 (dd, *J* = 4.8, 14.6 Hz, 1H), 2.67-2.81 (m, 3H), 2.92-3.03 (m, 3H), 3.09-3.22 (m, 2H), 3.32-3.41 (m, 1H), 3.53 (dd, *J* = 6.2, 11.0 Hz, 1H), 3.62 (dd, *J* = 4.6, 13.9 Hz, 1H), 3.69 (dd, *J* = 3.7, 13.7 Hz, 1H), 7.19-7.49 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 10.3, 21.4, 21.7, 27.5, 27.5, 28.6, 30.1, 30.2, 31.0, 31.6, 33.8, 34.0, 41.1, 46.2, 48.1, 48.2, 48.2, 48.5, 49.6, 56.6, 57.5, 59.0, 62.8, 67.7, 125.7, 125.9, 126.0, 127.9, 128.2, 149.1, 149.2; IR (neat) 3304, 2959, 2870, 1720, 1663, 1599, 1497, 1460, 1366, 1225. 1099 cm^{-1}; HRMS calcd for $C_{22}H_{36}NO$ (M^+ + H) 330.2797, found 330.2767.



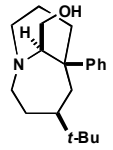
4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-yl)ethanol (294). According to the general procedure, the reaction of **275** (0.0126 g, 0.042 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M, hexanes, 0.084 mL, 0.084 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) for 13 h at rt, afforded after chromatography (1/10/90-1/30/70 NH_3/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.31, 1/10/90

NH_3/MeOH/CH_2Cl_2). Yield 58% (0.0076 g, 0.024 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.26 (d, *J* = 5.9 Hz, 3H), 0.90 (s, 9H), 1.54-1.63 (m, 3H), 1.78-1.93 (m, 5H), 2.16-2.26 (m, 1H), 2.39-2.48 (m, 1H), 2.66-2.80 (m, 2H), 2.96 (d, *J* = 8.8 Hz, 1H), 3.16 (dt, *J* = 4.4, 14.1 Hz, 1H), 3.54-3.61 (m, 1H), 3.62-3.70 (m, 1H), 7.18-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 22.7, 27.5, 30.0, 31.5, 34.0, 40.9, 47.8, 48.2, 48.6, 57.6, 62.8, 66.0, 126.0, 126.1, 128.0, 149.2; IR (neat) 3255, 2960, 2870, 1652, 1465, 1446, 1367, 1224, 1112, 1084 cm^{-1}; HRMS calcd for $C_{21}H_{34}NO$ (M^+ + H) 316.2641, found 316.2644. Note: the reaction of **275** (0.0124 g, 0.041 mmol, 1.0 equiv) with Me_3Al (2.0 M, toluene, 0.10 mL, 0.21 mmol, 5.0 equiv) in CH_2Cl_2 (10 mL) added at -78 °C, and slowly warmed to rt over 16 h, afforded **294** in 45% yield.



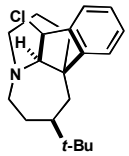
4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-yl)-2-hydroxy acetonitrile (295). According to the general procedure, the reaction of **275** (0.0156 g, 0.052 mmol, 1.0 equiv), TMSCN (0.071 mL, 0.52 mmol, 10.0 equiv) and Et_2AlCl (1.8 M, toluene, 0.060 mL, 0.10 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) for 15 h at rt, afforded after chromatography (1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.60, 1/1 EtOAc/hexanes). Yield 70% (0.0119 g, 0.037 mmol), dr = 65:35. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 0.89 (s, 9H, major isomer), 0.92 (s, 9H, minor isomer), 1.46-2.01 (m, 16H), 2.14-2.41 (m, 3H), 2.64-2.86 (m, 5H), 3.06-3.18 (m, 1H), 3.37 (dt, *J* = 3.9, 14.9 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.65-3.74

(m, 2H), 3.92 (d, J = 9.1 Hz, 1H, minor isomer), 4.02 (d, J = 6.5 Hz, 1H, major isomer), 7.22-7.48 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 20.6, 20.7, 27.5, 27.5, 29.1, 29.8, 30.0. 30.8, 33.8, 34.0, 39.6, 40.5, 47.1, 47.5, 47.9, 48.1, 48.2, 50.8, 56.3, 56.6, 56.8, 56.9, 60.8, 61.6, 119.6, 121.4, 126.4, 126.6, 127.5, 128.6, 128.7, 144.8, 146.3; IR (neat) 3305, 2959, 2870, 1720, 1669, 1600, 1463, 1446, 1366, 1227, 1094 cm^{-1}; HRMS calcd for $C_{21}H_{30}N_2O$ (M^+ + H) 327.2436, found 327.2404.



4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-yl)methanol (296). According to the general procedure, the reaction of **275** (0.0138 g, 0.046 mmol, 1.0 equiv), Et_3SiH (0.074 mL, 0.46 mmol, 10.0 equiv) and Et_2AlCl (1.8 M, toluene, 0.051 mL, 0.09 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) for 18 h at rt, afforded after chromatography (1/4 MeOH/EtOAc) the title compound as oil (R_f = 0.34, 20% MeOH/EtOAc). Yield 56% (0.0077 g, 0.026 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 9H), 1.54-1.66 (m, 3H), 1.76-1.90 (m, 3H), 1.97 (d, J = 12.1 Hz, 1H), 2.05-2.31 (m, 2H), 2.59 (dd, J = 4.4, 14.3 Hz, 1H), 2.73 (dt, J = 4.8, 13.7 Hz, 1H), 2.91-3.02 (m, 2H), 3.14 (t, J = 10.7 Hz, 2H), 3.53 (dd, J = 5.6, 10.8 Hz, 1H), 3.69 (dd, J = 5.0, 14.5 Hz, 1H), 7.12-7.55 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 27.5, 30.1, 31.0, 33.8, 39.6, 46.2, 48.2, 49.6, 56.6, 56.6, 59.0, 125.7, 125.9, 128.2, 149.1; IR (neat) 3357, 2957, 2944, 1459, 1366, 1324, 1274, 1226, 1037 cm^{-1}; HRMS calcd for

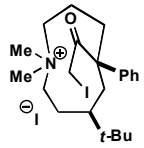
$C_{20}H_{32}NO$ (M^+ + H) 302.2484, found 302.2481. Note: the reaction of **275** (0.0174 g, 0.058 mmol, 1.0 equiv), allyltrimethylsilane (0.094 mL, 0.58 mmol, 10.0 equiv) and Et_2AlCl (1.8 M, toluene, 0.064 mL, 0.11 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) at rt for 14 h, afforded **293** in 87%.



Compound 297. According to the general procedure, the reaction of **275** (0.0129 g, 0.043 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M, hexanes, 0.086 mL, 0.086 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) for 13 h at rt, afforded after chromatography (2/1 EtOAc/hexanes) the title compound as oil (R_f = 0.48, EtOAc). Yield 68% (0.0093 g, 0.029 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.42-1.55 (m, 2H), 1.72-2.07 (m, 6H), 2.36 (dt, *J* = 2.5, 13.0 Hz, 1H), 2.65 (dt, *J* = 4.0, 13.6 Hz, 1H), 2.75-2.83 (m, 1H), 31.4 (dt, *J* = 3.4, 12.7 Hz, 1H), 3.61 (d, *J* = 9.6 Hz, 1H), 3.67-3.77 (m, 1H), 5.51 (d, *J* = 9.6 Hz, 1H), 7.13-7.18 (m, 1H), 7.25-7.32 (m, 2H), 7.46-7.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 27.7, 29.8, 33.8, 35.8, 41.2, 41.8, 47.7, 47.7, 54.9, 60.8, 72.7, 121.7, 125.4, 126.9, 128.7, 138.4, 152.0; IR (neat) 2943, 2866, 1471, 1458, 1363, 1095 cm^{-1}; HRMS calcd for $C_{20}H_{29}NCl$ (M^+ + H) 318.1988, found 318.1983.

Attempted rearrangement of 275 using BF_3•Et_2O. According to the general procedure, **275** (0.0152 g, 0.051 mmol, 1.0 equiv) was reacted with BF_3•Et_2O (10 drops, excess) in CH_2Cl_2 (5.0 mL) for 18 h at rt. Analysis of the crude reaction

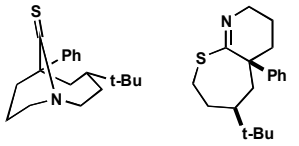
mixture indicated only presence of the starting material. Note: the use of **275** (0.0073 g, 0.024 mmol, 1.0 equiv), Et_3SiH (0.040 mL, 0.24 mmol, 10.0 equiv) and $BF_3•Et_2O$ (0.10 mL, excess) in CH_2Cl_2 (5.0 mL) for 14 h at rt, according to the procedure for **296** also resulted in <5% conversion. Note: the use of other acids known to promote Meinwald rearrangement, also resulted in no conversion. For example, **275** (0.0129 g, 0.043 mmol, 1.0 equiv) was reacted with $Cu(BF_4)_2•H_2O$ (0.0509 g, 0.22 mmol, 5.0 equiv) in CH_2Cl_2 (5.0 mL) for 15 h, and **275** (0.0121 g, 0.041 mmol, 1.0 equiv) was reacted with $Sc(OTf)_3$ (0.0299 g, 0.061 mmol, 1.5 equiv) in CH_2Cl_2 (5.0 mL) for 17 h at rt. Analysis of the crude reaction mixtures indicated only the presence of the starting material.



4-*tert*-Butyl-6-(2-iodoacetyl)-1,1-dimethyl-6-phenylazonanium iodide (285A, Table 31, entry 8). Epoxide **275** (0.0156 g, 0.052 mmol, 1.0 equiv), MeI (0.065 mL, 1.04 mmol, 20.0 equiv) and CH_2Cl_2 (3.0 mL) were heated in a sealed MW tube (10 mL, Biotage) at 60 °C for 22 h. After the reaction was cooled to rt, the solvent was removed under reduced pressure to afford the title compound as white solid (m.p. = 175-180 °C, decomp.). Yield 90% (0.0272 g, 0.047 mmol). ^1H NMR (400 MHz, DMSO-d_6) δ 0.43 (s, 9H), 0.81-0.88 (m, 1H), 1.51-1.62 (m, 1H), 1.72-2.16 (m, 5H), 2.28-2.43 (m, 2H), 2.55-2.64 (m, 1H), 3.05 (s, 3H), 3.10 (s, 3H), 3.58-3.76 (m, 3H), 3.81 (d, J = 13.2, Hz, 1H), 4.15 (d, J = 13.2, Hz, 1H), 7.20-7.42 (m,

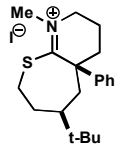
5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 8.1, 24.3, 26.7, 27.1, 34.6, 35.7, 43.3, 45.1, 52.9, 53.4, 59.0, 59.9, 127.8, 127.9, 129.1, 142.3, 206.1; IR (KBr) 2960, 2869, 1689, 1496, 1470, 1443, 1368, 1202, 1085 cm^{-1}; HRMS calcd for $C_{22}H_{35}NOI$ (M^+) 456.1763, found 456.1762. Note: when the reaction of **275** (0.0184, 0.062 mmol, 1.0 equiv) and MeI (0.038 mL, 0.62 mmol, 10 equiv) in CH_2Cl_2 was carried out at rt for 20 h, formation of the same product was observed along with the starting material.

