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CYCLOADDITION REACTIONS OF *N*-ALKYL-α,β-UNSATURATED IMINES: FACILE PREPARATION OF AZAHETEROCYCLES FOR SYNTHESIS AND BIOLOGICAL APPLICATIONS

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Abstract – In this review, we will describe the utilization of formal [4 + 4] cycloaddition reaction of *N*-alkyl-α,β-unsaturated imines derived from acrolein and biogenic alkylamines to synthesize 2,6,9-triazabicyclo[3.3.1]nonanes and 1,5-diazacyclooctanes. We also include here a new structural data of 1,5-diazacyclooctane determined by X-ray crystallography. Biological examination of 1,5-diazacyclooctanes revealed for the first-time its role in inhibition of amyloid-β (Aβ) 1-40 fibrillization. Eventually, we also found that when substituted or unsubstituted acrolein is reacted with chiral ethanolamine in the presence of formaldehyde, then hexahydropyrimidines or 1,3,5-triazacyclooctanes were produced in high yield and stereoselectivity through formal [4 + 2] or [4 + 2 + 2] cycloaddition reactions. Lastly, simple functional group manipulations of the cycloaddition products can be used to synthesize chiral 1,3-diamines, which could not be simply accessed by other methods.

CONTENTS

1. INTRODUCTION

α,β-Unsaturated imines, which are typically prepared by the condensation of α,β-unsaturated carbonyl compounds and primary amines, are versatile synthetic intermediates and used extensively in organic synthesis and bioconjugation chemistry.[1-8] The benefit of utilizing imine in bioconjugation and in vivo chemistry is that since a large part of amine-containing biomacromolecules are biosynthesized through imine chemistry, imine-mediated chemical reactions will not face the same challenges that classical synthetic organic chemical reactions face within living systems.

Recently, we are synthetically exploring the overlooked reactivity of *N*-alkyl-α,β-unsaturated imines, which derived from acrolein and alkylamines, for their potential in novel chemical reactions.[9-12] In parallel to this work, our studies have also shown that the unique reactivity of *N*-alkyl-α,β-unsaturated imines can be involved in pathways that regulate biologically important processes.[13-19] One such example is a formal [4 + 4] cycloaddition reaction between conjugated imines, which derived from biogenic amines and toxic acrolein produced during oxidatively stressed conditions, to generate 1,5-diazacyclooctane derivatives. Our studies have shown that the 1,5-diazacyclooctanes may be involved with various oxidative stress processes and amyloid aggregation.[14,17] We not only elucidated the biological functions of 1,5-diazacyclooctanes, but also applied "bio-mimetic" imine cyclization to the asymmetric synthesis of various chiral 1,3-diamines.[12]

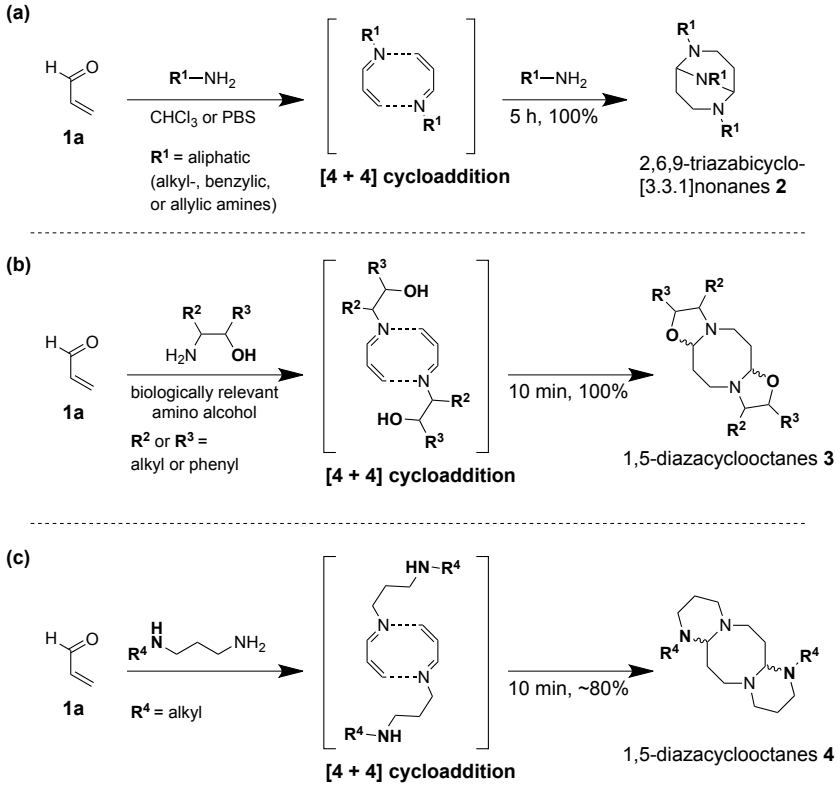
Here, we will describe our recent results from the discovery of the cycloaddition reaction of *N*-alkyl-α,β-unsaturated imines to its biological and chemistry application. A new X-ray crystallography data analysis of 1,5-diazacyclooctane is also included. We will also describe the future direction of our research toward identifying new organic transformations and revealing unexplored biofunctions within living systems.

