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Enantioselective synthesis of cyclic and linear diamines by imine cycloadditions

Tsung-Che Chang[1] | **Ambara R. Pradipta**[1,2] | **Katsunori Tanaka**[1,2,3,4]

[1]Biofunctional Synthetic Chemistry Laboratory, RIKEN Cluster for Pioneering Research, Saitama, Japan

[2]School of Materials and Chemical Technology, Department of Chemical Science and Engineering, Tokyo Institute of Technology, Tokyo, Japan

[3]Biofunctional Chemistry Laboratory, Alexander Butlerov Institute of Chemistry, Kazan Federal University, Kazan, Russia

[4]GlycoTargeting Research Laboratory, RIKEN baton Zone Program, Saitama, Japan

Correspondence
Ambara R. Pradipta and Katsunori Tanaka, Biofunctional Synthetic Chemistry Laboratory, RIKEN Cluster for Pioneering Research, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan.
Email: arpradipta@riken.jp; kotzenori@riken.jp

Abstract

Imine is one of the most versatile functional groups in chemistry and biochemistry fields. Although many biochemical reactions involve imine formation, the inherently unstable property of *N*-alkyl-α,β-unsaturated imines still hindered their utilization in organic synthesis. In this article, we described that the *N*-alkyl-α,β-unsaturated imines, which prepared from alkylamines and acrolein, could smoothly react through [4 + 4] cycloaddition to give eight-membered diazacyclooctane derivatives in excellent yields. Under a similar condition, in the presence of formaldehyde, the [4 + 2] and [4 + 2 + 2] cycloadditions could lead to the formation of six-membered hexahydropyrimidine or eight-membered triazacyclooctanes, depending on the substituent of aldehydes. Moreover, an easy functional group manipulation of the cyclic products obtained from these cycloadditions can provide variously substituted chiral linear diamines. We can utilize these novel reactivities to reveal the unknown and essential properties of many biological processes that involve *N*-alkyl-unsaturated imines.

KEYWORDS

1,3-diamine, acrolein, cycloaddition, diazacyclooctane, hexahydropyrimidine, triazabicyclononane, triazacyclooctane

1 | INTRODUCTION

By far, the α,β-unsaturated imine is one of the ubiquitous functional group that extensively utilized in organic synthesis, bioconjugation, and biochemistry fields.[1–8] The amphiphatic characters of one nucleophilic and two electrophilic centers in α,β-unsaturated imines lead to their wide utilization as synthetic precursors for the synthesis of nitrogen-bearing chemical molecules.[9–13] We can easily prepare the α,β-unsaturated imines from the reaction of α,β-unsaturated carbonyl compounds and amines. Unlike the α,β-unsaturated imines with an electron-withdrawing group on the nitrogen atom,[14–18] the *N*-alkyl-α,β-unsaturated imines are relatively more unstable, and their still a lot of room to explore their reactivities. Previously, several reports showed the preparation and utilization of α,β-unsaturated imine derivatives, particularly those generated from low molecular weight aldehydes.[19–24] One example reported the utilization of a stable *N*-alkyl-α,β-unsaturated imines, which prepared from acrolein, as synthetic precursors after attaching a bulky substituent at the nitrogen atom.[23,24] However, in many cases, it is still difficult to control the reactivity and selectivity of *N*-alkyl-α,β-unsaturated imines. Thus, it is worthy of exploring their reactivity in pursuit of developing new reactions or bioconjugation methods and revealing unknown biosynthetic pathways of the nitrogen-containing natural products.

On the other hand, because both α,β-unsaturated aldehydes and alkylamines are ubiquitous in living

systems, it is reasonable to predict that the reactions between biogenic alkylamines (e.g., amino acids, ethanolamines, and polyamines) and biogenic α,β-unsaturated aldehydes (e.g., oxidative stress-induced lipid peroxidation) in biosystems also could produce *N*-alkyl-α,β-unsaturated imines that involve in various biologically relevant processes.[25–27] Therefore, understanding the reactivity of *N*-alkyl-α,β-unsaturated imines will be useful not only for the development of organic synthesis but also for the relevant biochemistry and biology fields.

