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Proximity Effects in Nucleophilic Addition Reactions to Medium-Bridged Twisted Lactams: Remarkably Stable Tetrahedral Intermediates

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Abstract

The reactions of a series of strained bicyclic and tricyclic one-carbon bridged lactams with organometallic reagents have been investigated. These amides permit isolation of a number of remarkably stable hemiaminals upon nucleophilic addition to the twisted amide bonds present in the lactam precursors. The factors that affect the stability of the resulting bridged hemiaminals are presented. In some cases, the hemiaminals were found to collapse to the open-form amino ketones in a manner expected for traditional carboxylic acid derivatives. Transannular N···C=O interactions were also observed in some 9-membered amino ketones. Additionally, tricyclic bridged lactams were found to react with some nucleophiles that typically react with ketones but not with planar amides. The effect of geometry on the reactivity of amide bonds and the amide bond distortion range that marks the boundary of amide-like and ketone-like carbonyl reactivity of lactams are also discussed.

INTRODUCTION

The tetrahedral intermediate formed in the addition of nucleophiles to carboxylic acid derivatives is typically a short-lived species that is sometimes detected but rarely isolated.[1] Thus, although tetrahedral intermediates formed in the reaction of tertiary amides[2] and N-methoxy-N-methylamides[3] with organometallic reagents are relatively stable as their salts, and have been used extensively for synthesis of ketones, the tetrahedral intermediates themselves rapidly decompose upon protonation (Figure 1a). In addition, isolated tetrahedral intermediates would provide models for in vivo transacylation processes. Thus, the products of thiol-, alcohol- and amine-based nucleophiles with esters or amides are commonly encountered in enzymatic acylation reactions, but are difficult to investigate in the absence of enzyme stabilization.[4]

Transannular N···C=O interactions between tertiary amines and carbonyl groups[5] were the primary tool in a fundamental study by Bürgi and Dunitz[6] to designate the trajectory of the attack of nucleophiles on C=O bonds (Figure 1b). In this investigation, a set of conformationally-frozen amino-ketones kept the reactive groups in close proximity to limit the number of unproductive conformations. It is generally accepted that the Bürgi-Dunitz angle, so determined, is followed by nucleophiles in their attack on carboxylic acid derivatives, producing tetrahedral intermediates.7 Herein, we report that medium-bridged twisted amides[8] can serve as model systems to monitor a transition from stable tetrahedral

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

intermediates through intramolecular N···C=O interactions to unstable tetrahedral intermediates. As a result of this investigation, we also provide evidence that a rotation of an amide bond to ca. 50° (where 0° would correspond to planar amide and 90° to fully orthogonal amide bond)[9] is close to the border from an amide-like to ketone-like switch of reactivity of amide carbonyl groups.

Recently, our laboratory described that one-carbon bridged amides undergo novel C-N bond cleavage reactions, which are a direct result of the distortion of amide linkage.[10] We also found that despite significant twist values of the amide bonds, one-carbon bridged lactams are much less readily hydrolyzed by nucleophilic solvents when compared to fully twisted lactams.[11] 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 were additionally subjected to strong proximity effects. We hypothesized that such lactams might undergo facile nucleophilic addition reactions and additionally permit the isolation of stable tetrahedral intermediates. This supposition was supported by the very limited but important precedent obtained by Kirby[8h] and Coe[8i] groups in the study of highly constrained adamantane-like twisted amides, in which lactam transformations afforded stabilized hemiaminals.[12]

RESULTS AND DISCUSSION

Additions to bicyclic bridged amides

We began our study by investigating the behavior of one-carbon bridged amides in addition reactions of hydride, the smallest available nucleophile (Table 1). In agreement with our hypothesis, treatment of bridged bicyclic amide **1a** with $NaBH_4$ (1.0 equiv) in EtOH led to the formation of stable hemiaminal **2a** in excellent yield (entry 1). Since planar amides are typically not reduced by $NaBH_4$,[13] this transformation occurs due to the increased reactivity of the bridged amide bond. The stability of **2a** indicates that lone pairs of electrons at oxygen do not overlap with the $\sigma^*_{C–N}$ bond in the bicyclic hemiaminal system. Furthermore, since the reduction stops at the tetrahedral intermediate stage, the bridged nitrogen atom is incapable of donation of its n electrons into the $\sigma^*_{C–O}$. We recently reported that a series of epoxy-hemiaminals are similarly stabilized.[14] However, aside from Kirby and Coe precedents noted above, we are unaware of other conversions of non-adamantane twisted amides to a stable hemiaminal under mild, protic conditions.[15]

To examine the effect of structure on the stability of hemiaminals, the reduction was extended to a number of bridged amides. Bridged lactam substrates were prepared via the intramolecular Schmidt reaction as previously reported,[8l] generally as the minor component of a mixture also containing the regioisomeric fused lactam; the additional *tert*-butyl group was incorporated to enhance the proportion of bridged product obtained. Thus, bicyclic amides with electron-rich aromatic rings in the α-position as well as tricyclic lactams smoothly underwent the reduction providing isolable hemiaminals in all cases studied (Table 1, entries 2–6). However, an α-unsubstituted bridged amide and amides with sulfides in the α position led to a mixture of hemiaminals and primary alcohols (entries 7–9). This outcome suggests that although these structure types display similarly enhanced reactivity to fully planar lactams and thus reaction with $NaBH_4$, the products more readily collapse under the reaction conditions to afford aldehydes that undergo further in situ reduction.

Remarkably, reduction of bridged amides decorated with α-electron-withdrawing substituents afforded formamides (Scheme 1). In these examples, ready hemiaminal formation ultimately results in the formation of anions, stabilized by sulfonyl and 4-nitrophenyl groups (**1j** and **1k**) or allylic olefin and amide bond (**1l**). The hemiaminal intermediate may well be in equilibrium with the corresponding amino aldehyde intermediate, but the observed products

likely predominate because the anionic intermediate is readily protonated, rendering the overall conversion irreversible. Overall, the results from Table 1 and Scheme 1 demonstrate that the nature of the α-substituent plays a key role in determining the fate of tetrahedral intermediates generated from these bicyclic systems.