2. DISCOVERY OF FORMAL [4 + 4] CYCLOADDITION REACTION OF *N*-ALKYL-α,β-UNSATURATED IMINES

Acrolein is a highly toxic unsaturated aldehyde[20] produced during the partial burning of organic materials. It can also be generated by cells under oxidative stress conditions through the enzymatic oxidation of threonine or polyamines,[21-23] or during reactive oxygen species (ROS)-mediated oxidation of highly unsaturated lipids.[24] The unsubstituted and highly reactive acrolein produced through the latter pathway can react with nearby thiol, hydroxyl, or amino functional groups on DNA, proteins, or phosphatidyl

ethanolamines to accelerate the oxidative stress processes associated with various disease states. Studies of acrolein conjugates could, therefore, contribute to a better understanding of the relationship between acrolein and oxidative stress and, hence, various diseases at a molecular level.[25-27]

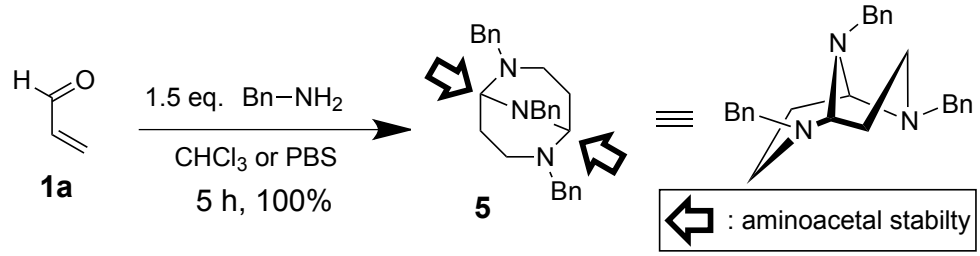
In our research program, which explores the novel reactivities of *N*-alkyl-α,β-unsaturated imines, we found by chance that imines derived from alkylamines and acrolein participate in hitherto unknown "head-to-tail" [4 + 4] dimerization in organic solvents or, more importantly, in aqueous media (Scheme 1). In literature, there was only one example reported the [4 + 4] cyclodimerization of azadiene, where 1,5-diazacyclooctane derivative was isolated from the reaction mixture as a byproduct.[28] In our case, depending on the structure of the alkyl substituents on the nitrogen atom, the reactions can provide 2,6,9-triazabicyclo[3.3.1]nonanes **2** (Scheme 1a)[9,13,29] or 1,5-diazacyclooctanes **3** and **4** (Schemes 1b and 1c)[10,14,15] as eight-membered heterocyclic products within 30 min in near quantitative yields. The extremely high reactivities of the unsaturated imines at low μM concentrations under physiological conditions is noteworthy and strongly suggests that these reactions likely to occur in biological systems, i.e., in and on cells.[17] These previously unrecognized azaheterocycles might be responsible for a variety of biological functions.



Scheme 1. Formation of azaheterocycles from acrolein and amines through a [4 + 4] cycloaddition of intermediary imines. (a) The 2,6,9-triazabicyclo[3.3.1]nonanes from aliphatic amines. (b) The 1,5-diazacyclooctanes from the biologically relevant vicinal aminoalcohols through a hydroxyl-mediated cycloaddition. (c) The 1,5-diazacyclooctanes from polyamines through an amine-mediated cycloaddition.

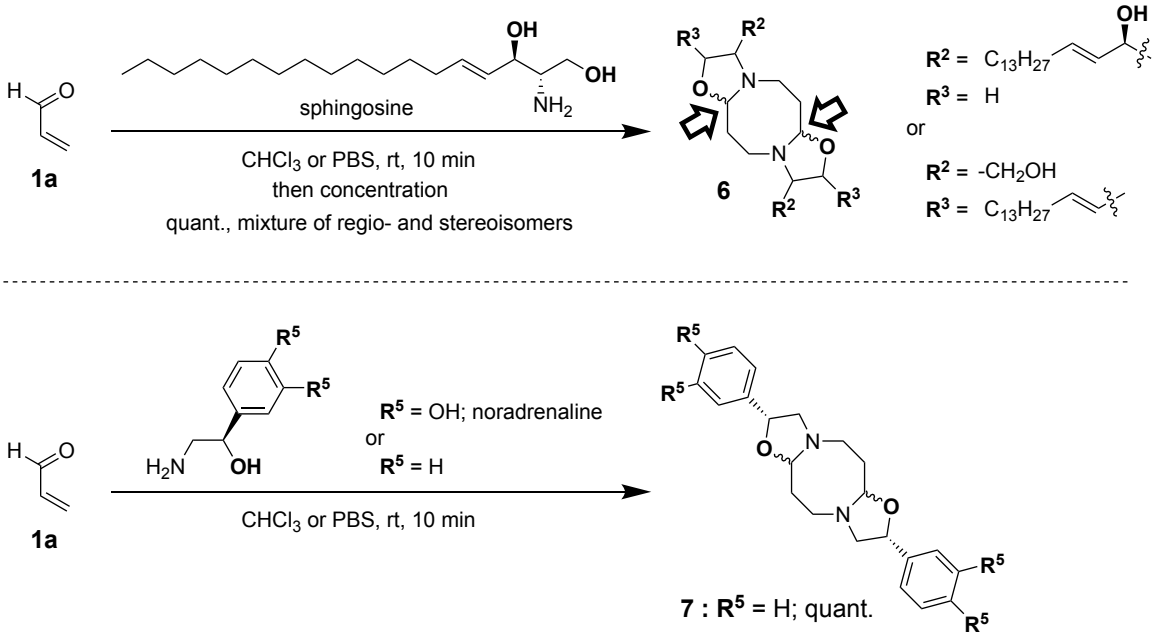
3. THE 1,5-DIAZACYCLOOCTANES FROM ACROLEIN AND BIOGENIC ALKYLAMINES

Acrolein readily reacts with various alkylamines to produce azaheterocycles via formal [4 + 4] cycloaddition of the *N*-alkyl-α,β-unsaturated imines intermediate. The resulting types of azaheterocycle structures depend on structure of the amine used as starting material. A reaction with excess aliphatic amines, e.g., alkyl-, benzylic, and allylic amines, which are abundant among biomolecules such as lysine ε-amino group, smoothly provided the 2,6,9-triazabicyclo[3.3.1]nonane derivatives in quantitative yield (the reaction with benzyl amine is illustrated in Scheme 2).[9,13] Although unsaturated imines obtained from acrolein and aliphatic amines were thought to be in equilibrium with the [4 + 4] dimerization products, this has not been observed. This is presumably due to unfavorable strain in the eight-membered ring, i.e., eight-membered dienamine, which shifts the equilibrium towards starting unsaturated imines. The use of excess amines potentially traps the eight-membered enamines efficiently as aminoacetals to produce the thermodynamically stable 2,6,9-triazabicyclo[3.3.1]nonane **5** (Scheme 2).