At the initial stage of our studies, we unexpectedly found that the imines derived from acrolein **1a** and primary amines could be able to implement the "head-to-tail" [4 + 4] homodimerization in both organic solvents and phosphate buffer with excellent efficiency (Scheme 1). Previously, a study reported the dimerization of azadiene, where eight-membered heterocycle derivative was isolated from the reaction mixture as a minor byproduct.[28] In our study, the insertion of an alkyl substituent on the nitrogen atom would affect the reactivities of the [4 + 4] cyclodimerization. As shown in Scheme 1, utilization of the less-hindered aliphatic substituents could give the 2,6,9-triazabicyclo[3.3.1]nonanes **2** in quantitative yields.[29–31] In this case, the excess amount of primary amines is necessary for the formation of the thermodynamically stable product.

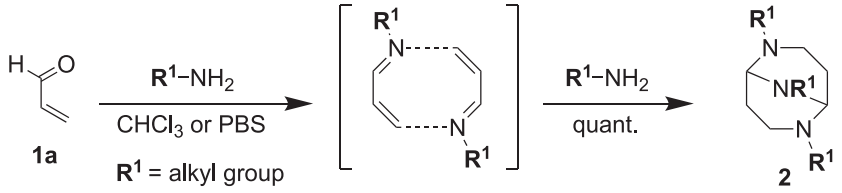
Because of their susceptibility toward polymerization and hydrolysis, the attempt to harness the reactivity of *N*-alkyl-unsaturated imines is quite challenging. However, it was somewhat surprising that there is no previous example that reports the facile preparation of the triazabicyclo[3.3.1]nonane derivatives through the controllable cycloaddition. Perhaps, we supposed that the exact equimolar amount of the amine usually is used to react with the aldehyde for preparation of *N*-alkyl unsaturated imines. Therefore, investigation of the viewpoint may offer a new path for controlling the reactivities of *N*-alkyl unsaturated imines.