Synthesis and Rearrangement of a Bridged Thioamide

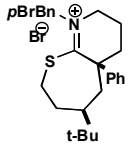


4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decane-10-thione (299) and 4-*tert*-Butyl-5a-phenyl-2,3,4,5,5a,6,7,8-octahydrothiepino[2,3-b]pyridine (300). 25 ml round bottom flask was charged with amide **34** (0.0200 g, 0.07 mmol, 1.0 equiv), P_4S_{10} (0.0080 g, 0.018 mmol, 0.25 equiv) and toluene (5.0 mL). After the reaction mixture was stirred at rt for 10 min, hexamethyldisiloxane (0.026 mL, 0.12 mmol, 1.7 equiv) was added and the reaction was heated at 90 °C for 22 h. After the reaction was cooled to rt, the solvent was removed and the reaction mixture was purified by chromatography (1/1 EtOAc/hexanes followed by 1/10/90 NH_3/MeOH/CH_2Cl_2) to afford **299** (R_f = 0.52, 1/4 EtOAc/hexanes) as oil (yield 5%, 0.0010 g, 0.0033 mmol) and **300** (Rf = 0.63, 1/10/90 NH_3/MeOH/CH_2Cl) as oil (yield 90%, 0.0189 g, 0.063 mmol). Compound **299**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 9H), 1.44 (q, *J* = 11.0 Hz, 1H), 1.68-1.77 (m, 2H), 1.90-2.02 (m, 3H), 2.17 (d, *J* = 10.1 Hz, 1H), 2.33-2.42 (m, 1H), 2.49 (d, *J* = 11.9 Hz, 1H), 3.03-3.11 (m, 1H), 3.44-3.52 (m, 1H), 3.72 (d, *J* = 12.2 Hz, 1H), 4.39 (dd, *J* = 7.2, 13.4 Hz, 1H), 7.22-7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 22.2, 27.1, 33.2, 37.6, 41.8, 46.3, 54.0, 57.5, 65.0, 125.1, 127.2, 127.5, 149.1, 225.5; IR (neat) 2955, 2918, 2851, 1491, 1445, 1367, 1315, 1180, 1080, 1070, 1047 cm^{-1}; HRMS calcd for $C_{19}H_{28}NS$ (M^+ + H) 302.1942, found 302.1955. Compound **300**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.26-1.48 (m, 2H), 160

(m, 2H), 1.84 (d, J = 13.0 Hz, 1H), 1.94-2.14 (m, 4H), 2.49 (dt, J = 4.6, 14.8 Hz, 1H), 2.85 (m, 1H), 3.58-3.69 (m, 1H), 3.86 (ddt, J = 1.6, 5.4, 18.0 Hz, 1H), 7.22-7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 27.4, 29.8, 32.0, 33.6, 39.8, 41.1, 43.9, 51.4, 51.8, 126.5, 126.9, 128.3, 146.4, 173.0; IR (neat) 2941, 2866, 2212, 1670, 1605, 1477, 1445, 1366, 1126, 1061 cm^{-1}; HRMS calcd for $C_{19}H_{28}NS$ (M^+ + H) 302.1942, found 302.1932.



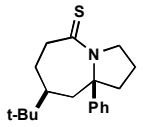
4-*tert*-Butyl-9-methyl-5a-phenyl-2,3,4,5,5a,6,7,8-octahydrothiepino[2,3-b] pyridin-9-ium iodide (300a). To a solution of **300** (0.0308 g, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (6.0 mL), MeI (0.13 mL, 2.0 mmol, 20.0 equiv) was added at rt, and the resulting reaction mixture was stirred at rt for 24 h. The solvent was removed to afford the title compound as yellow solid. Yield 96% (0.0434 g, 0.098 mmol). Recrystallization from $CHCl_3$ provided needles suitable for x-ray crystallography (m.p. = 167-8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.64 (m, 2H), 1.91 (m, 2H), 2.06 (m, 3H), 2.33 (d, J = 14.5 Hz, 1H), 2.53 (td, J = 2.3, 13.2 Hz, 1H), 2.97 (td, J = 4.1, 15.0 Hz, 1H), 3.11 (dd, J = 3.5, 15.0 Hz, 1H), 3.99 (s, 3H), 4.07 (dd, J = 5.3, 15.1 Hz, 1H), 4.49 (m, 1H), 7.21-7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 27.1, 28.3, 30.8, 33.4, 38.9, 41.9, 42.7, 48.9, 55.3, 58.8, 125.8, 128.2, 129.5, 143.5, 194.6; IR (neat) 2955, 2918, 2849, 2187, 1578, 1445, 1366, 1238 cm^{-1}; HRMS calcd for $C_{20}H_{30}NS$ (M^+) 316.2099, found 316.2094.



9-(4-bromobenzyl)-4-*tert*-Butyl-5a-phenyl-2,3,4,5,5a,6,7,8-octahydro thiepino [2,3-b]pyridin-9-ium (300b). To a solution of **300** (0.0130 g, 0.043 mmol, 1.0 equiv) in CH_2Cl_2 (6.0 mL), *p*-bromobenzylbromide (0.110 g, .043 mmol, 10.0 equiv) was added at rt, and the resulting reaction mixture was stirred at rt for 72 h. The solvent was removed, and the residue was chromatographed (1/10/90-1/20/80 NH_3/MeOH/CH_2Cl_2) to afford the title compound as colorless oil. Yield 98% (0.0233 g, 0.042 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.64 (m, 2H), 1.86 (m, 2H), 2.07 (m, 3H), 2.31 (d, *J* = 14.5 Hz, 1H), 2.50 (dt, *J* = 3.2, 13.3 Hz, 1H), 3.04 (m, 2H), 4.07 (dd, *J* = 2.8, 15.2 Hz, 1H), 4.55 (m, 1H), 5.64 (d, *J* = 15.6 Hz, 1H), 5.79 (d, *J* = 15.6 Hz, 1H), 7.25 (d, *J* = 7.3 Hz, 2H), 7.30-7.46 (m, 5H), 7.58 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 27.1, 28.2, 31.2, 33.4, 39.3, 42.2, 42.9, 55.8, 56.8, 63.0, 123.6, 125.6, 128.3, 129.4, 130.4, 130.9, 132.6, 143.7, 195.9; IR (neat) 2960, 2870, 2183, 1562, 1489, 1446, 1367, 1332 cm^{-1}; HRMS calcd for $C_{26}H_{33}BrNS$ (M^+) 470.1517, found 470.1484. Note: the compound is not crystalline.

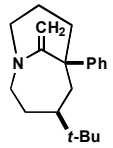
Thionation of 34 with Lawesson's reagent. 25 ml round bottom flask was charged with amide **34** (0.0200 g, 0.070 mmol, 1.0 equiv) Lawesson's reagent (0.0871 g, 0.21 mmol, 3.0 equiv), and toluene (7.0 mL), and the resulting mixture was heated to reflux for 24 h. After the reaction was cooled to rt, the solvent was removed and the reaction was analyzed by NMR. ^{1}H NMR indicated 31:6:63 mixture of

34:**299**:**300**. Note: the use of Lawesson's reagent complicates the purification of the final products; the lactams exhibit similar polarity to the decomposition products of the thionating reagent.

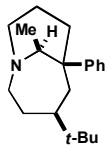


8-*tert*-Butyl-9a-phenylhexahydro-1H-pyrrolo[1,2-a]azepine-5(6H)-thione (301). According to the procedure described above, the reaction of amide **27** (0.0500 g, 0.175 mmol, 1.0 equiv), Lawesson's reagent (0.11 g, 0.26 mmol, 1.5 equiv) in toluene (7.0 mL) at reflux for 30 min, afforded after solvent removal and chromatography (1/10-1/4 EtOAc/hexanes), the title compound as white solid (m.p. = 152-3 °C, R_f = 0.73, 1/1 EtOAc/hexanes). Yield 93% (0.0488 g, 0.0162 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.22-1.38 (m, 2H), 1.43-1.52 (m, 1H), 1.64 (dd, *J* = 2.8, 10.8 Hz, 1H), 1.73-1.82 (m, 1H), 2.01 (m, 1H), 2.26 (m, 2H), 2.46 (d, *J* = 13.6 Hz, 1H), 2.60 (td, *J* = 6.1, 12.8 Hz, 1H), 2.99 (ddd, *J* = 1.8, 5.0, 12.4 Hz, 1H), 2.87-3.97 (m, 1H), 4.09 (dd, *J* = 4.8, 9.2 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 26.8, 27.0, 32.6, 39.6, 41.3, 42.7, 44.1, 56.0, 75.4, 124.8, 127.3, 128.7, 145.4, 200.5; IR (neat) 2950, 2916, 2868, 1470, 1443, 1367, 1331, 1252, 1148 cm^{-1}; HRMS calcd for $C_{19}H_{28}NS$ (M^+ + H) 302.1942, found 302.1953.

Bridged exocyclic enamine



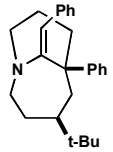
(4R,6R)-4-*tert*-Butyl-10-methylene-6-phenyl-1-azabicyclo[4.3.1]decane (304). 25 mL round bottom flask was charged with amide **34** (0.0214 g, 0.75 mmol, 1.0 equiv), toluene (6.0 mL), pyridine (0.06 mL) and Petasis reagent (0.58 M in toluene, 0.65 mL, 0.38 mmol, 5.0 equiv), sealed with septum, and the resulting reaction mixture was heated at 105 °C for 10 h. The reaction was cooled to rt, diluted with Et_2O (5 mL) and hexanes (5 mL), stirred for 10 min, and filtered through a short plug of celite (eluting with Et_2O). Chromatography (1/4 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.21, 1/4 EtOAc/hexanes). Yield 95% (0.0201 g, 0.071 mmol). Note: the compound is unstable. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.57-1.81 (m, 6H), 1.86-1.98 (m, 1H), 2.07-2.19 (m, 1H), 2.30 (d, *J* = 9.9 Hz, 1H), 2.59-2.71 (m, 1H), 2.99-3.09 (m, 1H), 3.39-3.48 (m, 1H), 3.52-3.59 (m, 1H), 4.19 (s, 1H), 4.76 (s, 1H), 7.20 (tt, *J* = 1.1, 6.7 Hz, 1H), 7.29-7.36 (m, 2H), 7.46-7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 27.8, 28.1, 34.0, 39.9, 43.9, 45.0, 47.0, 54.6, 55.4, 110.6, 125.6, 127.2, 127.7, 151.7, 157.0; IR (neat) 3088, 3055, 3028, 2943, 2866, 1628, 1555, 1443, 1393, 1366, 1101, 866, 762 cm^{-1}; HRMS calcd for $C_{20}H_{30}N$ (M^+ + H) 284.2378, found 284.2375.