Using amide **1a** as a test substrate, we also briefly investigated the role of a hydride source and reaction conditions on the formation and fates of stable hemiaminals (see Supporting Information (SI) for full details).[16] A number of reducing reagents (including $LiBH_4$, $LiAlH_4$, DIBAl-H and BH_3) afforded isolable hemiaminal **2a**. Interestingly, the reduction rate with $NaBH_4$ was found to be qualitatively slower in methanol as a solvent than in ethanol, which contrasts with the reduction of typical carbonyl groups by $NaBH_4$.[17] In addition, the reduction of **1a** was suppressed when $CeCl_3$ was utilized as an additive.[18] It is possible that the decreased reaction rates are due to the increased basicity of the non-planar amide bond nitrogen, leading to subsequent hydrogen bonding or metal coordination to the amide bond nitrogen. We have previously demonstrated that the facility of N-protonation, -alkylation, or -metallation occurred to a much greater degree in bridged lactams than in normal amides,[10] however it is not clear why in the present case coordination to the nitrogen did not increase the carbonyl reactivity by inductive effect. Importantly, when a one-carbon higher homologue of **1a** ([5.3.1] ring system) was treated with $NaBH_4$, reduction was not observed, indicating that the [5.3.1] scaffold is not sufficiently distorted to permit hydride addition under these conditions.

Since hemiaminals are versatile synthetic intermediates,[19] we examined the behavior of these bridged hemiaminals in a variety of settings (Scheme 2). Noteworthy transformations included the oxidation of **2a** to the parent amide **1a** and, conversely, full reduction to amine **5** (most likely proceeding via the intermediacy of a rarely encountered bridgehead iminium ion).[20] This latter possibility was also consistent with the isolation of aminals **6** and **7** as single diastereoisomers from a mixture of hemiketal isomers in acidic methanol and by the determination that hemiaminal **2a** readily epimerizes upon treatment with acid. Both reactions could occur either via the intermediate bridged iminium ion or through the acid-promoted opening to the aldehyde and re-closure to the more thermodynamically favored isomer. All of these reactions bode well for synthetic applications of bridged hemiaminals having this [4.3.1] ring system.

We next evaluated the stability of hemiaminals formed from the addition of more sterically demanding organometallic reagents. Thus, treatment of bicyclic amide **1a** with MeLi afforded amino ketone **8a** (Table 2, entry 1). Not surprisingly, an increase in steric hindrance at the hemiaminal carbon shifted the equilibrium from the hemiaminal toward the aminoketone species. Similarly, the reaction of **1a** with secondary and tertiary organolithiums furnished the corresponding amino ketones (entries 4 and 5). Interestingly, in all cases the addition stopped at the ketone stage despite the presence of a large excess of nucleophile. Re-subjection of the aminoketone **8a** 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. While it is known that planar tertiary amides react with organometallic reagents,[1a] the high yields obtained in the transformations of such sterically-congested bridged lactams are noteworthy and likely reflect the increased electrophilicity of the distorted amide bonds.

Additions to tricyclic bridged amides

The behavior of the bicyclic hemiaminals corresponding to amino-ketones **8a–d** prompted us to examine the behavior of their tricyclic analogues. We reasoned that the additional scaffolding afforded by the six-membered ring attached to the bridged system could further stabilize the

hemiaminal form of the product.[11] Indeed, exposure of **1e** to MeLi afforded hemiaminal **9a** in good yield (Table 3, entry 1). Increased bulk close to the reactive amide bond did not influence the reaction and **1m** furnished the corresponding hemiaminal product (entry 2). Remarkably, addition of a secondary organolithium also provided stable hemiaminals (entries 3 and 4). Ultimately, addition of *tert*-butyllithium finally tipped the balance in favor of the ketone-containing product (Table 3, entries 5 and 6).

Hemiaminals **9a–10b** are some of the most sterically hindered tetrahedral intermediates isolated to date.[1a] Although, it is possible that these structures exist in equilibrium with the corresponding amino ketones, the predominance of the hemiaminal form is secured by NMR[21] and IR[22] spectra. The major species observed by NMR is characterized by a hemiaminal carbon resonance at about 86–88 ppm in the ^{13}C NMR. The ketone peak is not detected in the ^{13}C NMR and only in two instances were very weak peaks corresponding to the CO group observed in the IR (see below and SI for additional discussion regarding IR spectra). Although the analogous equilibrium is also possible in the transannular amino *tert*-butylketones **9c** and **10c**, in these cases the open-form amino ketones seem to be predominant as evidenced by ^{13}C NMR and IR spectroscopy. Overall, these results indicate that the steric contribution can override the inherent stability of tetrahedral intermediates provided by the scaffolding effects.

We wished to directly compare the reactivity of distorted and planar amides in reactions with organometallic reagents. Thus, a couple of fused amides (obtained as complementary products to the bridged lactams in the intramolecular Schmidt reactions)[8l] were subjected to the same conditions utilized for transformations of bridged lactams (Scheme 3). The reaction of fused bicyclic amide **11** with MeLi afforded enamine **12**.[23] However, the dehydration was not general and addition of *n*-BuLi to **11** resulted in a complex mixture of products including the starting amide, ketone, enamine, and alcohol. Similarly, the reaction of a tricyclic fused amide **13** with MeLi led to an inseparable 3:1:1 mixture of enamine, ketone and alcohol, with the subsequent reduction affording amine **14**. The very different results obtained from fused vs. bridged lactams emphasize the effect of the amide bond geometry on the outcome of nucleophilic addition reactions to amide bonds.

Observation of N···C=O interactions

We hypothesized that the conformation of the 9-membered ring in **8a** (Table 2, entry 1) should favor the placement of the reactive nitrogen and ketone groupings on the same side of the ring, and thus permit observation of transannular interactions between the amine and carbonyl groups under appropriate reaction conditions.[5] It is generally accepted that N···C=O interactions between amines and electrophilic ketones or aldehydes result in formation of a pseudo-tetrahedral hemiaminal-type carbon adopting a hybridization state between sp^2 and sp^3 with a partial bonding being formed between the reactive moieties.[5b] Although this type of transannular interaction has been utilized extensively in conformational analysis,[21b] mechanistic physical-organic chemistry,[5a, 5b] total synthesis projects[24] and medicinal chemistry,[5f, 5h–i, 5l–n] 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 currently studied one-carbon bridged amides would provide reasonably flexible systems with the carbonyl moved one-carbon away from the ring. The transannular hypothesis was also supported by our previous finding that amino acids resulting from hydrolysis of some of the one-carbon bridged amides are subjected to strong proximity effects induced by the placement of the reactive carboxylic acid and amine moieties on the opposite sides of the medium-size rings.[11]

We were pleased to find that upon treatment of **8a** with MeOD-d_4 a transannular N···C=O interaction takes place (Scheme 4). Thus, the carbon NMR spectrum of **8a** in chloroform

exhibits a single set of signals, with a peak at 211 ppm corresponding to the methyl ketone. These observations are consistent with a simple ketone-containing structure as drawn. In methanol, the carbonyl peak is no longer present in the ^{13}C NMR, and other peaks are significantly broadened. We ascribe these characteristics to an N···C=O interaction affording a pseudo-tetrahedral hemiaminal-type carbon (**8aa**). Addition of DCl to the methanol solution terminated the equilibrium, affording a 9:1 mixture of protonated amino ketone **8ab** and hemiaminal **8ac**. Upon dissolving **8a** in DMSO-d_6, a ca. 3:1 mixture of amino ketone and hemiaminal was formed, further illustrating that the transannular closure is favored by increased solvent polarity.[5m]