2 | DISCOVERY OF STEREOCONTROLLED FORMAL [4 + 4], [4 + 2], AND [4 + 2 + 2] CYCLOADDITIONS

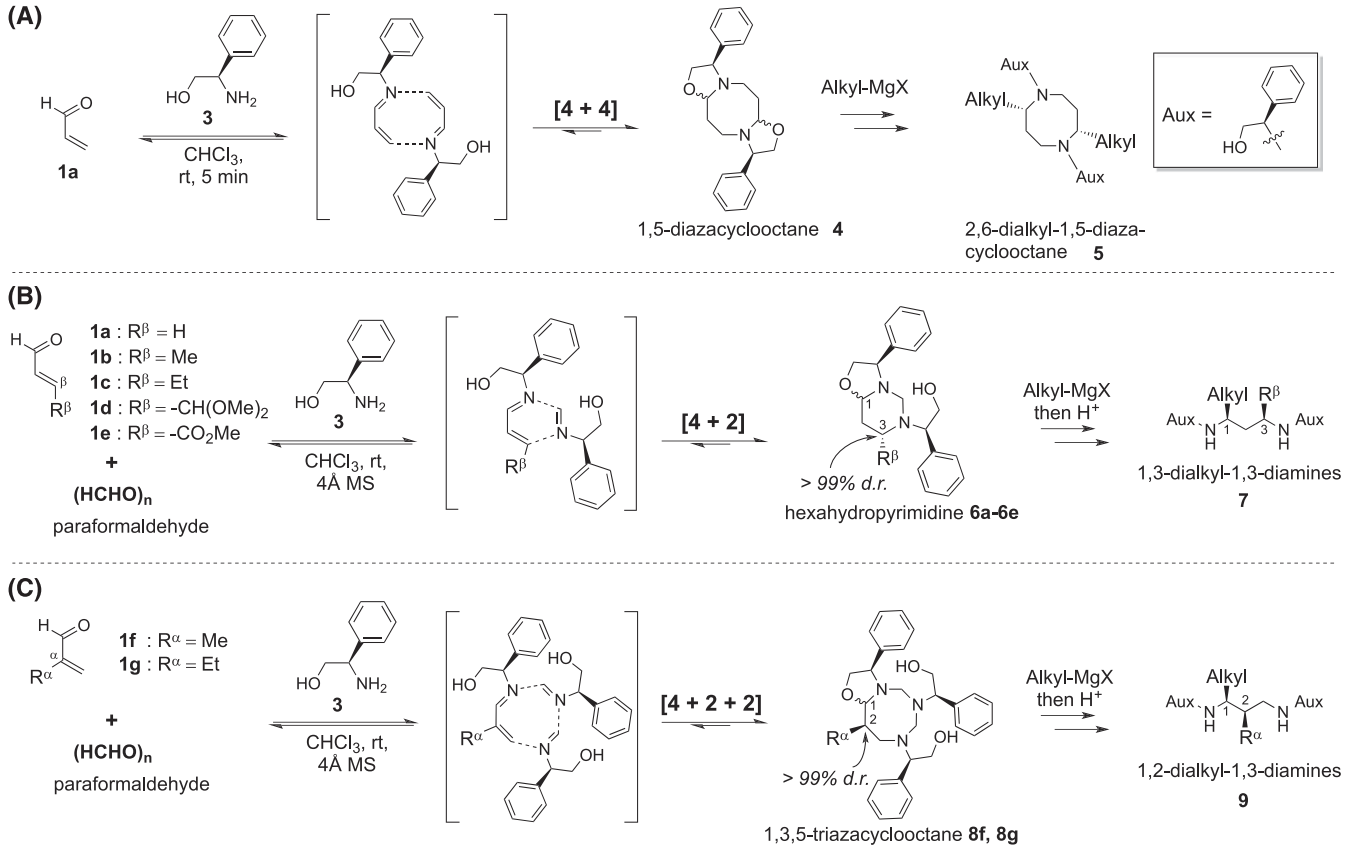
Encouraged by the controllable cycloaddition of *N*-alkyl unsaturated imines in Scheme 1, we hypothesized that the addition of an internal hydroxy group into the unsaturated imines probably could be able to mediate the [4 + 4]cycloaddition. Based on the consideration, we found that the 1,5-diazacyclooctane **4** could be easily synthesized in quantitative yield by using the *N*-alkyl-α,β-unsaturated imines, which derived from acrolein **1a** and (*R*)-phenylglycinol **3** via the [4 + 4] cycloadditions (Scheme 2A).[32] Herewith, the hydroxyl group on the unsaturated imine is crucial for accelerating and stabilizing the products. The 1,5-diazacyclooctane containing molecules have a widespread application in the area of synthetic chemistry, chemical biology, and pharmacy.[33–37] However, the synthesis of chiral substitution of 1,5-diazacylcooctane by other methods remain challenging because of low yields or lower stereoselectivities.[38–40] Herein, the eight-membered-heterocycles could be converted to variously substituted chiral 1,5-diazacyclooctane **5** through a simple, functional group manipulation (Scheme 2A).

At a further exploration of the [4 + 4] cycloaddition reaction, we isolated an exciting product, that is, the hexahydropyrimidine **6a** through the formal [4 + 2] cycloaddition upon reaction between (*R*)-phenylglycinol **3** and acrolein **1a** in the presence of paraformaldehyde (Scheme 2B). The other trials showed that using various β-substituted acrolein derivatives **1b–e** to proceed with the same condition also could produce hexahydropyrimidines **6b–e** (Scheme 2B).[41] In contrast, we could generate 1,3,5-triazacyclooctane derivatives **8f–g** through the other reaction pathway, that is, formal [4 + 2 + 2] cycloaddition by utilizing the α-substituted acroleins **1f–g** under similar reaction conditions (Scheme 2C). We noted that we could achieve excellent stereoselectivity at the newly generated stereogenic centers in six- and eight-membered heterocycles (Scheme 2B,C). The processes of heterocyclic ring formation in these six- and eight-membered products might mainly contribute to the excellent diastereoselectivity. For example, the substituents at the C3 position (R^{β}) in the unsaturated aldehydes **1b–e** might prefer the more thermodynamically stable at the end of the reaction. Moreover, the hydroxyl groups also have a significant effect on the asymmetric transformation because the acetal formation could shift the equilibrium toward the cyclic products.