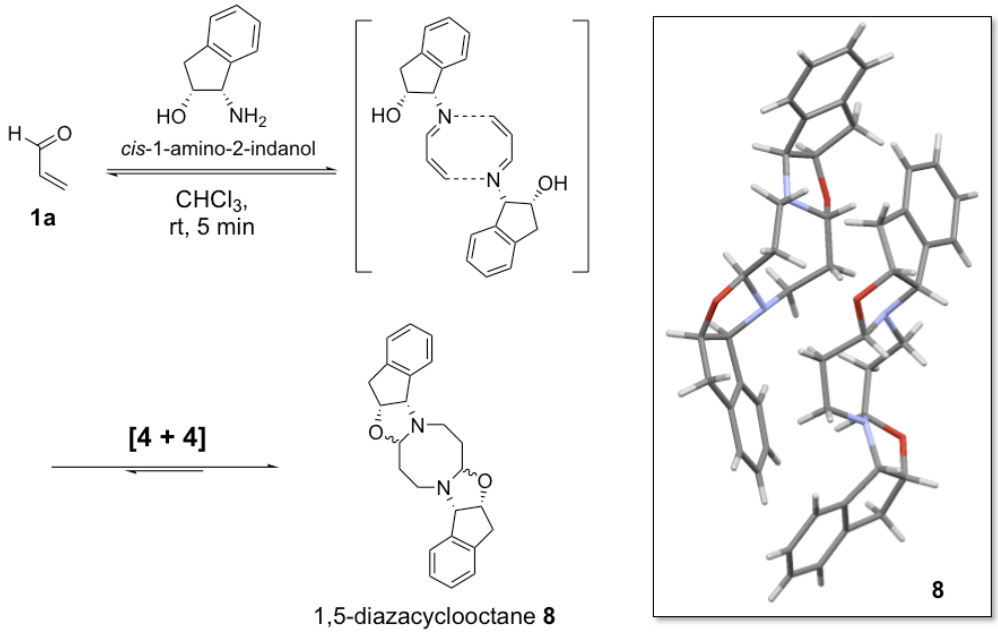
Scheme 2. The 2,6,9-triazabicyclo[3.3.1]nonane from reaction of acrolein with benzylamine, a model of lysine ε-amino group

On the other hand, the reaction of acrolein with one equivalent of biologically relevant 1,2-aminoalcohols, i.e., sphingosine or norepinephrine derivatives, readily provided 1,5-diazacyclooctanes **6** and **7** in quantitative yield (Scheme 3).[15] The nucleophilic hydroxyl groups of 1,5-diazacyclooctane molecules is believed to favorably stabilize 1,5-diazacyclooctane formation, via intramolecular interactions, more efficiently than 2,6,9-triazabicyclo[3.3.1]nonane formation.



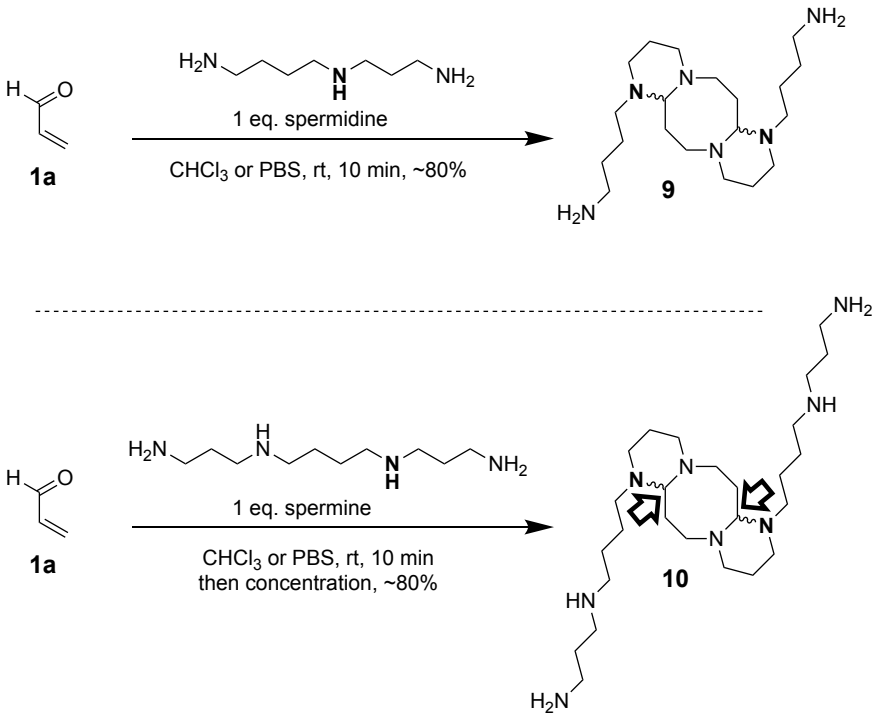
Scheme 3. The 1,5-diazacyclooctanes from reaction of acrolein with biologically relevant vicinal aminoalcohols

Eventually, we were able to determine the crystal structure of 1,5-diazacyclooctane **8** derived from (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol (Scheme 4). Crystal structural analysis shows that the eight-membered compound forms an interesting assembly with ladder structure. This X-ray crystallographic analysis could also be used as analogy to determine the structure of other 1,5-diazacyclooctane derivatives.