The transannular interaction between nitrogen and carbonyl group in **8a** could be independently detected by UV spectroscopy (Figure 2).[25, 5e, 5m–n] When the UV spectrum of **8a** was measured in chloroform, a weak absorption with the maximum at 241 nm was observed (ε = 793 L mol^{-1} cm^{-1}), corresponding to the $\pi \rightarrow \pi^*_{C=O}$ transition. However, the spectrum of **8a** in MeOH exhibited a new and significantly more intense absorption band appearing at a shorter wavelength (λ_{max} = 211 nm, ε = 5688 L mol^{-1} cm^{-1}), which could be ascribed to an $n_N \rightarrow \pi^*_{C=O}$ absorption. The change in absorption of **8a** in methanol is similar to that observed in earlier examples of N···C=O interactions. [25, 5e, 5m–n] Furthermore, a detailed examination of the IR spectra[22] of a series of bicyclic and tricyclic amino ketones and hemiaminals **8a–8d** and **9a–10c** also suggest the existence of the transannular interaction in the 9-membered ring systems (see SI for additional discussion).

Although the above data are clearly consistent the presence of N···C=O interaction, we cannot completely rule out a dynamic bond breaking and forming event taking place between the amino ketone and hemiaminal, with the latter species being stabilized in polar solvents. This type of weak covalent character of N···C=O interaction, as contrasted to the traditionally accepted $n_N \rightarrow \pi^*_{C=O}$ homoconjugation,[5b] has also been recently suggested in the literature.[5l]

It is noteworthy that this single bridged amide can be utilized to monitor a continuum of change: from isolable hemiaminal **2a** (stable tetrahedral intermediate) to amino ketone **8a** (resulting from the collapse of said tetrahedral intermediate) through N···C=O interaction (**8aa**, MeOH). This picture also includes a progressive change from hemiaminals **9a–10b** (stable tetrahedral intermediates) to amino ketones **9c** and **10c** (collapsed tetrahedral intermediates).

As noted above, we hypothesized that the difference in stability between the collapsed amino ketone **8a** (Table 2, entry 1) and the stable hemiaminal **9a** (Table 3, entry 1) could be due to the increased scaffolding effect gained by the presence of the additional cyclohexene ring in **9a**. However, we also considered that it could arise from a difference in distortion parameters of the two parent amides. As previously established by X-ray crystallographic analysis, the tricyclic lactam **1e** is characterized by Winkler-Dunitz distortion parameter,[9] twist angle, τ = 51.5°,[11] while a representative bicyclic lactam **1b** is slightly less distorted (τ = 43.2°).[26]

Reactions with additional nucleophiles

To investigate this point we subjected bicyclic and tricyclic bridged amides to reactions with some oxygen and nitrogen nucleophiles, which typically do not react with planar amides (Scheme 5). Thus, reactions of tricyclic lactams with 1,3-propanediol and benzylamine afforded bridged ketal **15** and bridged imine **16**, respectively, whereas fused bicyclic lactams were unreactive under these conditions as expected. In addition, the tricyclic **1e** furnished bridged hydrazone **17**. This particular reaction was also performed to allow comparison of one-carbon bridged lactams with an adamantane-type bridged amide reported by Coe and coworkers (Figure 3).[8i] Interestingly, although in the case of Coe's amide a subsequent full

reduction to the corresponding amine was carried out, we were unable to reduce **17** under Wolff-Kishner conditions.

Furthermore, although Kirby demonstrated that perfectly perpendicular 1-aza-2-adamantanone ($\tau = 90.5°$) undergoes Wittig olefination (Figure 3),[8h] similar treatment of the currently investigated amides did not result in enamines (only starting amides were re-isolated). However, the corresponding bridged exocyclic enamine **18** could be conveniently prepared from **1a** utilizing Petasis reagent (Scheme 6).[27] Although some planar amides undergo olefination under Petasis conditions, to the best of our knowledge this is the first example of a direct olefination of a bridged bicyclic lactam with a metalloorganic reagent. It is noteworthy that the oxatitanacyclobutane intermediate did not collapse with the opening to the nine-membered ring system (in a fashion similar to **8a**), and that the resulting enamine was stable to silica gel chromatography.

Overall, these results clearly demonstrate that lactams having a twist angle of ca. 50° display reactivity patterns much closer to those expected for twisted rather than planar amides. It is interesting to note that the bridged structures resulting from nucleophilic addition reactions to these distorted lactams (Scheme 5) are also stabilized through proximity effects.

CONCLUSION

In summary, we have shown that tetrahedral adducts formed from the addition of nucleophiles to one-carbon medium-bridged twisted amides exhibit remarkable proximity-induced stability. These amides can serve as models to delineate the transition from stable tetrahedral intermediates to N···C=O interactions to unstable tetrahedral intermediates. In addition, this work 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. Importantly, lactams characterized by the midway rotated amide bonds undergo certain reactions typically associated with ketones but not planar amides. Our laboratory is currently investigating the chemistry of one-carbon bridged amides and their derivatives, including heteroatom-substituted tetrahedral intermediates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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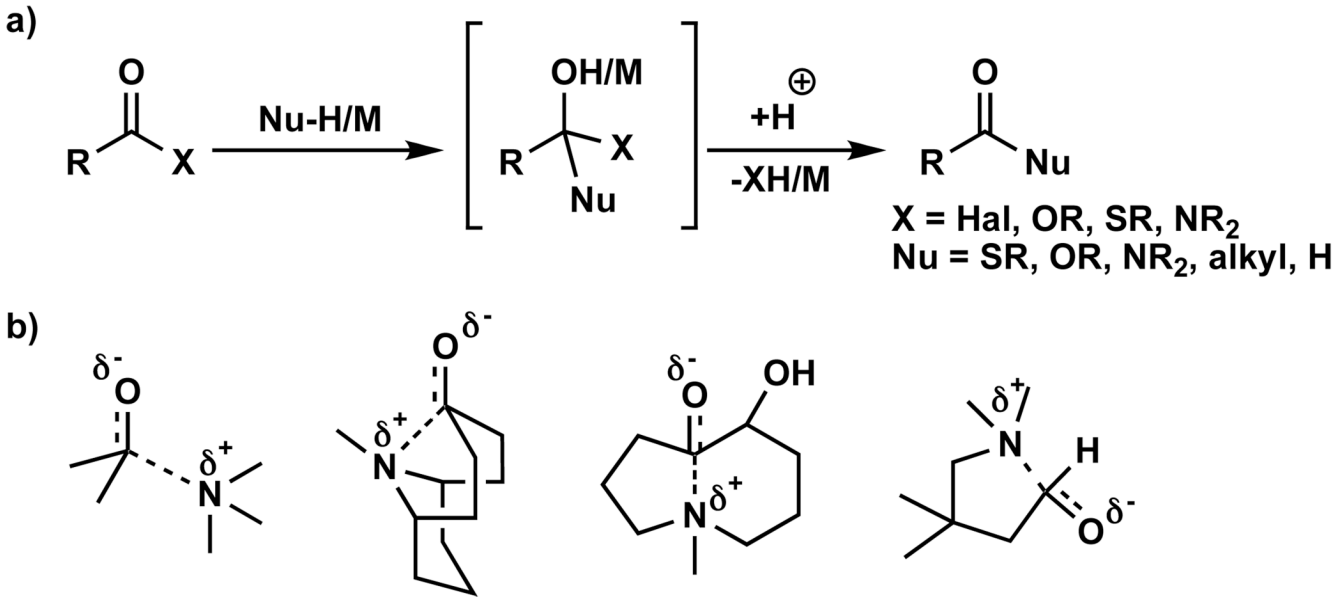