Also, we could introduce stereoselectively various substituents at the amino acetal centers. Thus, we



SCHEME 1 The reaction of acrolein **1a** with primary amines to give 2,6,9-triazabicyclo[3.3.1]nonane **2**



SCHEME 2 The formal (A) [4 + 4] cycloaddition to give 1,5-diazacyclooctanes; (B) [4 + 2] cycloaddition to give hexahydropyrimidines, and (C) [4 + 2 + 2] cycloaddition to give 1,3,5-triazacyclooctanes. Further modification of the cyclic products could give various substituted chiral 1,3-diamines

investigate the conversion of the heterocycles to their corresponding substituted chiral linear 1,3-diamines **7** and **9**, prospective intermediates of natural products and chiral ligands, which are difficult to be prepared through other protocols.

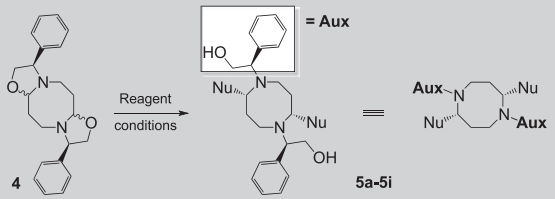
3 | ASYMMETRIC SYNTHESIS OF CHIRAL 1,5-DIAZACYCLOOCTANES

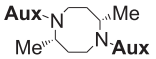
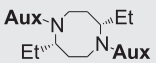
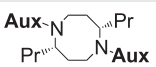
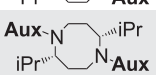
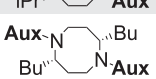
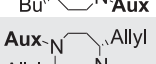
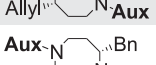
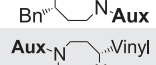
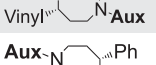
The aminoacetals of eight-membered compound **4** obtained by [4 + 4] cycloaddition, were alkylated to the substituted chiral macrocyclic 1,5-diazacyclooctanes (Table 1).[42] The reaction of **4** with various alkyl Grignard reagents produce the chiral eight-membered 2,6-dialkyl-1,5-diazacyclooctanes **5a–d** in 59%–71% yields as the single stereoisomers (Table 1, Entries 1–4). During our observation, we could only isolate the cis isomer and could not observe the other isomers. In contrast, using butyl and allyl Grignard reagents as nucleophilic agents in the reaction gave both major cis and minor trans isomers. Therefore, we isolated **5e** in 68% yield and **5f** in 60% yield, with cis to trans diastereoselectivity ratio of ca. 10:3 (Table 1, Entries 5–6).

Meanwhile, the reaction between 1,5-diazacyclooctane **4** with benzyl Grignard, vinyl Grignard, and phenyl Grignard reagents gave the chiral compounds **5g–i** in 56%–67% yields (Table 1, Entries 7–9). As for these cases, we only obtained one cis isomer. In the case of the alkenyl-substituted **5f** and **5h**, these compounds could be very useful synthetic precursors for the preparation of large macrocyclic molecules through the ring-closing metathesis reaction, which shows the significance of these reactions method.