Scheme 4. Formal [4 + 4] cycloaddition reaction of imine derived from acrolein **1a** and (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol to yield 1,5-diazacyclooctane **8**. The chemical structure of 1,5-diazacyclooctane **8** was determined unambiguously by X-ray crystallographic analysis. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition

number CCDC-1829610 for compound **8**. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
Polyamines, such as the consecutive 1,3- and 1,4-diamine containing spermidine and spermine, were also found to participate in smooth formal [4 + 4] cycloaddition reactions with one equivalent of acrolein to produce corresponding 1,5-diazacyclooctanes **9** and **10** (Scheme 5).[14] These azaheterocycles are believed to be stabilized by bis-aminoacetal formation via amino group substituents on the imino nitrogen.



Scheme 5. The 1,5-diazacyclooctanes from reaction of acrolein with polyamines

4. POLYAMINE-DERIVED 1,5-DIAZACYCLOOCTANES AS BIOGENIC INHIBITORS OF AMYLOID FIBRILLATION

With an increase of cellular polyamine or cytotoxic acrolein levels, many research has shown a correlation with the progression of certain diseases that are associated with oxidative stress (cancer,[30] stroke,[31,32] or Alzheimer's disease[33]). In the brains of Alzheimer's disease (AD) patients, observed levels of acrolein or spermine are increased,[34,35] whereas spermidine levels is decreased.[34] Recent reports also indicate that polyamines can promote amyloid-β peptide 1–40 (Aβ40) fibrillization, which is implicated in the acceleration of AD pathogenesis.[36] Our investigations into the biological significance of azaheterocycle polyamine–acrolein conjugates, i.e. 1,5-diazacyclooctanes, led us to focus on Aβ fibrillization, largely due to the fact that acrolein is produced in the brain tissues of AD patients as a polyamine metabolite during oxidative stress processes. It was speculated that the 1,5-diazacyclooctanes may potentially control and/or modulate disease progression.

Unlike previous reports suggesting that polyamines promote Aβ40 fibrillization, our study has clearly

shown that the biologically relevant 1,5-diazacyclooctanes **9** and **10** inhibit fibrillization and hence cytotoxicity (Figure 1). We thus incubated Aβ40 peptides in mixtures of acrolein, polyamines (i.e., spermine and spermidine), and 1,5-diazacyclooctanes **9** and **10** formed by acrolein and polyamines. Neither of the first two molecules alone had any effects on fibrillation, but the cyclic compounds turned out to be powerful inhibitors. We also found that when acrolein and polyamines were added together into living cells, they combined naturally through [4 + 4] cycloaddition to create the cyclic molecule. Based on detailed chemical and biological experiments, we found that these compounds inhibit formation of the highly toxic "soluble" oligomer species while minimizing the toxic "insoluble" Aβ40 fibrillization process.[17]

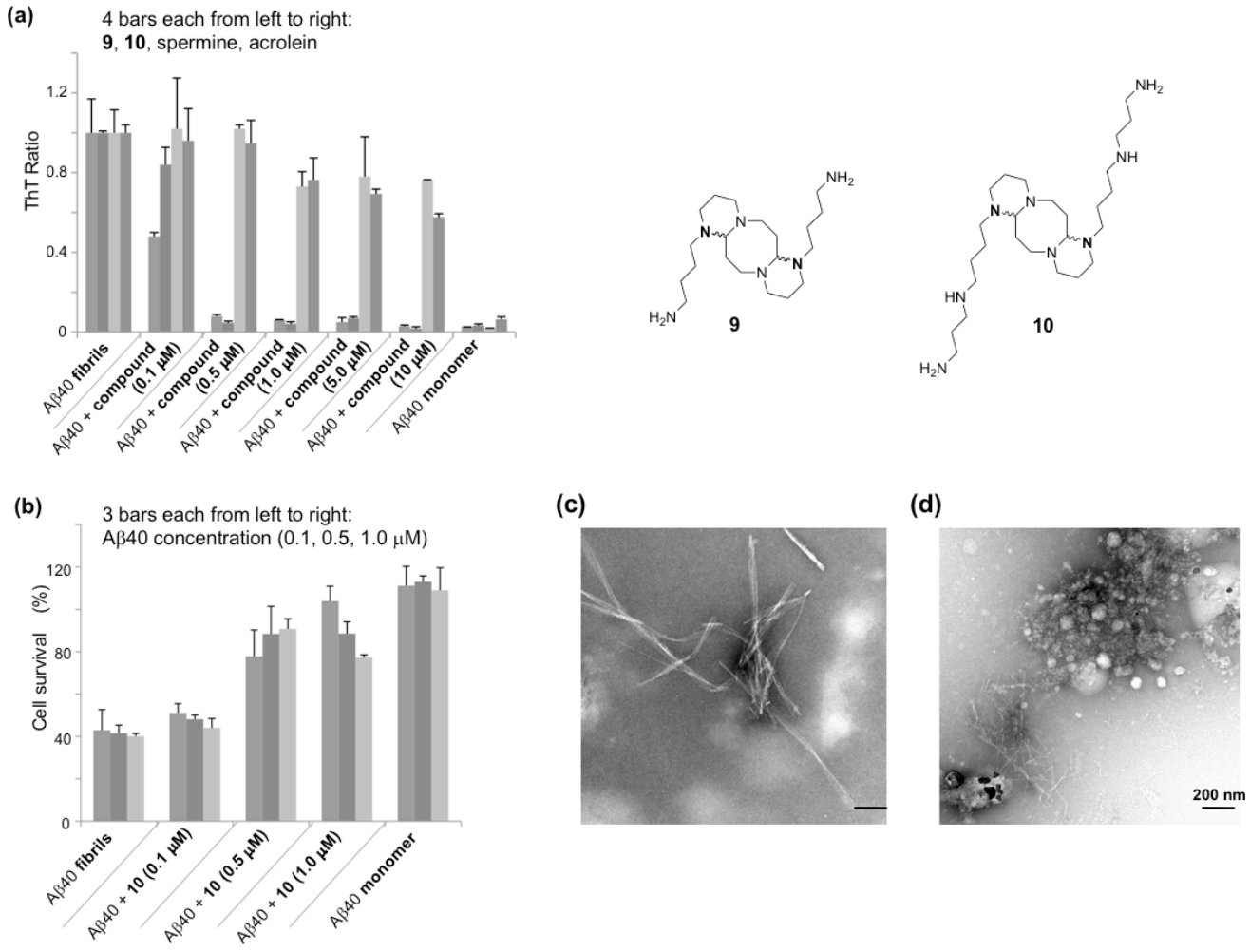


Figure 1. (a) Inhibitory effects of spermine and spermidine-derived **9** and **10** toward fibrillization of Aβ40 evaluated by ThT assay (incubated at 37 °C for 5 days). (b) Cytotoxicity of the Aβ40 peptides pre-treated with **10** toward PC12 cells derived from transplantable rat pheochromocytoma. (c) TEM images of Aβ40 fibrillization in the absence, or (d) presence of spermine-derived azaheterocycle **10**.