Figure 1.
a) Reaction of carboxylic acid derivatives with nucleophiles; b) examples of N···C=O interactions.

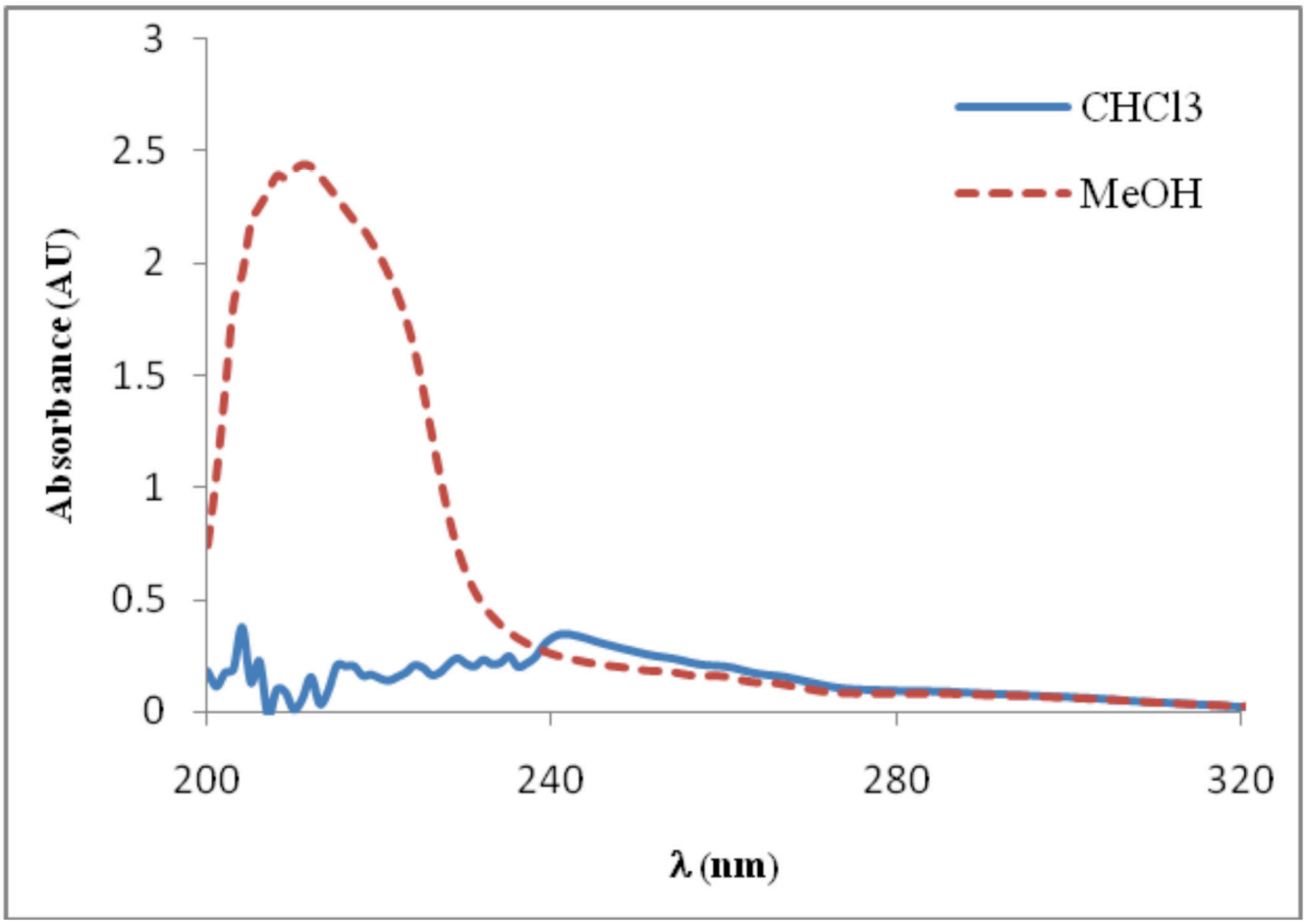


Figure 2.
UV spectra in $CHCl_3$ (solid line) and MeOH (dotted line) of **8a**.