(4R,6R,10S)-4-*tert*-Butyl-10-methyl-6-phenyl-1-azabicyclo[4.3.1]decane (305). To a solution of enamine **304** (0.0081 g, 0.029 mmol, 1.0 equiv) in EtOAc (3.0 mL), Pd/C (5%, 0.010 g) was added, and the reaction was stirred under H_2 balloon at rt for 15 h. Filtration through a short pad of celite (eluting with EtOAc/Et_2O), followed by chromatography (20% MeOH/EtOAc-1/20/80 NH_4OH/MeOH/CH_2Cl_2) afforded the title compound as oil (R_f = 0.36, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 75% (0.0062 g, 0.022 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.07 (d, *J* =7.1 Hz, 3H), 1.61-1.74 (m, 2H), 1.84-2.07 (m, 5H), 2.15-2.28 (m, 2H), 2.76-2.86 (m, 1H), 3.09-3.17 (m, 1H), 3.42 (td, *J* = 3.9, 13.7 Hz, 1H), 3.62-3.86 (m, 2H), 7.18-7.24 (m, 1H), 7.31-7.37 (m, 2H), 7.42-7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.7, 27.9, 29.5, 34.2, 36.4, 38.5, 41.5, 44.8, 50.6, 55.4, 62.5, 126.0, 126.1, 128.4, 149.0; IR (neat) 2960, 2870, 1645, 1558, 1464, 1444, 1369, 1253, 1228, 1083 cm^{-1}; HRMS calcd for $C_{20}H_{32}N$ (M^+ + H) 286.2535, found 286.2529.

Attempted reduction of 304 under acidic conditions. To a solution of enamine **304** (0.0057 g, 0.020 mmol, 1.0 equiv) in THF (2 mL), $NaBH_4$ (0.077 g, 0.20 mmol, 10.0 equiv), followed by AcOH (0.024 mL, 0.40 mmol, 20.0 equiv) was added, and the reaction mixture was stirred at rt for 20 min. The reaction was basified with sat. $NaHCO_3$, extracted with ether, washed with brine, dried and concentrated. Analysis of the crude reaction mixture by NMR indicated only the presence of the starting material. The reduction product was not present in the reaction mixture. Note:

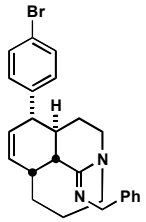
a reaction under identical conditions for 24 h at rt led to decomposition of the starting material.



(4R,6R)-10-Benzylidene-4-*tert*-butyl-6-phenyl-1-azabicyclo[4.3.1]decane (304a). To a solution of olefin **304** (0.0138 g, 0.049 mmol, 1.0 equiv) in DMF (5.0 mL), PhI (0.0031 g, 0.15 mmol, 3.0 equiv), $Pd(OAc)_2$ (0.0050 g, 0.022 mmol, 0.5 equiv), PPh_3 (0.0040 g, 0.015 mmol, 0.3 equiv), and Ag_2CO_3 (0.035 g, 0.13 mmol, 2.5 equiv) were added, and the reaction mixture was stirred at 80 °C for 3.5 h. The reaction was cooled to rt, quenched with water (10 mL), extracted with EtOAc (3 x 50 mL), washed with water (4 x 20 mL), brine (1 x 20 mL), dried and concentrated. Chromatography (1/20 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.70, 1/20 EtOAc/hexanes) Yield 21% (0.0037 g, 0.01 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.28-1.41 (m, 1H), 1.58-1.75 (m, 3H), 1.79-1.88 (m, 2H), 1.92-2.02 (m, 1H), 2.13-2.20 (m, 1H), 2.41 (d, *J* = 11.5 Hz, 1H), 2.50 (dt, *J* = 4.9, 12.8 Hz, 1H), 3.05-3.14 (m, 1H), 3.36-3.44 (m, 1H), 3.61-3.68 (m, 1H), 5.34 (s, 1H), 7.06-7.11 (m, 1H), 7.19-7.38 (m, 5H), 7.51-7.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 27.9, 28.8, 30.0, 40.3, 44.7, 45.1, 48.4, 51.1, 54.6, 123.3, 125.5, 125.6, 127.8, 127.9, 128.0, 137.6, 150.7, 151.7; IR (neat) 2947, 2866, 1491, 1444, 1394, 1365, 1224, 1147, 1031, 912 cm^{-1}; HRMS calcd for $C_{26}H_{34}N$ (M^+ + H) 360.2691, found 360.2649.

Miscellaneous Reactions (representative examples from Table 36)

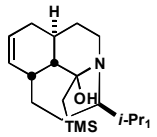
Attempted Wittig olefination. According to the procedure by Fitjer *et al.*[400] for demanding olefinations. To a solution of triphenyl methyl triphenylphosphonium bromide (0.256 g, 0.70 mmol, 10.0 equiv) in toluene (5 mL) KO*t*Bu (0.089 g, 0.70 mmol, 10.0 equiv) was added and the resulting mixture was heated at 105 °C for 1 h. The reaction was cooled to rt, amide **34** (0.0200 g, 0.070 mmol, 1.0 equiv) in toluene (2 mL) was added, and the reaction was heated at 105 °C for 24 h. The reaction was quenched with water (5 mL), extracted with ether (3 x 20 mL), washed with water (1 x 10 mL), brine (1 x 10 mL), dried and concentrated. Analysis of the crude reaction mixture by NMR indicated only the presence of the starting material. Enamine **304** was not present in the reaction mixture. Similarly, the reaction of amide **229** with 3.0 equiv of triphenylphosphonium methylide (generated from methyl triphenylphosphonium bromide and *n*BuLi) in refluxing THF for 24 h did not afford the desired enamine. In addition, amide **230** was reacted with triphenyl methyl triphenylphosphonium bromide (10.0 equiv) and KO*t*Bu (10.0 equiv) for 22 h at 105 °C. Analysis of the crude reaction mixture indicated only the presence of the starting material.



Imine 310. Lactam **229** (0.0100 g, 0.029 mmol, 1.0 equiv), benzylamine (0.063 mL, 0.058 mmol, 20.0 equiv) and *p*TsOH (1 crystal) were heated in toluene (20 mL) under Dean-Stark trap for 23 h. Solvent removal and chromatography (2/1 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.44, 1/1 EtOAc/hexanes). Yield 84% (0.0106 g, 0.024 mmol). The compound was obtained as a single imine isomer. Geometry was determined by HSQC, HMBC and NOESY correlations. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.72 (m, 5H), 1.86 (q, *J* = 11.0 Hz, 1H), 2.06-2.15 (m, 1H), 2.48-2.62 (m, 2H), 2.70-2.80 (m, 1H), 2.91 (dd, *J* = 4.4, 10.8 Hz, 1H), 3.17 (d, *J* = 10.8 Hz, 1H), 3.45 (dd, *J* = 6.1, 11.8 Hz, 1H), 3.54 (dt, *J* = 3.2, 11.9, 1H), 4.29 (d, *J* = 14.6 Hz, 1H), 4.87 (d, *J* = 14.5 Hz, 1H), 5.56 (d, *J* = 9.8 Hz, 1H), 5.90-5.97 (m, 1H), 7.05 (d, *J* = 8.3 Hz, 2H), 7.19-7.36 (m, 5H), 7.45 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 26.0, 33.8, 39.4, 40.6, 49.6, 53.3, 53.7, 55.8, 56.2, 120.2, 126.4, 128.1, 128.3, 129.8, 130.7, 131.5, 134.0, 140.8, 142.6, 165.8; IR (neat) 3021, 2922, 2855, 1655, 1487, 1451, 1405, 1073 cm^{-1}; HRMS calcd for $C_{25}H_{28}BrN_2$ (M^+ + H) 435.1436, found 435.1410. Note: the reaction of bicyclic amide **34** under similar conditions did not afford the desired imine (only starting material was observed by NMR). More forcing conditions, for example, neat amide (1.0 equiv), benzylamine (50 equiv) and *p*TsOH (10 equiv) at 170 °C for 15 h led to decomposition of the starting material.

It was also determined that the reaction of imine **310** under conditions used for epoxidation of bridged amides did not afford the desired oxaziridine (no conversion, recovery of the starting material). As expected only imines activated with

strong electron withdrawing substituent (e.g. Ts) undergo epoxidation with methylides under Corey-Chaykovsky conditions. However, such imines cannot be prepared from bridged tricylic amides due to the lower nuclophilicity of amine nitrogen. In addition, subjection of imine **310** to standard conditions used for oxidation of imines (*m*CPBA, -78 C, 0.5 h) led to the decomposition of the starting material, suggesting that N-oxidation and following elimination reactions are much faster than the desired oxidation.

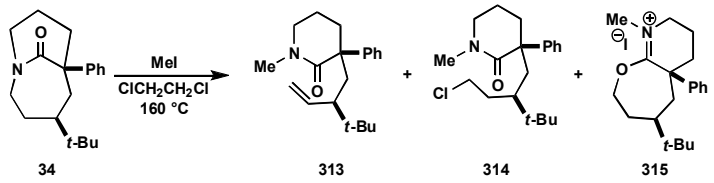


2m

Aminal **312.** According to the general procedure, lactam **260** (0.0110 g, 0.047 mmol, 1.0 equiv) was reacted with $TMSCH_2Li$ (1.0 M in pentanes, 0.47 mL, 0.47 mmol, 10 equiv) to afford after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.60, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 96% (0.0146 g, 0.045 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 0.07, 0.11 (s, 9H), 0.82-0.93 (m, 6H), 1.22-2.13 (m, 11H), 2.26-2.46 (m, 2H), 2.62-2.86 (m, 3H), 3.31-3.42 (m, 1H), 3.64-3.92 (m, 1H), 5.51-5.59 (m, 1H), 5.79-5.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of isomers) δ -0.7, 0.6, 17.7, 19.4, 25.3, 26.8, 26.9, 28.6, 9.2, 29.7, 32.8, 34.7, 35.5, 35.6, 35.7, 37.7, 50.4, 51.0, 63.0, 70.0, 73.2, 125.4, 135.6 (aminal peak was not detected, conformation assigned in analogy to **262**); IR (neat) 3400, 3013, 2951, 1456, 1381, 1248, 1223, 1107, 1069, 1007, 986 cm^{-1}; HRMS calcd for

$C_{19}H_{36}NOSi$ (M^+ + H) 322.2566, found 322.2546. Note: the reaction of **34** under identical reaction conditions did not afford the addition product, only starting material was observed in analysis of the crude reaction mixture by NMR.