These results are important for several reasons. First, it gives us insight into the mechanism that polyamines, which we know to be tremendously biologically important, exert their action. And secondly, because acrolein and polyamines combine naturally in cells to form these powerful anti-fibrillation

substances, it may open a path for researchers to influence the progression of debilitating neurological disorders such as Alzheimer's.

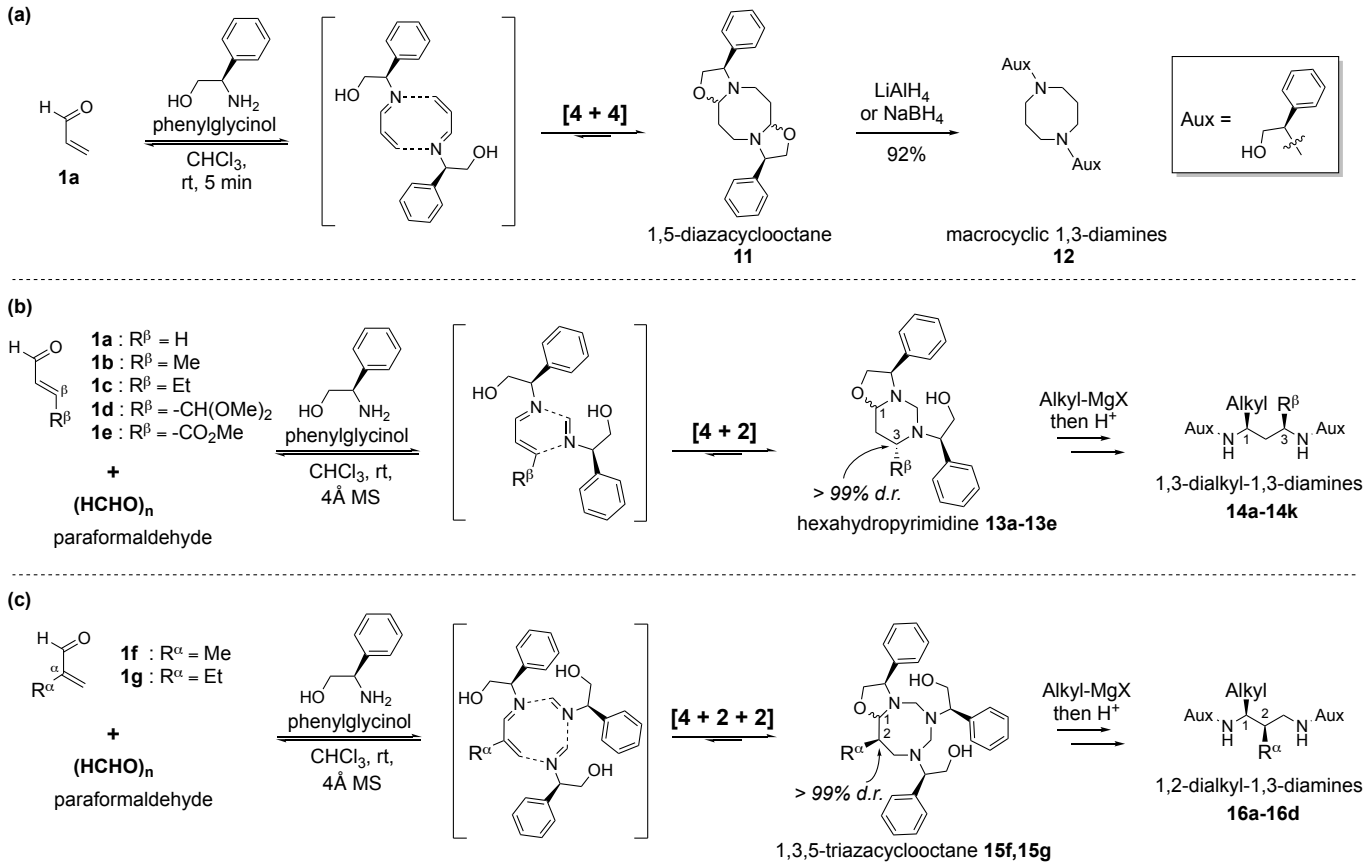
5. A SIMPLE PROCEDURE FOR PREPARATION OF CHIRAL 1,3-DIAMINES VIA FORMAL [4 + 2] AND [4 + 2 + 2] CYCLOADDITION REACTIONS

The potential utility of α,β-unsaturated imines as synthetic precursors to nitrogen-containing molecules is highlighted by the amphiphilic properties of the two electrophilic and one nucleophilic centers.[37-40] Whereas α,β-unsaturated imines bearing electron-withdrawing groups on a nitrogen atom have been applied widely in organic synthesis,[41-45] the *N*-alkyl-unsaturated imines have not received much attention due to their susceptibility toward hydrolysis and polymerization. In fact, only a few studies have reported the stable isolation and use of *N*-alkyl-unsaturated imines, particularly those derived from highly reactive low molecular weight aldehydes.[46-51] Shimizu and co-workers reported that *N*-alkyl-unsaturated imines derived from the smallest acrolein could be handled as stable substrates for various organic transformations once a bulky diphenylethyl group was attached onto the nitrogen atom.[50, 51]