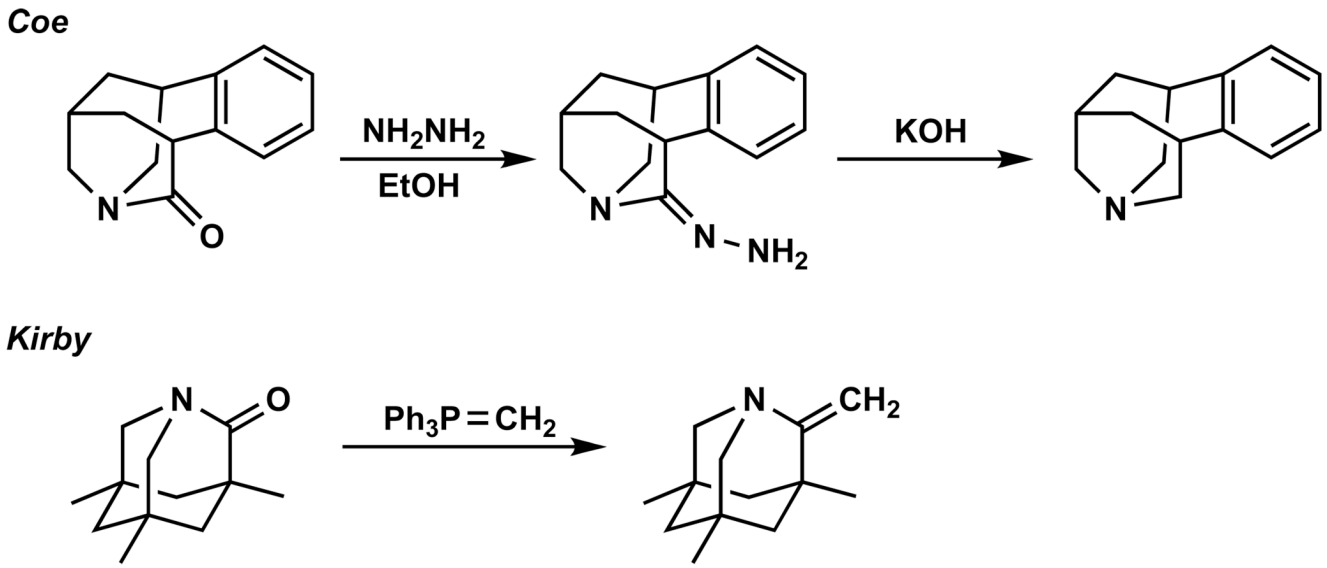
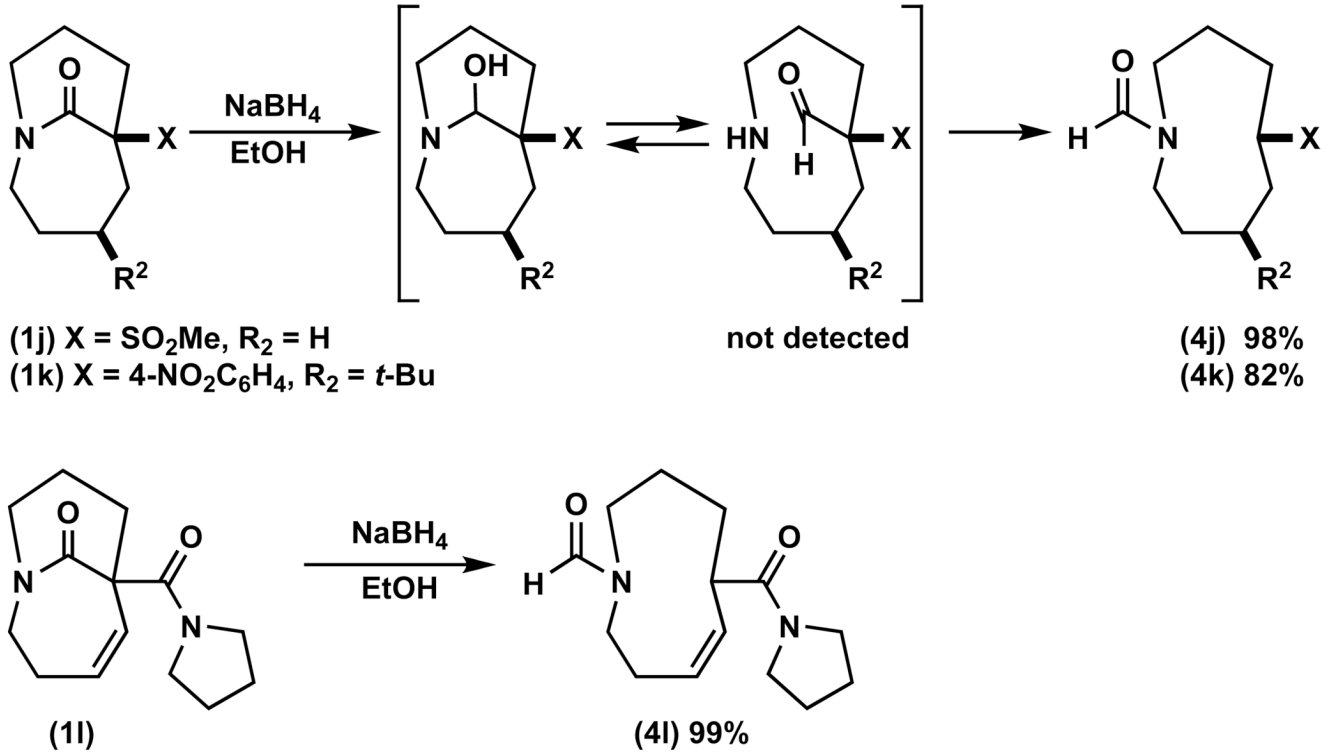
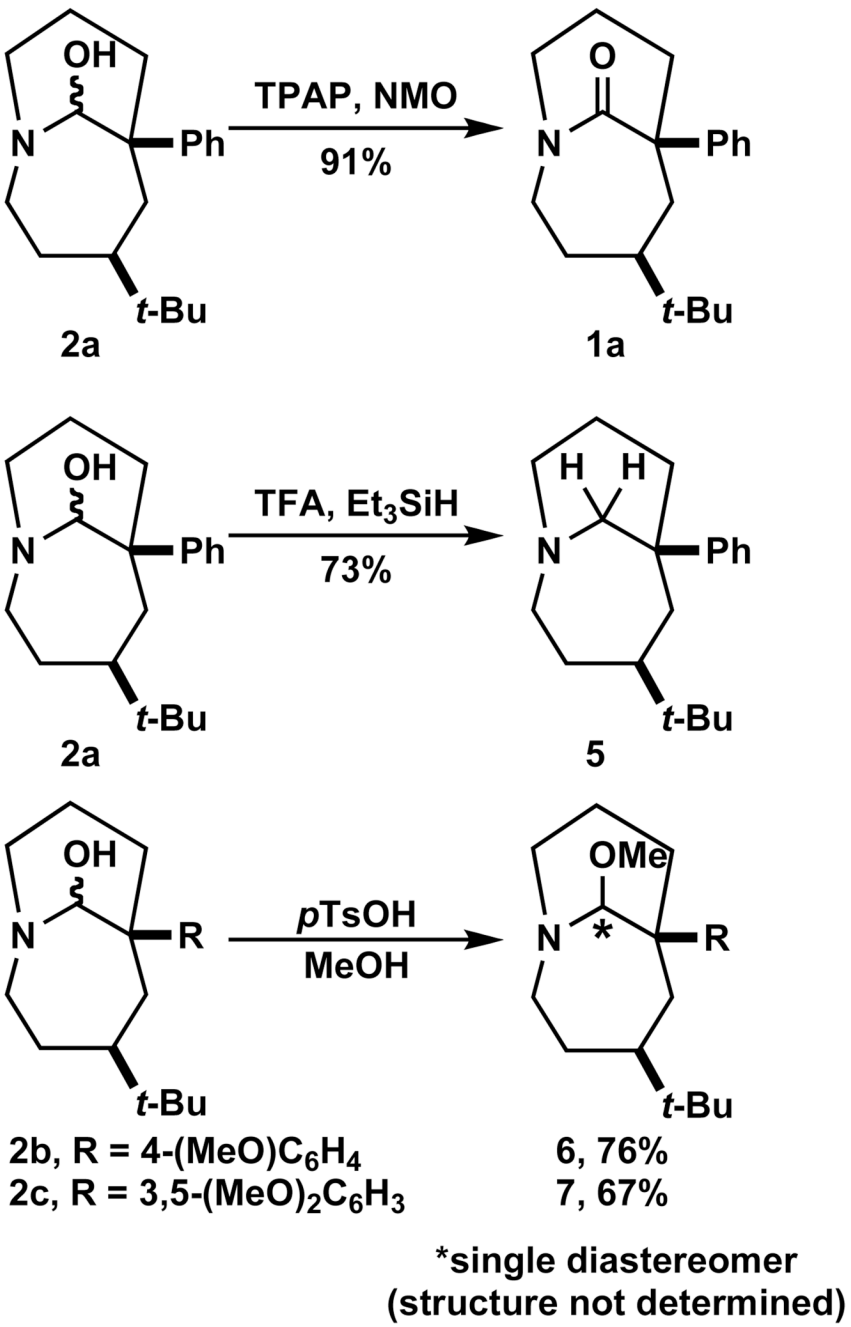