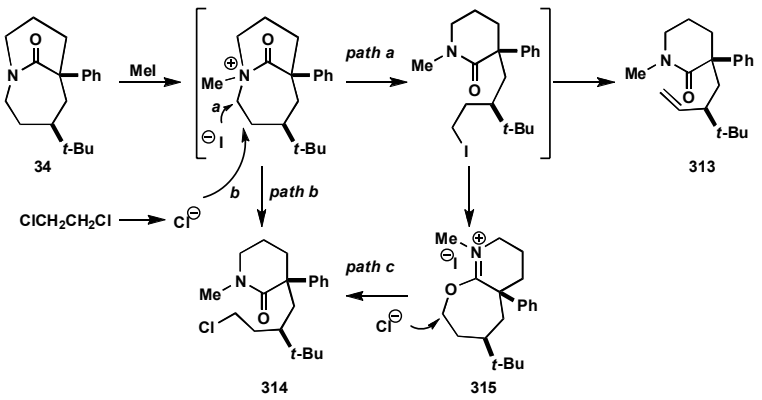
N-methylation of lactam 34



(R)-3-((R)-2-*tert*-Butylbut-3-enyl)-1-methyl-3-phenylpiperidin-2-one (313), (R)-3-((R)-2-(2-Chloroethyl)-3,3-dimethylbutyl)-1-methyl-3-phenyl piperidin-2-one (314) and (4R,5aR)-4-*tert*-Butyl-9-methyl-5a-phenyl-2,3,4,5,5a,6,7,8-octahydro oxepino[2,3-b]pyridin-9-ium iodide (315). 10 mL Biotage MW vial was charged with amide 1a (0.0200 g, 0.070 mmol, 1.0 equiv), dichloroethane (3.0 mL) and MeI (0.043 mL, 0.70 mmol, 10 equiv), the vial was sealed and heated in MW at 160 °C for 3 h. Solvent removal and chromatography (PTLC, 1/4 EtOAc/hexanes-EtOAc) afforded **313** and **314** (R_f = 0.51, 1/4 EtOAc/hexanes) as inseparable mixture (2:1) in 62% yield (0.0135 g, 0.043 mmol) and **315** as oil (R_f = 0.60, 1/10 MeOH/EtOAc) in 35% yield (0.0105 g, 0.025 mmol). Compound **313** and **314**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 12.5 H), 1.58-180 (m, 4H), 1.82-1.97 (m, 3H), 2.01-2.22 (m, 3H), 2.23-2.38 (m, 3H), 2.94 (s, 3H), 3.01 (s, 1.5H), 3.09-3.21 (m, 1.5H), 3.24-3.43 (m, 2H), 3.51-3.58 (m, 0.5H), 4.86-5.02 (m, 1H), 5.62-5.73 (m, 1H), 7.19-7.26 (m, 1.5H), 7.29-7.37 (m, 3H), 7.39-7.46 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 19.3, 27.6, 27.8, 23.0, 30.9, 32.9, 34.6, 35.4, 35.5, 35.6, 39.7, 41.5, 43.0, 45.5, 50.1, 50.3, 50.6, 51.0, 51.4, 114.7, 126.2, 126.5, 127.0, 127.1, 128.2, 128.4, 142.1, 143.8, 144.9, 172.7, 173.1; IR (neat) 2955, 2868, 1636, 1495, 1470, 1447, 1396, 1366, 1329, 1202, 908 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO$ (M^+ + H) 300.2327, found 300.2321; HRMS calcd for $C_{20}H_{30}NOCl$ (M^+ + Na) 358.1914, found 358.1909. Compound **315**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.26-1.32 (m, 1H), 1.43-1.53 (m, 1H), 1.71-1.80 (m, 1H), 1.94-2.08 (m, 2H), 2.23-2.28 (m, 1H), 2.43-2.63 (m, 3H), 3.73 (s, 3H), 3.75-3.82 (m, 1H), 4.27-4.38 (m, 2H), 4.81 (dd, *J* = 5.8, 12.0 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 7.40-7.46 (m, 1H), 7.51 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 26.9, 27.9, 33.2, 38.4, 41.2, 41.7, 42.2, 51.1, 54.0, 72.9, 125.3, 128.8, 129.9, 141.4, 177.4; IR (neat) 2954, 2918, 2866, 1635, 1446, 1406, 1348, 1242, 1031, 995 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO$ (M^+) 300.2327, found 300.2308. Note: the reaction of **34** for 10 h at 120 °C led to 88% conversion; for 3 h at 160 °C > 95% conversion. Control reaction w/o MeI (120 °C, 10 h) gave no conversion (only starting material observed by NMR). Control reaction with planar analogue of **34**, lactam **27** (10 equiv of MeI, 160 °C, 3 h) resulted in no reaction (only starting material observed by NMR). Note: tricyclic amides undergo similar reaction at 40 °C.

Proposed mechanism for the formation of **313, 314 and 315**:



Attempted N-protonation of bicyclic amides. To amide **38** (0.0119 g, 0.038 mmol, 1.0 equiv) dissolved in Et_2O (5 mL), HCl (2.0 M in Et_2O, 0.10 mL, 0.20 mmol, 5.0 equiv) was added at rt, and the resulting solution was stirred at rt for 8 h. Solvent was removed under reduced pressure and analysis of the residue by NMR indicated 1.0:1.2 mixture of the starting material and the corresponding amino acid. The protonated amide was not detected.

To amide **38** (0.0159 g, 0.051 mmol, 1.0 equiv) dissolved in acetone (5 mL), *p*TsOH (0.0096 g, 0.051 mmol, 1.0 equiv) in acetone (0.5 mL) was added, and the resulting mixture was put at -20 °C for 24 h. The reaction was allowed to warm to rt, solvent was removed under reduced pressure. Analysis of the residue by NMR indicated traces of the starting material and the corresponding amino acid (ratio <1:50). The protonated amide was not detected. Note: under identical conditions α-unsubstituted amide **3** hydrolyzed to the corresponding amino acids, while tricyclic amides undergo efficient N-protonation (possibly via the open 9-membered amino acids) to the corresponding salts.

References

1. Greenberg, A., *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*. 1st ed.; Wiley-Interscience: 2000.
2. Pauling, L., *The Nature of the Chemical Bond*. Oxford University Press: London: 1940.
3. Chalupsky, J.; Vondrasek, J.; Spirko, V. *J. Phys. Chem. A* **2008**, *112*, 693-699.
4. Mannfors, B. E.; Mirkin, N. G.; Palmo, K.; Krimm, S. *J. Phys. Chem. A* **2003**, *107*, 1825-1832.
5. Shin, S. B. Y.; Yoo, B.; Todaro, L. J.; Kirshenbaum, K. *J. Am. Chem. Soc.* **2007**, *129*, 3218-3225.
6. Poteau, R.; Trinquier, G. *J. Am. Chem. Soc.* **2005**, *127*, 13875-13889.
7. Ramachandran, G. N. *Biopolymers* **1968**, *6*, 1494-1496.
8. MacArthur, M. W.; Thornton, J. M. *J. Mol. Biol.* **1996**, *264*, 1180-1195.
9. Bednarova, L.; Malon, P.; Bour, P. *Chirality* **2007**, *19*, 775-786.
10. Edison, A. S. *Nat. Struct. Biol.* **2001**, *8*, 201-202.
11. Greenberg, A., The Amide Linkage as a Ligand-Its Properties and the Role of Distortion. In *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*, 1st ed.; Arthur Greenberg, Curt M. Breneman, Joel F. Liebman Ed. Wiley-Interscience: 2000; pp 47-83.
12. Brown, R., Studies in Amide Hydrolysis: The Acid, Base, and Water Reactions. In *The Amide Linkage: Structural Significance in Chemistry,*

*Biochemistry, and Materials Science*1st ed.; Arthur Greenberg, Curt M. Breneman, Joel F. Liebman, Ed. Wiley-Interscience: 2000; pp 85-114.

13. Lopez, X.; Mujika, J. I.; Blackburn, G. M.; Karplus, M. *J. Phys. Chem. A* **2003**, *107*, 2304-2315.

14. Mujika, J. I.; Formoso, E.; Mercero, J. M.; Lopez, X. *J. Phys. Chem. B* **2006**, *110*, 15000-15011.

15. Mujika, J. I.; Mercero, J. M.; Lopez, X. *J. Am. Chem. Soc.* **2005**, *127*, 4445-4453.

16. Liu, J.; Albers, M. W.; Chen, C. M.; Schreiber, S. L.; Walsh, C. T. *Proc. Natl. Acad. Sci. U. S. A.* **1990**, *87*, 2304-2308.

17. Fischer, G. *Chem. Soc. Rev.* **2000**, *29*, 119-127.

18. G. Fischer, F. X. S., Peptidyl-prolyl *cis/trans* isomerases. In *Molecular Chaperones and Folding Catalysts: Regulation, Cellular Functions and Mechanisms*, 1st ed.; Bakau, B., Ed. CRC: 1999; pp 461-489.

19. Georg, G. I., *The Organic Chemistry of Beta-lactams*. Wiley-VCH: 1992.

20. Bose, A. K.; Manhas, M. S.; Banik, B. K.; Srirajan, V., β-Lactams: Cyclic Amides of Distinction. In *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*, Arthur Greenberg, Curt M. Breneman, Joel F. Liebmam, Ed. Wiley: 2000; pp 157-214.

21. Silverman, R. B., *The Organic Chemistry of Drug Design and Drug Action*. 2nd ed.; Elsevier Academic Press: 2004.

22. Sneader, W., *Drug Discovery: A History*. Wiley: 2005.

23. Greenberg, A.; Venanzi, C. A. *J. Am. Chem. Soc.* **1993**, *115*, 6951-6957.

24. Greenberg, A.; Moore, D. T.; DuBois, T. D. *J. Am. Chem. Soc.* **1996**, *118*, 8658-8668.

25. Wasserman, H. H. *Nature (London, U. K.)* **2006**, *441*, 699-700.

26. Tani, K.; Stoltz, B. M. *Nature (London, U. K.)* **2006**, *441*, 731-734.

27. Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990-6992.

28. Yoshida, K.; Nomura, S.; Nishibata, Y.; Ban, Y. *Heterocycles* **1986**, *24*, 2239-2245.

29. Schill, G.; Lower, H.; Priester, C. U.; Windhovel, U. F.; Fritz, H. *Tetrahedron* **1987**, *43*, 3729-3745.

30. Schill, G.; Priester, C. U.; Windhovel, U. F.; Fritz, H. *Tetrahedron* **1987**, *43*, 3747-3763.

31. Lei, Y.; Wrobleski, A. D.; Golden, J. E.; Powell, D. R.; Aubé, J. *J. Am. Chem. Soc.* **2005**, *127*, 4552-4553.

32. Kajita, Y.; Matsubara, S.; Kurahashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 6058-6059.

33. Ito, M.; Sakaguchi, A.; Kobayashi, C.; Ikariya, T. *J. Am. Chem. Soc.* **2007**, *129*, 290-291.

34. Yoshino, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 7494-7495.

35. Miura, T.; Yarnauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085-3088.

36. Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098-6099.

37. Yamada, S., Sterically Hindered Twisted Amides. In *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*, Arthur Greenberg, Curt M. Breneman, Joel F. Liebman, Ed. Wiley: 2000; pp 215-246.