Alternatively, in the context of bioorganic transformations, biogenic alkylamines (e.g., lysine amino groups, ethanol amines, or polyamines) react with various α,β-unsaturated aldehydes (e.g., lipid metabolites produced under oxidative stress conditions) to produce *N*-alkyl-α,β-unsaturated imines or their further reaction products during certain biologically relevant processes.[52-54] Considering that both alkylamines and α,β-unsaturated aldehydes are abundant in biological systems, it is reasonable to hypothesize that their condensation products, the *N*-alkyl-unsaturated imines, may provide unrecognized reactivity associated with biologically relevant processes. For example, as described in the previous section, we serendipitously found that *N*-alkyl-unsaturated imines obtained from the condensation of acrolein **1a** and certain aminoalcohol or diamines, e.g., polyamines, sphingosine, norepinephrine, or more preferably from a synthetic point of view (*R*)-phenylglycinol, readily participate in formal [4 + 4] cycloadditions to give 1,5-diazacyclooctane **11** in quantitative yield (Scheme 6a).[10] In this reaction, the nucleophilic hydroxyl group on an imino nitrogen is important for accelerating and stabilizing the 1,5-diazacyclooctane products. The aminoacetals of 1,5-diazacyclooctane **11** can be easily reduced by either lithium aluminum hydride or sodium borohydride to produce macrocyclic 1,3-diamines **12** in 92% yield (Scheme 6a).[10]

During an investigation of the formal [4 + 4] cycloaddition reaction, we further found accidentally that the hexahydropyrimidines **13a**–**13e** were produced through formal [4 + 2] reaction upon treatment of the unsubstituted or various β-substituted acrolein derivatives **1a**–**1e** (H, Me, Et, $-CH(OMe)_2$, or $-CO_2Me$) with (*R*)-phenylglycinol in the presence of paraformaldehyde (Scheme 6b). The hexahydropyrimidines **13a**–**13e** were obtained in 80–92% yields as single stereoisomers at the newly generated C3 stereogenic

centers. On the other hand, utilization of the α-substituted acroleins **1f–1g** (Me or Et) under identical reaction conditions provided 1,3,5-triazacyclooctane derivatives **15f** (78% yield) and **15g** (75% yield), respectively, through formal [4 + 2 + 2] cycloaddition reaction (Scheme 6c). It should be noted that the six- and eight-membered azaheterocycles could be obtained in a highly stereocontrolled manner at the newly generated stereogenic centers, i.e., the diastereoselectivity at C3 and C2 exceeded 99% (Scheme 6b and 6c). In addition, these azaheterocycles contain aminoacetal centers, where various substituents could be introduced stereoselectively.[12] We therefore envisioned transforming these hexahydropyrimidines and 1,3,5-triazacyclooctanes to their corresponding substituted chiral 1,3-diamines, potential intermediates of natural alkaloids and chiral ligands, which are not readily obtained by other methods.[55]



Scheme 6. Stereoselective formation of (a) 1,5-diazacyclooctane, (b) hexahydropyrimidines and (c) 1,3,5-triazacyclooctanes via formal [4 + 4], [4 + 2] and [4 + 2 + 2] cycloaddition reactions, and their transformations to various substituted chiral 1,3-diamines.

The stereoselective transformation of the hexahydropyrimidines **13** to various substituted 1,3-diamine derivatives was achieved as shown in Table 1. Treatment of the unsubstituted azaheterocycle **13a** with lithium aluminum hydride selectively reduced the aminoacetal function at C1, which without purification, was hydrolyzed by methanolic hydrochloric acid to give 1,3-diamine **14a** in 95% yield in two steps

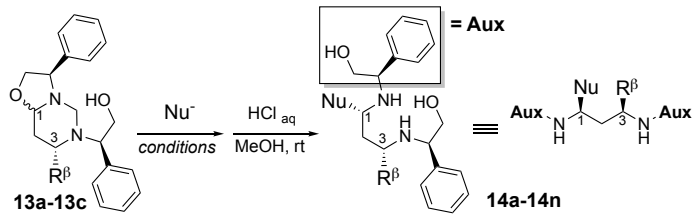
(Table 1, Entry 1). Nucleophilic alkylation at C1 was achieved by reacting **13a** with methyl, deuterated methyl, and phenyl Grignard reagents, followed by the aqueous hydrolysis of the aminal to provide the chiral 1-alkyl-1,3-diamines, **14b–14d**, in 82–87% yields with good diastereoselectivities (ca. 8 : 1, Entries 2–4).

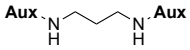
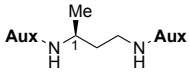
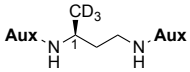
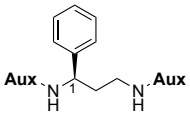
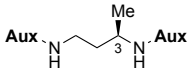
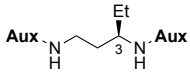
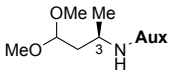
The reduction/hydrolysis protocol could similarly be applied to the C3-substituted **13b** and **13c**; thus, the chiral 3-methyl- and 3-ethyl-substituted 1,3-diamines **14e** and **14f** were stereoselectively obtained in 92 and 90% yields (Entries 5 and 6). It should be noted that the methyl stereochemistry at C3 obtained for **14e** was opposite to that obtained for **14b**; hence different stereoisomers could be prepared selectively from the same chiral auxiliary by employing appropriate unsaturated aldehydes and nucleophiles (Grignard or reducing reagents). Alternatively, direct treatment of **13b** with methanolic hydrochloric acid stereoselectively yielded β-amino aldehyde dimethyl acetal **14g** in quantitative yield (Entry 7). Our formal [4 + 2] cycloaddition protocol is thus useful for the synthesis of nonracemic β-amino acids as well as 1,3-amino alcohols.