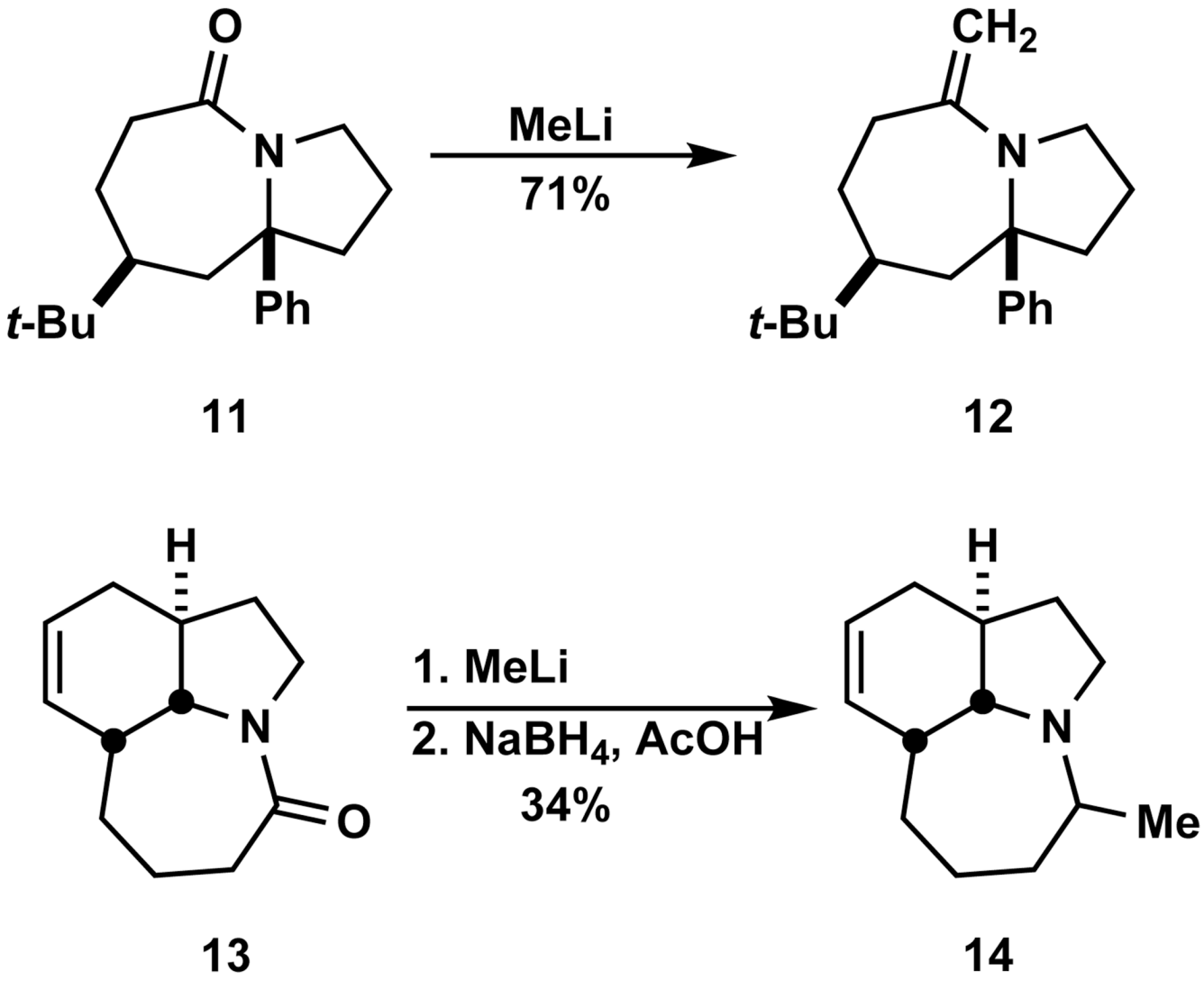
Figure 3.
Transformations of adamantane-type bridged amides.



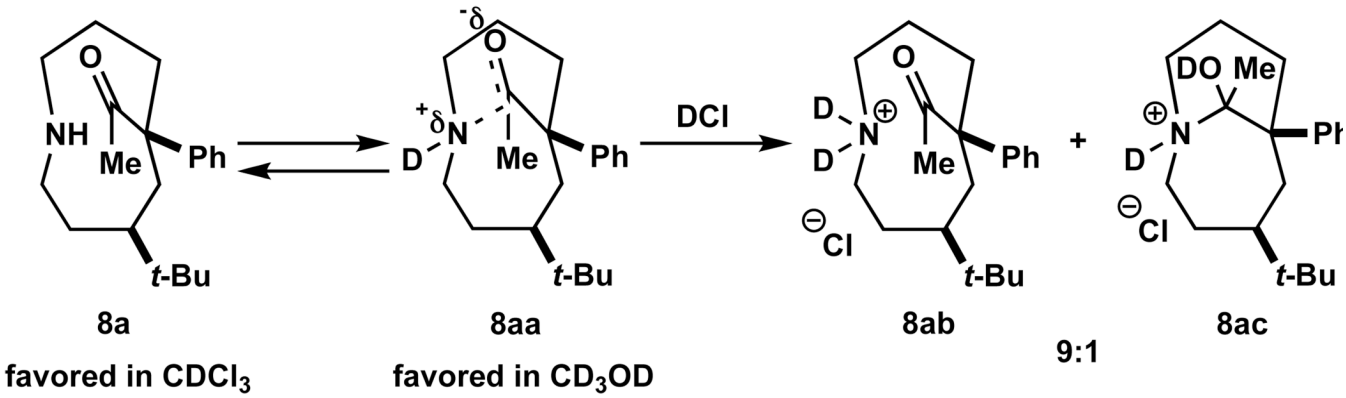
Scheme 1.
Reduction of Bridged Lactams with Cleavage of C–C Bond