38. Yamada, S. *Rev. Heteroat. Chem.* **1999**, *19*, 203-236.

39. Hall, H. K.; Elshekeil, A. *Chem. Rev. (Washington, DC, U. S.)* **1983**, *83*, 549-555.

40. Lease, T. G.; Shea, K. J., A Compilation and Analysis of Structural Data of Distorted Bridgehead Olefins and Amides. In *Advances in Theoretically Interesting Molecules*, JAI Press Inc. : 1992; Vol. 2, pp 79-112.

41. Clayden, J.; Moran, W. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7118-7120.

42. Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169-182.

43. Otani, Y.; Nagae, O.; Naruse, Y.; Inagaki, S.; Ohno, M.; Yamaguchi, K.; Yamamoto, G.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 15191-15199.

44. Kemnitz, C. R.; Loewen, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 2521-2528.

45. Mujika, J. I.; Matxain, J. M.; Eriksson, L. A.; Lopez, X. *Chem.--Eur. J.* **2006**, *12*, 7215-7224.

46. Gillson, A. M. E.; Glover, S. A.; Tucker, D. J.; Turner, P. *Org. Biomol. Chem.* **2003**, *1*, 3430-3437.

47. Yamada, S. *J. Org. Chem.* **1996**, *61*, 941-946.

48. Bennet, A. J.; Somayaji, V.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 7563-7571.

49. Yamada, S. *Angew. Chem., Int. Ed.* **1993**, *32*, 1083-1085.

50. Duspara, P. A.; Matta, C. F.; Jenkins, S. I.; Harrison, P. H. M. *Org. Lett.* **2001**, *3*, 495-498.

51. Evans, P. A.; Holmes, A. B.; Collins, I.; Raithby, P. R.; Russell, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2325-2326.

52. Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3188-3191.

53. Yamada, S.; Sugaki, T.; Matsuzaki, K. *J. Org. Chem.* **1996**, *61*, 5932-5938.

54. Szostak, M.; Yao, L.; Aubé, J. *J. Org. Chem.* **2009**, *74*, 1869-1875.

55. Lukes, R. *Collect. Czech. Chem. Commun.* **1938**, *10*, 148.

56. Fawcett, F. S. *Chem. Rev. (Washington, DC, U. S.)* **1950**, *47*, 219-274.

57. Keese, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 528-538.

58. Warner, P. M. *Chem. Rev. (Washington, DC, U. S.)* **1989**, *89*, 1067-1093.

59. Lease, T. G.; Shea, K. J. *J. Am. Chem. Soc.* **1993**, *115*, 2248-2260.

60. Albertson, N. F. *J. Am. Chem. Soc.* **1950**, *72*, 2594-2599.

61. Yakhontov, L. N.; Rubtsov, M. V. *J. Gen. Chem. USSR* **1957**, *27*, 83-87.

62. Levkoeva, E. I.; Nikitskaya, E. S.; Yakhontov, L. N. *Dokl. Akad. Nauk* **1970**, *192*, 342-345.

63. Kostyanovsky, R. G.; Mikhlina, E. E.; Levkoeva, E. I.; Yakhontov, L. N. *Org. Mass Spectrom.* **1970**, *3*, 1023-1029.

64. Levkoeva, E. I.; Nikitskaya, E. S.; Yakhontov, L. N. *Khim. Geterotsikl. Soedin.* **1971**, 378-384.

65. Yakhontov, L. *Heterocycles* **1977**, *7*, 1033-1090.

66. Pracejus, H. *Ber.* **1959**, *92*, 988-998.

67. Pracejus, H. *Ber.* **1965**, *98*, 2897-2905.

68. Pracejus, H.; Kehlen, M.; Kehlen, H.; Matschin.H *Tetrahedron* **1965**, *21*, 2257-2270.

69. Blackburn, G. M.; Skaife, C. J.; Kay, I. T. *J. Chem. Res., Synop.* **1980**, 294-295.

70. Somayaji, V.; Brown, R. S. *J. Org. Chem.* **1986**, *51*, 2676-2686.

71. Somayaji, V.; Skorey, K. I.; Brown, R. S.; Ball, R. G. *J. Org. Chem.* **1986**, *51*, 4866-4872.

72. Somayaji, V.; Brown, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 4738-4739.

73. Somayaji, V.; Keillor, J.; Brown, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 2625-2629.

74. Skorey, K. I.; Somayaji, V.; Brown, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 5205-5206.

75. Skorey, K. I.; Somayaji, V.; Brown, R. S. *J. Am. Chem. Soc.* **1989**, *111*, 1445-1452.

76. Wang, Q. P.; Bennet, A. J.; Brown, R. S.; Santarsiero, B. D. *Can. J. Chem.* **1990**, *68*, 1732-1739.

77. Bennet, A. J.; Wang, Q. P.; Slebockatilk, H.; Somayaji, V.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1990**, *112*, 6383-6385.

78. Keillor, J. W.; Brown, R. S. *J. Am. Chem. Soc.* **1991**, *113*, 5114-5116.

79. Wang, Q. P.; Bennet, A. J.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 5757-5765.

80. Schwartz, M. A.; Buckwalter, F. H. *J. Pharm. Sci.* **1962**, *51*, 1119-1128.

81. Denzer, M.; Ott, H. *J. Org. Chem.* **1969**, *34*, 183-187.

82. Steliou, K.; Poupart, M. A. *J. Am. Chem. Soc.* **1983**, *105*, 7130-7138.

83. Brehm, R.; Ohnhauser, D.; Gerlach, H. *Helv. Chim. Acta* **1987**, *70*, 1981-1987.

84. Hall, H. K. *J. Am. Chem. Soc.* **1960**, *82*, 1209-1215.

85. Hall, H. K.; Shaw, R. G.; Deutschmann, A. *J. Org. Chem.* **1980**, *45*, 3722-3724.

86. Hall, H. K.; Johnson, R. C. *J. Org. Chem.* **1972**, *37*, 697-699.

87. Hall, H. K.; Ekechukwu, O. E.; Deutschmann, A.; Rose, C. *Polym. Bull.* **1980**, *3*, 375-382.

88. Hall, H. K.; Elshekeil, A. *Polym. Bull.* **1980**, *2*, 829-836.

89. Hall, H. K.; Elshekeil, A. *J. Org. Chem.* **1980**, *45*, 5325-5328.

90. Greenberg, A.; Wu, G. L.; Tsai, J. C.; Chiu, Y. Y. *Struct. Chem.* **1993**, *4*, 127-129.

91. Buchanan, G. L. *J. Chem. Soc., Chem. Commun.* **1981**, 814-815.

92. Buchanan, G. L.; Kitson, D. H.; Mallinson, P. R.; Sim, G. A.; White, D. N. J.; Cox, P. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1709-1712.

93. Buchanan, G. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2669-2670.

94. McCabe, P. H.; Milne, N. J.; Sim, G. A. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1459-1462.

95. Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697-1699.

96. Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Teasdale, A.; Thorntonpett, M.; Worakun, T. *Tetrahedron* **1991**, *47*, 9703-9720.

97. Grigg, R.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1998**, *39*, 4139-4142.

98. Grigg, R.; York, M. *Tetrahedron Lett.* **2000**, *41*, 7255-7258.

99. Paquette, L. A.; Dura, R. D.; Fosnaugh, N.; Stepanian, M. *J. Org. Chem.* **2006**, *71*, 8438-8445.

100. Dura, R. D.; Paquette, L. A. *J. Org. Chem.* **2006**, *71*, 2456-2459.

101. Paquette, L. A.; Barton, W. R. S.; Gallucci, J. C. *Org. Lett.* **2004**, *6*, 1313-1315.

102. Gallucci, J. C.; Dura, R. D.; Paquette, L. A. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2007**, *63*, O3417-U2616.

103. Ribelin, T. P.; Judd, A. S.; Akritopoulou-Zanze, I.; Henry, R. F.; Cross, J. L.; Whittern, D. N.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 5119-5122.

104. Paquette, L. A.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126-8127.

105. Paquette, L. A.; Ra, C. S.; Schloss, J. D.; Leit, S. M.; Gallucci, J. C. *J. Org. Chem.* **2001**, *66*, 3564-3573.

106. Preston, A. J.; Gallucci, J. C.; Paquette, L. A. *J. Org. Chem.* **2006**, *71*, 6573-6578.

107. Shea, K. J.; Cooper, D. K.; England, W. P.; Ziller, J. W.; Lease, T. G. *Tetrahedron Lett.* **1990**, *31*, 6843-6846.

108. Sparks, S. M.; Vargas, J. D.; Shea, K. J. *Org. Lett.* **2000**, *2*, 1473-1475.

109. Chow, C. P.; Shea, K. J.; Sparks, S. M. *Org. Lett.* **2002**, *4*, 2637-2640.

110. Sparks, S. M.; Chow, C. P.; Zhu, L.; Shea, K. J. *J. Org. Chem.* **2004**, *69*, 3025-3035.

111. Molina, C. L.; Chow, C. P.; Shea, K. J. *J. Org. Chem.* **2007**, *72*, 6816-6823.

112. Zhu, L.; Lauchli, R.; Loo, M.; Shea, K. J. *Org. Lett.* **2007**, *9*, 2269-2271.

113. Williams, R. M.; Lee, B. H. *J. Am. Chem. Soc.* **1986**, *108*, 6431-6433.

114. Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073-1081.

115. Aszodi, J.; Rowlands, D. A.; Mauvais, P.; Collette, P.; Bonnefoy, A.; Lampilas, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2489-2492.

116. Arata, Y.; Kobayashi, T. *Chem. Pharm. Bull.* **1970**, *18*, 2361-2363.

117. Arata, Y.; Kobayashi, T. *Chem. Pharm. Bull.* **1972**, *20*, 325-329.

118. Miyano, S.; Mibu, N.; Irie, M.; Fujii, S.; Fujisaki, F.; Abe, N.; Sumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 313-316.

119. Miyano, S.; Irie, M.; Mibu, N.; Miyamoto, Y.; Nagata, K.; Sumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1057-1063.

120. Schill, G.; Priester, C. U.; Windhovel, U. F.; Fritz, H. *Helv. Chim. Acta* **1986**, *69*, 438-441.

121. Schill, G.; Priester, C. U.; Windhovel, U. F.; Fritz, H. *Tetrahedron* **1987**, *43*, 3765-3786.

122. Schill, G.; Priester, C. U.; Windhovel, U. F.; Fritz, H. *Tetrahedron* **1990**, *46*, 1211-1220.

123. Schill, G.; Priester, C. U.; Windhovel, U. F.; Fritz, H. *Tetrahedron* **1990**, *46*, 1221-1230.

124. Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657-3668.