The previous report shows the predominant stereochemical outcome of nucleophilic reactions by using 2-phenylglycinol as chiral auxiliary.[43–47] Likewise, the stereochemical outcome of the reactions listed in Table 1 resulted from the contribution of the (*R*)-phenylglycinol **3**. As for the mechanism of the reaction, the iminium ions formation leads to the ring-opening of the hemiaminals, followed by a subsequent attack of the Grignard reagents to the iminium ions from the less sterically hindered site of the heterocyclic ring. On the other hand, even though the detail is unclear, we found that different kinds of alkyl substituents probably affect the molecular properties of the 1,5-diazacyclooctane; that includes the diastereoselectivity decrease (Table 1,

TABLE 1 Transformation to the chiral 1,5-diazacyclooctanes



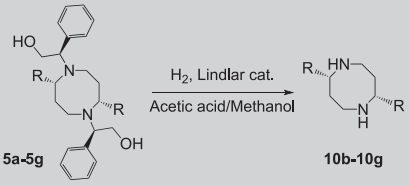
Entry	Reagent	Product		Yield (cis: trans)
1	MeMgI		**5a**	71% (cis only)
2	EtMgBr		**5b**	62% (cis only)
3	PrMgBr		**5c**	59% (cis only)
4	iPrMgBr		**5d**	61% (cis only)
5	BuMgBr		**5e**	89% (68:21)
6	AllylMgBr		**5f**	77% (60:17)
7	BnMgBr		**5g**	58% (cis only)
8	VinylMgBr		**5h**	56% (cis only)
9	PhMgBr		**5i**	67% (cis only)

Entries 5 and 6) and the retardation during auxiliary removal of 2,6-dimethyl-1,5-diazacyclooctane **5a** (Table 2, Entry 1).

In the next step, the chiral auxiliary, 2-phenylethanol group, could be removed smoothly by hydrogenolysis under mildly acidic conditions. Therefore, the hydrogenolysis of the cis-isomer of **5b–g** gives the corresponding 2,6-dialkyl-1,5-diazacyclooctanes **10b–g** in good yields (Table 2, Entries 2–7). Following the identical condition, the hydrogenolysis of heterocycle **5f** was followed by hydrogenation of the allyl group to achieve chiral 2,6-dipropyl-1,5-diazacyclooctanes **10c** in 94% yield (Table 2, Entry 6). In particular, the hydrogenolysis of **5a** did not proceed under similar conditions. The X-ray analysis of **5a** revealed sterically shielded C—N bonds in **5a**, which leads to the difficulty for hydrogenation to proceed.[42]

In contrast with the well-studied all-carbon-containing cyclooctane ring,[48–50] the eight-membered ring bearing two nitrogen atoms struggled to receive attention because of difficulties in its synthesis. Here, we provided a simple sequence of reactions. The reactions involve mixing

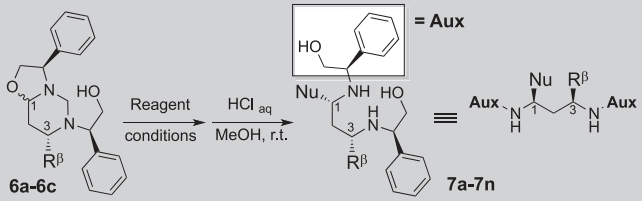
TABLE 2 Cleavage of the chiral auxiliary to give 2,6-dialkyl-1,5-diazacyclooctanes **10b–g**

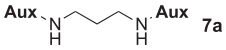
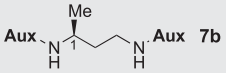
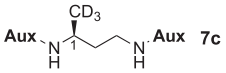
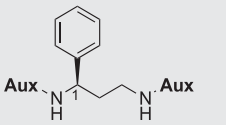
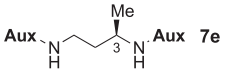
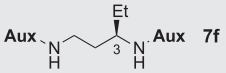
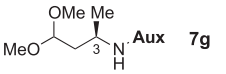
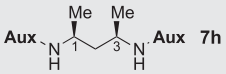
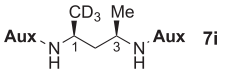
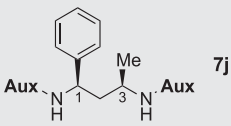
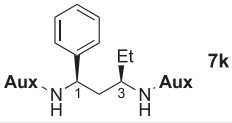
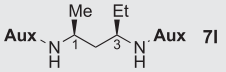
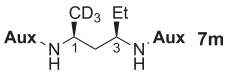
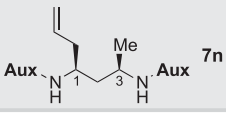