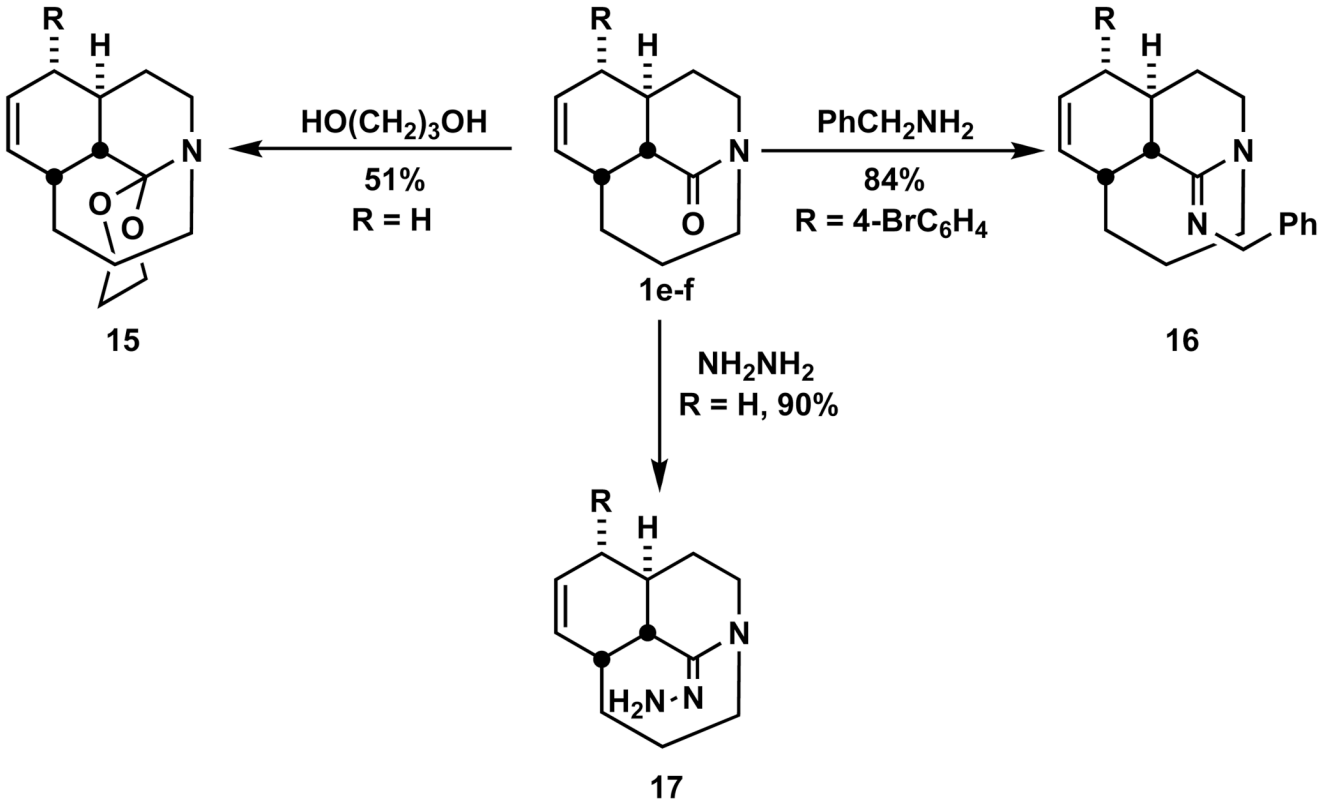
Scheme 2.
Synthetic Transformations of Bridged Hemiaminals



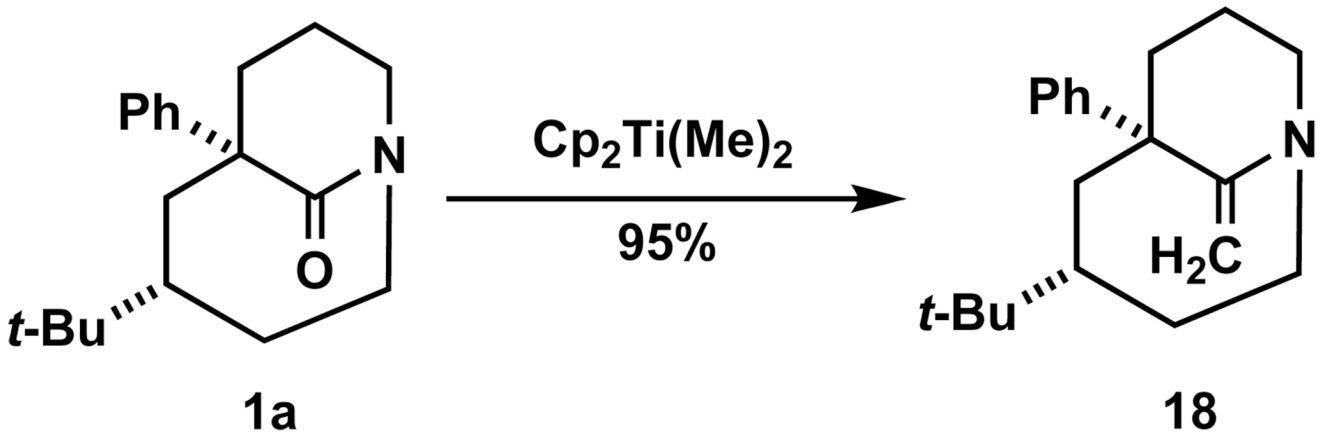
Scheme 3.
Organometallic Addition to Planar Analogues of Bridged Amides