125. Yoshida, K.; Sakuma, Y.; Ban, Y. *Heterocycles* **1987**, *25*, 47-50.

126. Coqueret, X.; Bourellewargnier, F.; Chuche, J. *J. Org. Chem.* **1985**, *50*, 909-910.

127. Smissman, E. E.; Robinson, R. A.; Matuszak, A. J. *J. Org. Chem.* **1970**, *35*, 3823-3824.

128. Smissman, E. E.; Robinson, R. A.; Carr, J. B.; Matuszak, A. J. *J. Org. Chem.* **1970**, *35*, 3821-3822.

129. Smissman, E. E.; Robinson, R. A. *J. Org. Chem.* **1970**, *35*, 3532-3534.

130. Smissman, E. E.; Ayres, J. W. *J. Org. Chem.* **1971**, *36*, 2407-2409.

131. Smissman, E. E.; Wirth, P. J.; Aberneth.Dr; Ayres, J. W. *J. Org. Chem.* **1972**, *37*, 3486-3488.

132. Smissman, E. E.; Wirth, P. J.; Glynn, D. R. *J. Org. Chem.* **1975**, *40*, 281-283.

133. Smissman, E. E.; Wirth, P. J. *J. Org. Chem.* **1975**, *40*, 1576-1578.

134. Brouillette, W. J.; Smissman, E. E.; Grunewald, G. L. *J. Org. Chem.* **1979**, *44*, 839-843.

135. Brouillette, W. J.; Friedrich, J. D.; Muccio, D. D. *J. Org. Chem.* **1984**, *49*, 3227-3230.

136. Brouillette, W. J.; Einspahr, H. M. *J. Org. Chem.* **1984**, *49*, 5113-5116.

137. Akhtar, M. S.; Brouillette, W. J.; Waterhous, D. V. *J. Org. Chem.* **1990**, *55*, 5222-5225.

138. Brouillette, W. J.; Jestkov, V. P.; Brown, M. L.; Akhtar, M. S.; Delorey, T. M.; Brown, G. B. *J. Med. Chem.* **1994**, *37*, 3289-3293.

139. Beddoes, R. L.; Davies, M. P. H.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1992**, 538-540.

140. Baylis, A. M.; Thomas, E. J. *Tetrahedron* **2007**, *63*, 11666-11671.

141. Baylis, A. M.; Davies, M. P. H.; Thomas, E. J. *Org. Biomol. Chem.* **2007**, *5*, 3139-3155.

142. Booker-Milburn, K. I.; Anson, C. E.; Clissold, C.; Costin, N. J.; Dainty, R. F.; Murray, M.; Patel, D.; Sharpe, A. *Eur. J. Org. Chem.* **2001**, 1473-1482.

143. Kutney, J. P.; Balsevich, J.; Bokelman, G. H.; Hibino, T.; Honda, T.; Itoh, I.; Ratcliffe, A. H.; Worth, B. R. *Can. J. Chem.* **1978**, *56*, 62-70.

144. Magnus, P.; Ladlow, M.; Elliott, J.; Kim, C. S. *J. Chem. Soc., Chem. Commun.* **1989**, 518-520.

145. Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232-10245.

146. Arata, Y.; Tanaka, K. I.; Yoshifuji, S.; Kanatomo, S. *Chem. Pharm. Bull.* **1979**, *27*, 981-983.

147. Smet, M.; Van Oosterwijck, C.; Van Hecke, K.; Van Meervelt, L.; Vandendriessche, A.; Dehaen, W. *Synlett* **2004**, 2388-2390.

148. Waly, M. A.; Kodier, M. N.; Hossini, M. S. *Chin. Pharm. J.* **1994**, *46*, 135-144.

149. Boivin, J.; Gaudin, D.; Labrecque, D.; Jankowski, K. *Tetrahedron Lett.* **1990**, *31*, 2281-2282.

150. Enders, D.; Lenzen, A.; Backes, M.; Janeck, C.; Catlin, K.; Lannou, M. I.; Runsink, J.; Raabe, G. *J. Org. Chem.* **2005**, *70*, 10538-10551.

151. Enders, D.; Lenzen, A.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 3766-3769.

152. Magnus, P.; Gazzard, L.; Hobson, L.; Payne, A. H.; Rainey, T. J.; Westlund, N.; Lynch, V. *Tetrahedron* **2002**, *58*, 3423-3443.

153. Kuehne, M. E.; Li, Y. L.; Wei, C. Q. *J. Org. Chem.* **2000**, *65*, 6434-6440.

154. Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116-8129.

155. Harleymason, J. *Pure Appl. Chem.* **1975**, *41*, 167-174.

156. Amat, M.; Coll, M. D.; Bosch, J.; Espinosa, E.; Molins, E. *Tetrahedron: Asymmetry* **1997**, *8*, 935-948.

157. Moon, B.; Han, S.; Yoon, Y.; Kwon, H. *Org. Lett.* **2005**, *7*, 1031-1034.

158. Bremner, J. B.; Eschler, B. M.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1994**, *47*, 1935-1952.

159. Wu, A.; Snieckus, V. *Tetrahedron Lett.* **1975**, 2057-2060.

160. Kardosbalogh, Z.; Soti, F.; Incze, M.; Kajtarperedy, M.; Szantay, C. *Tetrahedron Lett.* **1985**, *26*, 5593-5596.

161. Kardosbalogh, Z.; Soti, F.; Incze, M.; Kajtarperedy, M.; Szantay, C. *Heterocycles* **1989**, *29*, 1589-1593.

162. Ishikura, M.; Takahashi, N.; Yamada, K.; Abe, T. *Heterocycles* **2008**, *75*, 107-118.

163. Kirby, A. J.; Komarov, I. V.; Wothers, P. D.; Feeder, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 785-786.

164. Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Am. Chem. Soc.* **1998**, *120*, 7101-7102.

165. Kirby, A. J.; Komarov, I. V.; Wothers, P. D.; Feeder, N.; Jones, P. G. In *Stereoelectronic interactions between hetero-atoms*, 1999; pp 385-391.

166. Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Chem. Soc., Perkin Trans. 2* **2001**, 522-529.

167. Bashore, C. G.; Samardjiev, I. J.; Bordner, J.; Coe, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 3268-3272.

168. Ly, T.; Krout, M.; Pham, D. K.; Tani, K.; Stoltz, B. M.; Julian, R. R. *J. Am. Chem. Soc.* **2007**, *129*, 1864-1865.

169. Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316-4318.

170. Grecian, S.; Aubé, J., Schmidt Rearrangement Reactions with Alkyl Azides. In *Organic Azides: Syntheses and Applications*, Bräse, S.; Banert, K., Eds. John Wiley and Sons: 2009.

171. Nyfeler, E.; Renaud, P. *Chimia* **2006**, *60*, 276-284.

172. Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, *35*, 146-156.

173. Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449-10459.

174. Iyengar, R.; Schildknegt, K.; Aubé, J. *Org. Lett.* **2000**, *2*, 1625-1627.

175. Iyengar, R.; Schildknegt, K.; Morton, M.; Aubé, J. *J. Org. Chem.* **2005**, *70*, 10645-10652.

176. Reddy, P. G.; Varghese, B.; Baskaran, S. *Org. Lett.* **2003**, *5*, 583-585.

177. Reddy, P. G.; Baskaran, S. *J. Org. Chem.* **2004**, *69*, 3093-3101.

178. Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W. K.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183-10194.

179. Pearson, W. H.; Hutta, D. A.; Fang, W. K. *J. Org. Chem.* **2000**, *65*, 8326-8332.

180. Pearson, W. H.; Walavalkar, R. *Tetrahedron* **2001**, *57*, 5081-5089.

181. Lertpibulpanyaa, D.; Marsden, S. P. *Org. Biomol. Chem.* **2006**, *4*, 3498-3504.

182. Zhao, Y. M.; Gu, P.; Zhang, H. J.; Zhang, Q. W.; Fan, C. A.; Tu, Y. Q.; Zhang, F. M. *J. Org. Chem.* **2009**, *74*, 3211-3213.

183. Gu, P. M.; Zhao, Y. M.; Tu, Y. Q.; Ma, Y. F.; Zhang, F. M. *Org. Lett.* **2006**, *8*, 5271-5273.

184. Zhao, Y. M.; Giu, P.; Tu, Y. Q.; Fan, C. A.; Zhang, Q. *Org. Lett.* **2008**, *10*, 1763-1765.

185. Morten, M. A. University of Kansas, 1996.

186. Zeng, Y. B.; Aubé, J. *J. Am. Chem. Soc.* **2005**, *127*, 15712-15713.

187. Frankowski, K. J.; Golden, J. E.; Zeng, Y. B.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018-6024.

188. Yao, L.; Aubé, J. *J. Am. Chem. Soc.* **2007**, *129*, 2766-2767.

189. Yao, L. University of Kansas, 2007.

190. Dougherty, D. A. *Science (Washington, DC, U. S.)* **1996**, *271*, 163-168.

191. Ma, J. C.; Dougherty, D. A. *Chem. Rev. (Washington, DC, U. S.)* **1997**, *97*, 1303-1324.

192. Yamada, S. *Org. Biomol. Chem.* **2007**, *5*, 2903-2912.

193. Smith, D. M.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4*, 1195-1201.

194. Katz, C. E.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 13948-13949.

195. Katz, C. E.; Ribelin, T.; Withrow, D.; Basseri, Y.; Manukyan, A. K.; Bermudez, A.; Nuera, C. G.; Day, V. W.; Powell, D. R.; Poutsma, J. L.; Aubé, J. *J. Org. Chem.* **2008**, *73*, 3318-3327.

196. Ribelin, T.; Katz, C. E.; English, D. G.; Smith, S.; Manukyan, A. K.; Day, V. W.; Neuenswander, B.; Poutsma, J. L.; Aubé, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6233-6235.

197. Doering, W. E.; Chanley, J. D. *J. Am. Chem. Soc.* **1946**, *68*, 586-588.

198. Werstiuk, N. H.; Brown, R. S.; Wang, Q. *Can. J. Chem.* **1996**, *74*, 524-532.

199. Ye, Q.; Komarov, I. V.; Kirby, A. J.; Jones, M. *J. Org. Chem.* **2002**, *67*, 9288-9294.

200. Hanisch, P.; Jones, A. J.; Casey, A. F.; Coates, J. E. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1202-1208.

201. Leonard, N. J. *Acc. Chem. Res.* **1979**, *12*, 423-429.

202. Rademacher, P. *Chem. Soc. Rev.* **1995**, *24*, 143-150.

203. Leonard, N. J.; Sato, T. *J. Org. Chem.* **1969**, *34*, 1066-1070.

204. Fürstner, A.; Korte, A. *Chem.--Asian J.* **2008**, *3*, 310-318.

205. Pilme, J.; Berthoumieux, H.; Robert, V.; Fleurat-Lessard, P. *Chem.--Eur. J.* **2007**, *13*, 5388-5393.

206. Griffith, R.; Bremner, J. B.; Titmuss, S. J. *J. Comput. Chem.* **1997**, *18*, 1211-1221.

207. Carroll, J. D.; Jones, P. R.; Ball, R. G. *J. Org. Chem.* **1991**, *56*, 4208-4213.

208. Gautier, A.; Pitrat, D.; Hasserodt, J. *Bioorg. Med. Chem.* **2006**, *14*, 3835-3847.

209. Waibel, M.; Hasserodt, J. *J. Org. Chem.* **2008**, *73*, 6119-6126.

210. Daum, S. J.; Martini, C. M.; Kullnig, R. K.; Clarke, R. L. *J. Med. Chem.* **1975**, *18*, 496-501.

211. Burgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065-5067.

212. Bell, M. R.; Archer, S. *J. Am. Chem. Soc.* **1960**, *82*, 151-155.

213. Leonard, N. J.; Fox, R. C.; Oki, M.; Chiavarelli, S. *J. Am. Chem. Soc.* **1954**, *76*, 630-631.

214. Kirby, A. J.; Komarov, I. V.; Bilenko, V. A.; Davies, J. E.; Rawson, J. M. *Chem. Commun. (Cambridge, U. K.)* **2002**, 2106-2107.