Lastly, the 1,3-dialkyl-substituted 1,3-diamines **14h–14n** were obtained by alkylating C3-substituted azaheterocycles. Reactions of **13b** and **13c** with methyl, CD_3, phenyl, and allyl Grignard reagents, along with subsequent acid hydrolysis gave **14h–14n** in 78–84% yields (Entries 8–14). The disubstituted chiral 1,3-diamines produced by this procedure displayed excellent diastereoselectivity at C3 (>99 : 1, generated through the formal [4 + 2] cycloaddition reaction), and good selectivity at C1 (ca. 6:1, generated by alkylation).

The 1,3,5-triazacyclooctanes **15f** and **15g** were similarly transformed to substituted chiral 1,3-diamines using the procedures established in Table 2. As a result, the reduction and hydrolysis of the methyl derivative **15f** produce 2-methylpropane-1,3-diamine **16a** in 87% yield (Table 2, Entry 1). C1-Alkylation of **15f** by methyl and deuterated methyl Grignard reagents, followed by hydrolysis, gave the chiral 1,2-dialkyl-1,3-diamines **16b** and **16c** in 78% yields with good diastereoselectivity at C1 (6 : 1) and at C2 (>99 : 1) (Entries 2 and 3). Similarly, the reaction of the ethyl congener **15g** with the phenyl Grignard reagent and subsequent hydrolysis stereoselectively yielded **16d** in 72% (Entry 4).

Table 1. Transformation of hexahydropyrimidines to substituted chiral 1,3-diamines



Entry	R^{β}	Nu^-	Product		Yield (d.r.)
1	H (**13a**)	$LiAlH_4$		**14a**	95%
2	H (**13a**)	MeMgI		**14b**	86% (87 : 13 at C1)
3	H (**13a**)	CD_3MgI		**14c**	87% (89 : 11 at C1)
4	H (**13a**)	PhMgI		**14d**	82% (90 : 10 at C1)
5	Me (**13b**)	$LiAlH_4$		**14e**	92% (99 : 1 at C3)
6	Et (**13c**)	$LiAlH_4$		**14f**	90% (99 : 1 at C3)
7	Me (**13b**)	–		**14g**	quant (99 : 1 at C3)

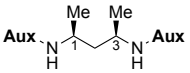
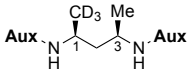
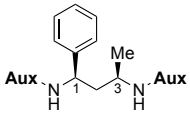
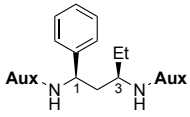
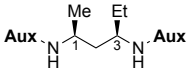
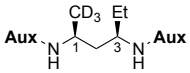
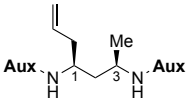
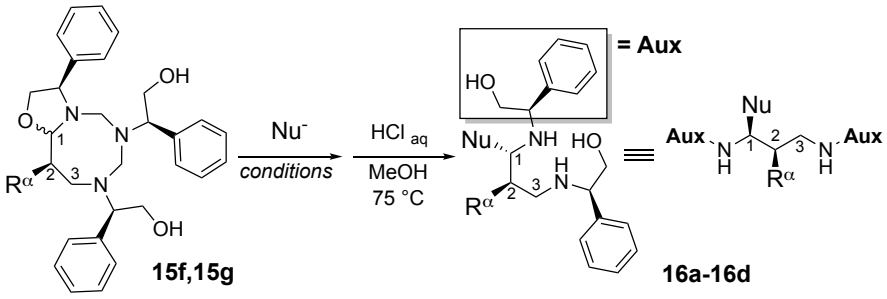
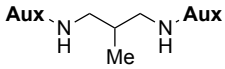
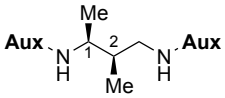
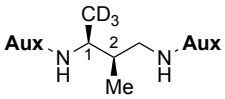
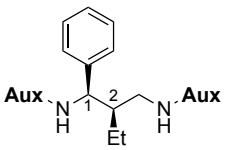
Entry	R^{β}	Nu^-	Product		Yield (d.r.)
8	Me (**13b**)	MeMgI		**14h**	80% (82 : 18 at C1) (99 : 1 at C3)
9	Me (**13b**)	CD_3MgI		**14i**	81% (84 : 16 at C1) (99 : 1 at C3)
10	Me (**13b**)	PhMgI		**14j**	79% (86 : 14 at C1) (99 : 1 at C3)
11	Et (**13c**)	PhMgI		**14k**	78% (83 : 17 at C1) (99 : 1 at C3)
12	Et (**13c**)	MeMgI		**14l**	84% (85 : 15 at C1) (99 : 1 at C3)
13	Et (**13c**)	CD_3MgI		**14m**	82% (85 : 15 at C1) (99 : 1 at C3)
14	Me (**13b**)	AllylMgBr		**14n**	79% (87 : 13 at C1) (99 : 1 at C3)