Scheme 4.
Transannular Interaction in Bicyclic System



Scheme 5.
Transformations of Bridged Amides



1a 18

Scheme 6.
Petasis Olefination of Lactam **1a**

Table 1

Hydride Addition to Bridged Amides

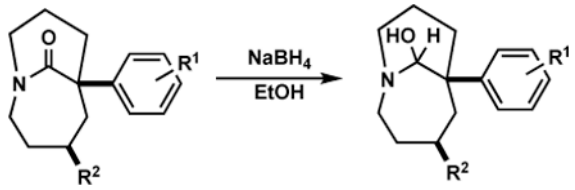
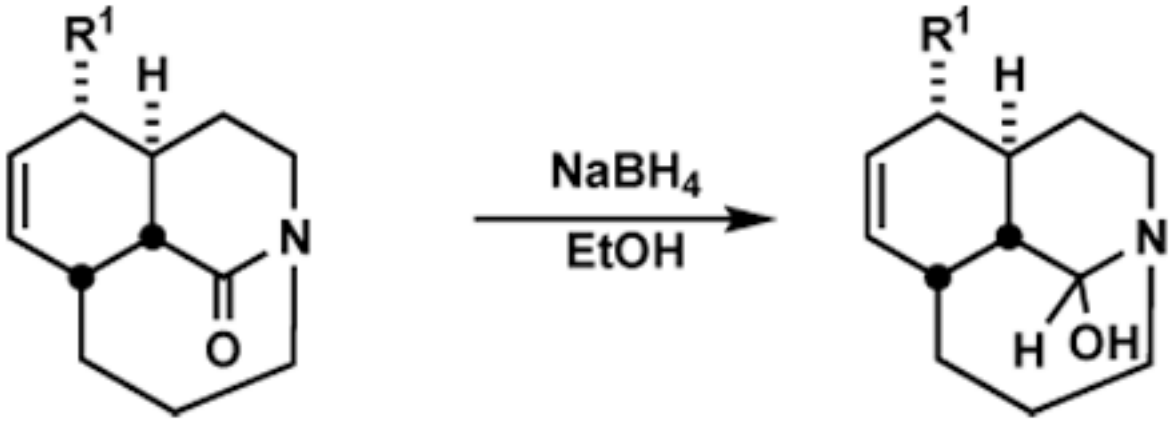
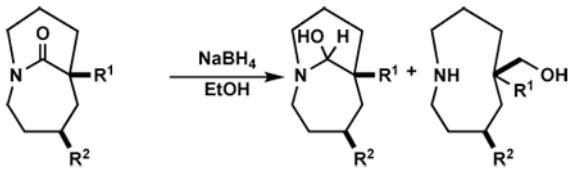
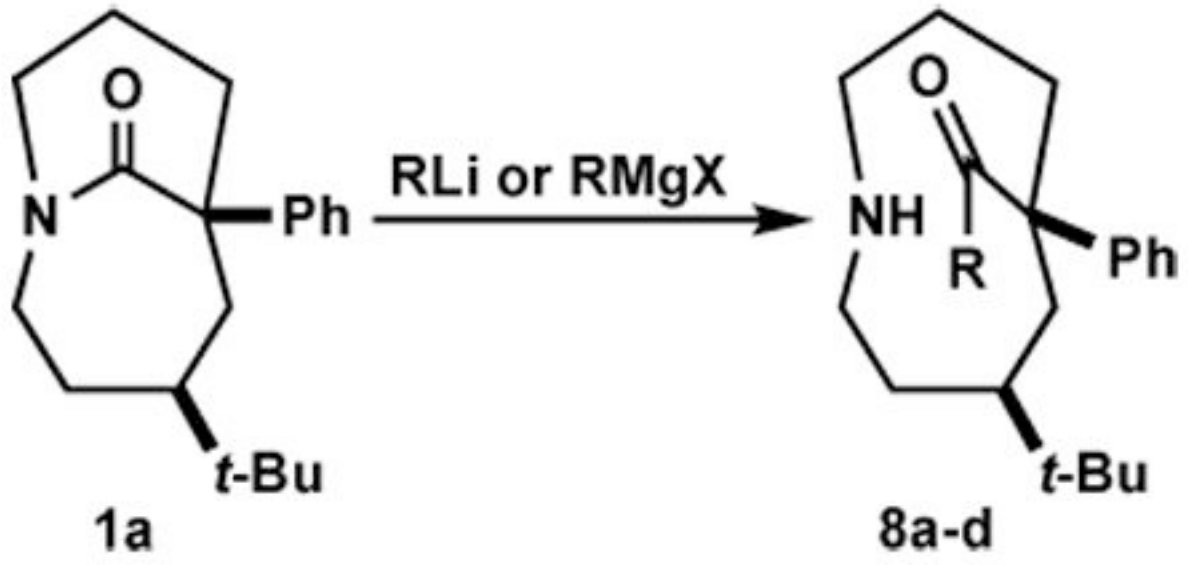
entry	bridged amide	product	yield [%]
			
1	(**1a**) R^1 = H, R^2 = *t*-Bu		(**2a**) 90
2	(**1b**) R^1 = 4-(MeO), R^2 = *t*-Bu		(**2b**) 91
3	(**1c**) R^1 = 3,5-$(MeO)_2$, R^2 = *t*-Bu		(**2c**) 94
4	(**1d**) R^1 = 3,4-(OCH_2O), R^2 = *t*-Bu		(**2d**) 95
			
5	(**1e**) R^1 = H		(**2e**) 91
6	(**1f**) R^1 = 4-BrC_6H_4		(**2f**) 88
			
7	(**1g**) R^1 = H, R^2 = *t*-Bu	(**2g**) 24	(**3g**) 52
8	(**1h**) R^1 = SMe, R^2 = H	(**2h**) 40	(**3h**) 48
9	(**1i**) R^1 = SPh, R^2 = H	(**2i**) 62	(**3i**) 34

Table 2

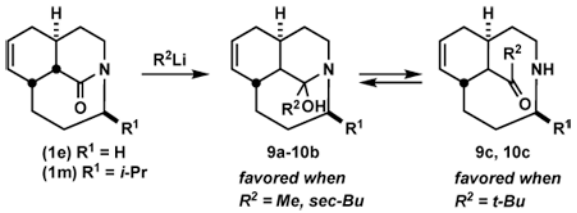
Organometallic Addition to Bicyclic Amides



entry	amino-ketone	R	reagent	yield [%]
1	**8a**	Me	MeLi	89
2	**8a**	Me	MeMgI	73
3	**8b**	*n*-Bu	*n*-BuLi	83
4	**8c**	*sec*-Bu	*sec*-BuLi	93
5	**8d**	*tert*-Bu	*tert*-BuLi	80

Table 3

Organometallic Addition to Tricyclic Amides



entry	amide	hemiaminal/ amino-ketone	R^2	reagent	yield [%]
1	**1e**	**9a**	Me	MeLi	95
2	**1m**	**10a**	Me	MeLi	92
3	**1e**	**9b**	*sec*-Bu	*sec*-BuLi	80
4	**1m**	**10b**	*sec*-Bu	*sec*-BuLi	88
5	**1e**	**9c**	*tert*-Bu	*tert*-BuLi	90
6	**1m**	**10c**	*tert*-Bu	*tert*-BuLi	90