215. McCrindle, R.; McAlees, A. J. *J. Chem. Soc., Chem. Commun.* **1983**, 61-62.

216. Waibel, M.; Pitrat, D.; Hasserodt, J. *Bioorg. Med. Chem.* **2009**, *17*, 3671-3679.

217. Leonard, N. J.; Morrow, D. F.; Rogers, M. T. *J. Am. Chem. Soc.* **1957**, *79*, 5476-5479.

218. Adler, M.; Adler, S.; Boche, G. *J. Phys. Org. Chem.* **2005**, *18*, 193-209.

219. Iwasawa, T.; Hooley, R. J.; Rebek, J. *Science (Washington, DC, U. S.)* **2007**, *317*, 493-496.

220. Cox, C.; Wack, H.; Lectka, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 798-800.

221. Adler, M.; Marsch, M.; Nudelman, N. S.; Boche, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1261-1263.

222. Smith, B. T.; Gracias, V.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 3771-3774.

223. Gracias, V.; Zeng, Y. B.; Desai, P.; Aubé, J. *Org. Lett.* **2003**, *5*, 4999-5001.

224. Yamada, S.; Misono, T.; Tsuzuki, S. *J. Am. Chem. Soc.* **2004**, *126*, 9862-9872.

225. Wrobleski, A. D. University of Kansas, 2003.

226. Szostak, M.; Yao, L.; Aubé, J. *J. Org. Chem.* **2009**, *to be submitted*.

227. Eliel, E. L.; Wilen, S. H., *Stereochemistry of Organic Compounds* Wiley-Interscience: 1994.

228. Szostak, M.; Yao, L.; Aubé, J. *Org. Lett.* **2009**, *11, 4386-4389*.

229. Forsee, J. E.; Aubé, J. *J. Org. Chem.* **1999**, *64*, 4381-4385.

230. Block, E., In *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulphur Analogues*, Patai, S., Ed. Wiley: New York: 1980; p 539.

231. Toshimitsu, A.; Terao, K.; Uemura, S. *Tetrahedron Lett.* **1984**, *25*, 5917-5920.

232. Toshimitsu, A.; Terao, K.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1986**, 530-531.

233. Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1987**, *52*, 2018-2026.

234. Doodeman, R. University of Amsterdam (Netherlands), 2002.

235. Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073-2077.

236. Nubbemeyer, U., Synthesis of medium-sized ring lactams. In *Stereoselective Heterocyclic Synthesis Iii*, 2001; Vol. 216, pp 125-196.

237. Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5740-5750.

238. David, O.; Meester, W. J. N.; Bieraugel, H.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4373-4375.

239. Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529-3533.

240. Kan, T.; Fujiwara, A.; Kobayashi, H.; Fukuyama, T. *Tetrahedron* **2002**, *58*, 6267-6276.

241. Maier, W. F.; Schleyer, P. V. *J. Am. Chem. Soc.* **1981**, *103*, 1891-1900.

242. Kim, J. S. *Bull. Korean Chem. Soc.* **1997**, *18*, 488-495.

243. van Eis, M. J.; Wijsman, G. W.; de Wolf, W. H.; Bickelhaupt, F.; Rogers, D. W.; Kooijman, H.; Spek, A. L. *Chem.--Eur. J.* **2000**, *6*, 1537-1546.

244. Bonjoch, J.; Fernandez, J. C.; Valls, N. *J. Org. Chem.* **1998**, *63*, 7338-7347.

245. El-Subbagh, H.; Wittig, T.; Decker, M.; Elz, S.; Nieger, M.; Lehmann, J. *Arch. Pharm. (Weinheim, Ger.)* **2002**, *335*, 443-448.

246. Reichardt, C., *Solvents and Solvent Effects in Organic Chemistry*. Wiley-VCH: 2003.

247. Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75-89.

248. Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013-3043.

249. Deiters, A.; Martin, S. F. *Chem. Rev. (Washington, DC, U. S.)* **2004**, *104*, 2199-2238.

250. Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919-3952.

251. Compain, P. *Adv. Synth. Catal.* **2007**, *349*, 1829-1846.

252. Miller, S. J.; Kim, S. H.; Chen, Z. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108-2109.

253. Carreira, E. M.; Kvaerno, L., *Classics in Stereoselective Synthesis* Wiley-VCH: 2009.

254. Bamford, S. J.; Goubitz, K.; van Lingen, H. L.; Luker, T.; Schenk, H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 345-351.

255. Harris, P. W. R.; Brimble, M. A.; Gluckman, P. D. *Org. Lett.* **2003**, *5*, 1847-1850.

256. Kaul, R.; Surprenant, S.; Lubell, W. D. *J. Org. Chem.* **2005**, *70*, 3838-3844.

257. Szostak, M.; Aubé, J. *Org. Lett.* **2009**, *11*, 3878-3881.

258. Fürstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem.--Eur. J.* **2001**, *7*, 4811-4820.

259. Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8-23.

260. Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12904-12906.

261. Farina, V.; Shu, C.; Zeng, X.; Wei, X.; Han, Z.; Yee, N. K.; Senanayake, C. H. *Org. Process Res. Dev.* **2009**, *13*, 250-254.

262. Campagne, J. M.; Ghosez, L. *Tetrahedron Lett.* **1998**, *39*, 6175-6178.

263. Brouwer, A. J.; Liskamp, R. M. J. *J. Org. Chem.* **2004**, *69*, 3662-3668.

264. Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130-9136.

265. Jourdant, A.; Gonzalez-Zamora, E.; Zhu, J. P. *J. Org. Chem.* **2002**, *67*, 3163-3164.

266. Snider, B. B. *Chem. Rev. (Washington, DC, U. S.)* **1996**, *96*, 339-363.

267. Paquette, L. A.; Poupart, M. A. *J. Org. Chem.* **1993**, *58*, 4245-4253.

268. Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678-8693.

269. Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568-7569.

270. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C., *Spectroscopic Identification of Organic Compounds*. John Wiley and Sons: New York: 1991.

271. Alder, R. W.; East, S. P. *Chem. Rev. (Washington, DC, U. S.)* **1996**, *96*, 2097-2111.

272. Kim, M. G.; Bodor, E. T.; Wang, C.; Harden, T. K.; Kohn, H. *J. Med. Chem.* **2003**, *46*, 2216-2226.

273. Hanessian, S.; Mauduit, M.; Demont, E.; Talbot, C. *Tetrahedron* **2002**, *58*, 1485-1490.

274. Wonnacott, S.; Gallagher, T. *Mar. Drugs* **2006**, *4*, 228-254.

275. 4870081, US Patent.

276. Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1955**, *77*, 3164-3164.

277. Hudlicky, M., *Reductions in Organic Chemistry*. American Chemical Society: 1996.

278. Brown, H. C.; Mead, E. J.; Rao, B. C. S. *J. Am. Chem. Soc.* **1955**, *77*, 6209-6213.

279. Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459.

280. Brown, H. C.; McFarlin, R. F. *J. Am. Chem. Soc.* **1958**, *80*, 5372-5376.

281. Brown, H. C.; Krishnam, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159-7161.

282. Brown, H. C.; Weissman, P. M.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1458-1463.

283. Yoon, N. M.; Gyoung, Y. S. *J. Org. Chem.* **1985**, *50*, 2443-2450.

284. Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1-12.

285. Brummond, K. M.; Lu, J. L. *Org. Lett.* **2001**, *3*, 1347-1349.

286. Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280-8281.

287. Hoffmann, H. M. R.; Frackenpohl, J. *Eur. J. Org. Chem.* **2004**, 4293-4312.

288. Izzo, P. T.; Safir, S. R. *J. Org. Chem.* **1959**, *24*, 701-703.

289. Hwang, Y. C.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 3885-3890.

290. Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

291. Leonard, N. J.; Oki, M.; Brader, J.; Boaz, H. *J. Am. Chem. Soc.* **1955**, *77*, 6237-6239.

292. Quast, U.; Schneider, W. *Liebigs Ann. Chem.* **1982**, 1501-1508.

293. Yudin, A. K., *Aziridines and Epoxides in Organic Synthesis*. Wiley-VCH: 2006.

294. Smith, J. G. *Synthesis* **1984**, 629-656.

295. Xia, Q. H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. *Chem. Rev. (Washington, DC, U. S.)* **2005**, *105*, 1603-1662.

296. Jacobsen, E. N.; Yamamoto, H.; Pfaltz, A., *Comprehensive Asymmetric Catalysis*. Springer: 1999; Vol. 2, p pp 621− 696.

297. Parker, R. E.; Isaacs, N. S. *Chem. Rev. (Washington, DC, U. S.)* **1959**, *59*, 737-799.

298. Kas'yan, L. I.; Kas'yan, A. O.; Tarabara, I. N. *Russ. J. Org. Chem.* **2001**, *37*, 1361-1404.

299. Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6666.

300. Danishefsky, S. J.; McClure, K. F.; Randolph, J. T.; Ruggeri, R. B. *Science (Washington, DC, U. S.)* **1993**, *260*, 1307-1309.

301. Nagorny, P.; Fasching, B.; Li, X. C.; Chen, G.; Aussedat, B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 5792-5799.

302. Stevens, C. L.; Pillai, P. M. *J. Am. Chem. Soc.* **1967**, *89*, 3084-3085.

303. Stevens, C. L.; Pillai, M. P. *J. Org. Chem.* **1972**, *37*, 173-178.

304. Stevens, C. L.; Cahoon, J. M.; Pillai, P. M.; Potts, T. R. *J. Org. Chem.* **1972**, *37*, 3130-3133.

305. Coffen, D. L.; Korzan, D. G. *J. Org. Chem.* **1971**, *36*, 390-395.

306. Mithani, S.; Drew, D. M.; Rydberg, E. H.; Taylor, N. J.; Mooibroek, S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1997**, *119*, 1159-1160.

307. Bernier, D.; Blake, A. J.; Woodward, S. *J. Org. Chem.* **2008**, *73*, 4229-4232.

308. Szostak, M.; Aubé, J. *J. Am. Chem. Soc.* **2009**, *131*, 13246-13247.

309. Corey, E. J.; Chaykovski, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364.

310. Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611-620.

311. McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev. (Washington, DC, U. S.)* **2007**, *107*, 5841-5883.

312. Trost, B. M.; Melvin, L. S., *Sulfur Ylides: Emerging Synthetic Intermediates*. New York: Academic Press: 1975.

313. Corey, E. J.; Oppolzer, W. *J. Am. Chem. Soc.* **1964**, *86*, 1899-1900.

314. Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5298-5307.