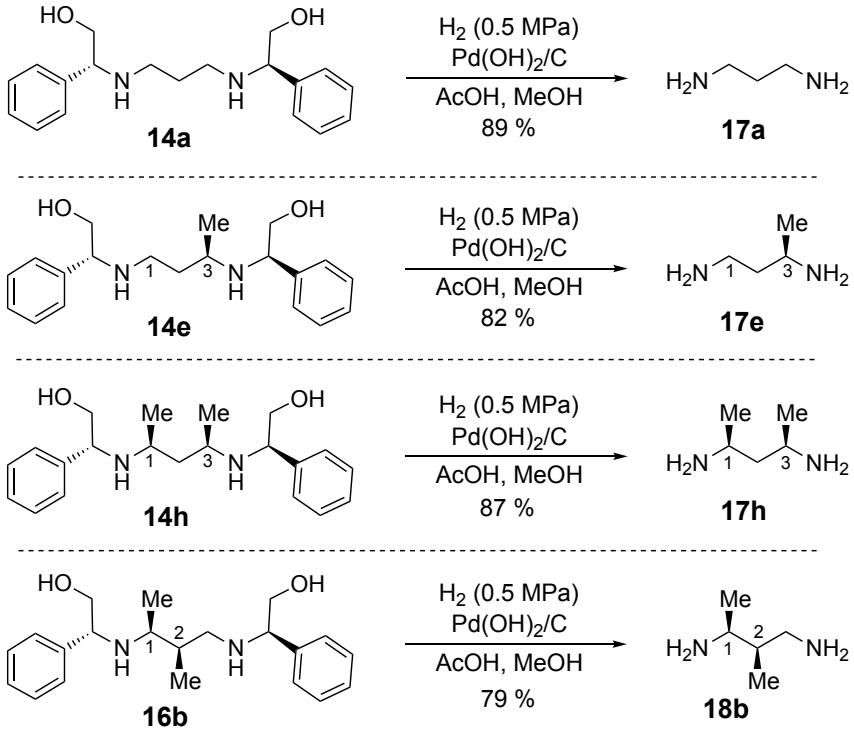
Table 2. Transformation of 1,3,5-triazacyclooctanes to substituted chiral 1,3-diamines



Entry	R^{α}	Nu^-	Product		Yield (d.r.)
1	Me (**15f**)	$LiAlH_4$		**16a**	87%
2	Me (**15f**)	MeMgI		**16b**	78% (83 : 17 at C1) (99 : 1 at C2)
3	Me (**15f**)	CD_3MgI		**16c**	78% (88 : 12 at C1) (99 : 1 at C2)
4	Et (**15g**)	PhMgI		**16d**	72% (91 : 9 at C1) (99 : 1 at C2)

The phenylethanol group used as a chiral auxiliary in Tables 1 and 2 was removed without incident by hydrogenolysis over Pearlman's catalyst in the presence of acetic acid in methanol. Hydrogenolysis of **14a**, **14e**, **14h**, and **16b** gave the corresponding chiral 1,3-diamines **17a**, **17e**, **17h**, and **18b** in 79–89% yields (Scheme 7). Thus, we have developed a stereocontrolled synthesis of substituted chiral 1,5-diazacyclooctanes, hexahydropyrimidines and 1,3,5-triazacyclooctanes through a formal [4 + 4], [4 + 2] and [4 + 2 + 2] cycloaddition reactions with readily available starting materials, such as substituted unsaturated aldehydes, chiral phenylglycinol, or paraformaldehyde. Various aldehyde substrates were selected to control the pathways to six- or eight-membered azaheterocycles under thermodynamic conditions. Derivatization of these cyclic azaheterocycles by reduction or nucleophilic alkylation, followed by acid hydrolysis, produced various substituted chiral 1,3-diamine derivatives. Overall, the phenylglycinol auxiliary and formaldehyde efficiently (i) facilitated the handling of the previously little-used *N*-alkyl-unsaturated imines as stable six- and eight-membered equivalents for further synthetic transformations, and (ii) provided various stereoselective reactions by virtue of the thermodynamic and auxiliary effects of the conformationally restricted heterocycles. Although this method uses two chiral auxiliaries, the simple procedure and good stereoselectivity of the asymmetric reaction are advantageous for the synthesis of chiral mono- and disubstituted 1,3-diamines, a class of compounds that is ubiquitous

in a wide range of bioactive natural products and metal ligands. The deuterium-labeled polyamine precursors are especially difficult to synthesize using any other method, hence highlighting the importance of this new protocol.



Scheme 7. Removal of the chiral auxiliary

Alternatively, it should be noted that aside from alkylamine and unsaturated aldehyde, formaldehyde is a biogenic substance present in living systems. Our attempts to explore the unrecognized reactivities of *N*-alkyl-unsaturated imines (similar to those observed for [4 + 4] iminocyclization in inhibition of Aβ40 fibrillization) potentially open a path towards identifying new organic transformations and to reveal new biofunctions within living systems.

6. SUMMARY

We have serendipitously discovered novel cycloaddition reactions of *N*-alkyl-α,β-unsaturated imines, which derived from acrolein and biogenic amines (e.g., polyamines, norepinephrine, and sphingosine), to yield 2,6,9-triazabicyclo[3.3.1]nonanes and 1,5-diazacyclooctanes in near-quantitative yield through formal [4 + 4] cycloaddition reaction. The facile formation of 1,5-diazacyclooctanes at μM concentrations under physiological conditions was discovered, which has largely been overlooked until now. Reasons for this may include (i) the 1,5-diazacyclooctanes are present in equilibrium with the starting imines, or (ii) these azaheterocycles are unstable under biological conditions. Furthermore, (iii) these products may be

transformed into a variety of unidentified compounds upon exposure to acidic, basic, or heated conditions, and they are most likely undetectable using standard analytical methods (chromatographic separation conditions, including exposure to silica gel or LC-MS techniques).

Experimentally we found that the formation of 1,5-diazacyclooctanes from polyamines could inhibit Aβ40 peptide fibrillization and significantly suppress cytotoxicity. There is much potential for acrolein/polyamine-derived [4 + 4] cycloaddition processes to be effectively used to modulate oxidative stress processes associated with neuronal diseases.

Finally, we also developed a stereocontrolled synthesis of substituted chiral hexahydropyrimidines and 1,3,5-triazacyclooctanes through formal [4 + 2] and [4 + 2 + 2] cycloaddition reactions with readily available starting material, such as chiral phenylglycinol. We found that the hydroxyl groups of unsaturated imines, when oriented at the appropriate positions, could contribute significantly to the formation of the azaheterocyclic compounds through cycloaddition reaction. Various aldehyde substrates were selected to control the pathways to the six- or eight-membered azaheterocycles under thermodynamic conditions. Derivatization of these azaheterocyclic compounds by reduction of nucleophilic alkylation, followed by acid hydrolysis, produced various substituted chiral 1,3-diamine derivatives.

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