315. Aggarwal, V. K.; Hebach, C. *Org. Biomol. Chem.* **2005**, *3*, 1419-1427.

316. Aggarwal, V. K.; Bae, I.; Lee, H. Y.; Richardson, J.; Williams, D. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3274-3278.

317. Schulz, V.; Davoust, M.; Lemarie, M.; Lohier, J. F.; Santos, J. S. D.; Metzner, P.; Briere, J. F. *Org. Lett.* **2007**, *9*, 1745-1748.

318. Burford, C.; Cooke, F.; Roy, G.; Magnus, P. *Tetrahedron* **1983**, *39*, 867-876.

319. Cainelli, G.; Ronchi, A. U.; Tangari, N. *Tetrahedron* **1972**, *28*, 3009-3013.

320. Lundeen, A. J.; Oehlschlager, A. C. *J. Organomet. Chem.* **1970**, *25*, 337-344.

321. Schneider, C.; Brauner, J. *Eur. J. Org. Chem.* **2001**, 4445-4450.

322. Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, *24*, 1377-1380.

323. Pfaltz, A.; Mattenberger, A. *Angew. Chem., Int. Ed.* **1982**, *21*, 71-72.

324. Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597-3600.

325. Zhao, H.; Engers, D. W.; Morales, C. L.; Pagenkopf, B. L. *Tetrahedron* **2007**, *63*, 8774-8780.

326. Chen, A. Q.; Willis, C. L. *Chin. Chem. Lett.* **2001**, *12*, 855-858.

327. Robinson, M. W. C.; Pillinger, K. S.; Graham, A. E. *Tetrahedron Lett.* **2006**, *47*, 5919-5921.

328. Karame, I.; Tommasino, M. L.; Lemaire, M. *Tetrahedron Lett.* **2003**, *44*, 7687-7689.

329. Jung, M. E.; Anderson, K. L. *Tetrahedron Lett.* **1997**, *38*, 2605-2608.

330. Lee, K. Y.; Park, D. Y.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1617-1619.

331. Wipf, P.; Xu, W. J. *J. Org. Chem.* **1993**, *58*, 825-826.

332. Lautens, M.; Ouellet, S. G.; Raeppel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4079-4082.

333. Sudha, R.; Narasimhan, K. M.; Saraswathy, V. G.; Sankararaman, S. *J. Org. Chem.* **1996**, *61*, 1877-1879.

334. Maruoka, K.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1985**, *24*, 668-682.

335. Maruoka, K.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 3303-3312.

336. Ooi, T.; Kagoshima, N.; Maruoka, K. *J. Am. Chem. Soc.* **1997**, *119*, 5754-5755.

337. Cooper, D. S. *N. Engl. J. Med.* **2005**, *352*, 905-917.

338. Wang, F.; Langley, R.; Gulten, G.; Dover, L. G.; Besra, G. S.; Jacobs, W. R.; Sacchettini, J. C. *J. Exp. Med.* **2007**, *204*, 73-78.

339. Hughes, C. C.; MacMillan, J. B.; Gaudencio, S. R.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2009**, *48*, 725-727.

340. Miwa, J. H.; Patel, A. K.; Vivatrat, N.; Popek, S. M.; Meyer, A. M. *Org. Lett.* **2001**, *3*, 3373-3375.

341. Miwa, J. H.; Pallivathucal, L.; Gowda, S.; Lee, K. E. *Org. Lett.* **2002**, *4*, 4655-4657.

342. Brown, T. J.; Chapman, R. F.; Cook, D. C.; Hart, T. W.; McLay, I. M.; Jordan, R.; Mason, J. S.; Palfreyman, M. N.; Walsh, R. J. A.; Withnall, M. T.; Aloup, J. C.; Cavero, I.; Farge, D.; James, C.; Mondot, S. *J. Med. Chem.* **1992**, *35*, 3613-3624.

343. Metzner, P., Thiocarbonyl compounds as specific tools for organic synthesis. In *Organosulfur Chemistry I*, 1999; Vol. 204, pp 127-181.

344. Jagodzinski, T. S. *Chem. Rev. (Washington, DC, U. S.)* **2003**, *103*, 197-227.

345. Murai, T., Thio-, seleno-, telluro-amides. In *Chalcogenocarboxylic Acid Derivatives*, 2005; Vol. 251, pp 247-272.

346. Murai, T.; Sano, H.; Kawai, H.; Aso, H.; Shibahara, F. *J. Org. Chem.* **2005**, *70*, 8148-8153.

347. Geng, X. L.; Wang, J.; Li, G. X.; Chen, P.; Tian, S. F.; Qu, J. *J. Org. Chem.* **2008**, *73*, 8558-8562.

348. Arshad, N.; Hashim, J.; Kappe, C. O. *J. Org. Chem.* **2009**, *74*, 5118-5121.

349. Suzuki, Y.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5026-5029.

350. Zielinski, T.; Kedziorek, M.; Jurczak, J. *Chem.--Eur. J.* **2008**, *14*, 838-846.

351. Mejia-Oneto, J. M.; Padwa, A. *Helv. Chim. Acta* **2008**, *91*, 285-302.

352. Reiner, A.; Wildemann, D.; Fischer, G.; Kiefhaber, T. *J. Am. Chem. Soc.* **2008**, *130*, 8079-8084.

353. Lee, H. J.; Choi, Y. S.; Lee, K. B.; Park, J.; Yoon, C. J. *J. Phys. Chem. A* **2002**, *106*, 7010-7017.

354. Wiberg, K. B.; Rablen, P. R. *J. Am. Chem. Soc.* **1995**, *117*, 2201-2209.

355. Wiberg, K. B.; Rush, D. J. *J. Org. Chem.* **2002**, *67*, 826-830.

356. Lauvergnat, D.; Hiberty, P. C. *J. Am. Chem. Soc.* **1997**, *119*, 9478-9482.

357. Cow, C. N.; Britten, J. F.; Harrison, P. H. M. *Chem. Commun. (Cambridge, U. K.)* **1998**, 1147-1148.

358. Hori, T.; Otani, Y.; Kawahata, M.; Yamaguchi, K.; Ohwada, T. *J. Org. Chem.* **2008**, *73*, 9102-9108.

359. Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461-6473.

360. Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev. (Washington, DC, U. S.)* **2007**, *107*, 5210-5278.

361. Szostak, M.; Aubé, J. *Chem. Commun. (Cambridge, U. K.)* **2009**, *accepted*.

362. Olah, G. A.; Nakajima, T.; Prakash, G. K. S. *Angew. Chem., Int. Ed.* **1980**, *19*, 811-812.

363. Cook, A. G., *Enamines: Synthesis, Structure and Reactions*. Marcel Deker: New York and London, 1969.

364. Rappoport, Z., *The Chemistry of Enamines*. John Wiley & Sons: 1994.

365. Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029-2030.

366. Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138-6171.

367. Doering, W. V.; Birladeanu, L.; Andrews, D. W.; Pagnotta, M. *J. Am. Chem. Soc.* **1985**, *107*, 428-432.

368. Yotphan, S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2452-2453.

369. Nielsen, A. T. *J. Org. Chem.* **1966**, *31*, 1053-1059.

370. Bender, D. R.; Coffen, D. L. *J. Org. Chem.* **1968**, *33*, 2504-2509.

371. Warawa, E. J.; Campbell, J. R. *J. Org. Chem.* **1974**, *39*, 3511-3516.

372. O'Neil, I. A.; Wynn, D.; Lai, J. Y. Q. *Tetrahedron Lett.* **2000**, *41*, 271-274.

373. Hamama, W. S.; Abd El-Magid, O. M.; Zoorob, H. H. *J. Heterocycl. Chem.* **2006**, *43*, 1397-1420.

374. Takeda, T., *Modern Carbonyl Olefination*. Wiley-VCH: 2004.

375. Hartley, R. C.; McKiernan, G. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2763-2793.

376. Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392-6394.

377. Petasis, N. A.; Lu, S. P.; Bzowej, E. I.; Fu, D. K.; Staszewski, J. P.; Akritopoulou-Zanze, I.; Patane, M. A.; Hu, Y. H. *Pure Appl. Chem.* **1996**, 667-670.

378. Dollinger, L. M.; Ndakala, A. J.; Hashemzadeh, M.; Wang, G.; Wang, Y.; Martinez, I.; Arcari, J. T.; Galluzzo, D. J.; Howell, A. R.; Rheingold, A. L.; Figuero, J. S. *J. Org. Chem.* **1999**, *64*, 7074-7080.

379. Aggarwal, V. K.; Olofsson, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5516-5519.

380. Allinger, N. L.; Blatter, H. M.; Freiberg, L. A.; Karkowski, F. M. *J. Am. Chem. Soc.* **1966**, *88*, 2999-3011.

381. Carreno, M. C.; Dominguez, E.; Garciaruano, J. L.; Rubio, A. *J. Org. Chem.* **1987**, *52*, 3619-3625.

382. Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498-1500.

383. Seebach, D.; Teschner, M. *Tetrahedron Lett.* **1973**, 5113-5116.

384. Seebach, D.; Teschner, M. *Ber.* **1976**, *109*, 1601-1616.

385. Cluzeau, J.; Oishi, S.; Ohno, H.; Wang, Z.; Evans, B.; Peiper, S. C.; Fujii, N. *Org. Biomol. Chem.* **2007**, *5*, 1915-1923.

386. Ovaa, H.; Stapper, C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H.; Blechert, S. *Tetrahedron* **2002**, *58*, 7503-7518.

387. Phapale, V. B.; Bunuel, E.; Garcia-Iglesias, M.; Cardenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790-8795.

388. Pour, M.; Spulak, M.; Balsanek, V.; Kunes, J.; Kubanova, P.; Buchta, V. *Bioorg. Med. Chem.* **2003**, *11*, 2843-2866.

389. Elseoud, O. A.; Doamaral, A. T.; Campos, M. M.; Doamaral, L. *J. Org. Chem.* **1974**, *39*, 1915-1920.

390. Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473-1478.

391. Iwama, T.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 5725-5728.

392. Lachia, M.; Denes, F.; Beaufils, F.; Renaud, P. *Org. Lett.* **2005**, *7*, 4103-4106.

393. Hendi, S. B.; Hendi, M. S.; Wolfe, J. F. *Synth. Comm.* **1987**, *17*, 13-18.

394. Zacuto, M. J.; Cai, D. W. *Tetrahedron Lett.* **2005**, *46*, 447-450.

395. Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887-4902.

396. Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216-7227.

397. Hirt, E. University of Kansas, 2009.

398. Fuller, P. H.; Kim, J. W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638-17639.

399. Ronn, M.; McCubbin, Q.; Winter, S.; Veige, M. K.; Grimster, N.; Alorati, T.; Plamondon, L. *Org. Process Res. Dev.* **2007**, *11*, 241-245.

400. Fitjer, L.; Quabeck, U. *Synth. Comm.* **1985**, *15*, 855-864.