Entry	Starting material [cis isomer]	R-	Product (yield)
1	**5a**	CH_3-	—
2	**5b**	CH_3CH_2-	**10b** (90%)
3	**5c**	$CH_3CH_2CH_2$-	**10c** (96%)
4	**5d**	$(CH_3)_2CH$-	**10d** (70%)
5	**5e**	$CH_3CH_2CH_2CH_2$-	**10e** (77%)
6	**5f**	$CH_2 = CHCH_2$-	**10c** (94%)
7	**5g**	$C_6H_5CH_2$-	**10g** (82%)

(*R*)-phenylglycinol and acrolein, which continued with alkylation. Then, followed by hydrogenolysis, which finally led to the first enantioselective synthesis of chirally oriented 1,5-diazacyclooctane derivatives. These synthetic chiral compounds might be an essential pharmacophore that is difficult to be synthesized by other methods.

TABLE 3 Synthesis of the substituted chiral linear 1,3-diamines from derivatization of hexahydropyrimidines



Entry	R^{β}	Reagent	Product		Yield (ratio of d.r.)
1	H (**6a**)	$LiAlH_4$		**7a**	95%
2	H (**6a**)	MeMgI		**7b**	86% (87:13 at C1)
3	H (**6a**)	CD_3MgI		**7c**	87% (89:11 at C1)
4	H (**6a**)	PhMgI		**7d**	82% (90:10 at C1)
5	Me (**6b**)	$LiAlH_4$		**7e**	92% (99:1 at C3)
6	Et (**6c**)	$LiAlH_4$		**7f**	90% (99:1 at C3)
7	Me (**6b**)	-		**7g**	Quant (99:1 at C3)
8	Me (**6b**)	MeMgI		**7h**	80% (82:18 at C1) (99:1 at C3)
9	Me (**6b**)	CD_3MgI		**7i**	81% (84:16 at C1) (99:1 at C3)
10	Me (**6b**)	PhMgI		**7j**	79% (86:14 at C1) (99: 1 at C3)
11	Et (**6c**)	PhMgI		**7k**	78% (83:17 at C1) (99: 1 at C3)
12	Et (**6c**)	MeMgI		**7l**	84% (85:15 at C1) (99: 1 at C3)
13	Et (**6c**)	CD_3MgI		**7m**	82% (85: 15 at C1) (99:1 at C3)
14	Me (**6b**)	AllylMgBr		**7n**	79% (87: 13 at C1) (99: 1 at C3)

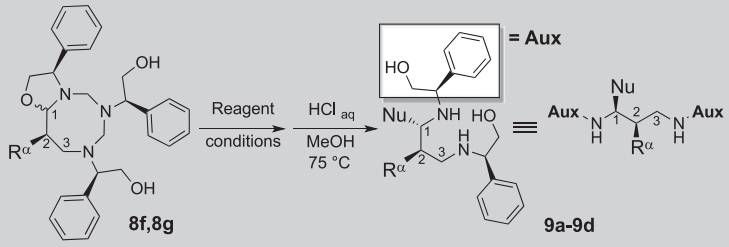
4 | ASYMMETRIC SYNTHESIS OF CHIRAL LINEAR 1,3-DIAMINES

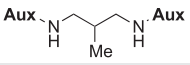
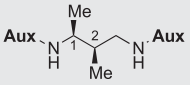
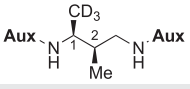
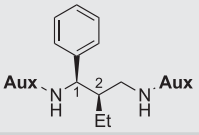
The stereoselective transformation of the hexahydro-pyrimidines **6**, via [4 + 2] cyclization products, to various substituted 1,3-diamine derivatives, were presented in Table 3.[41]

Treatment of the heterocycle **6a** with $LiAlH_4$ selectively reduced the amino acetal moiety at C1, which directly hydrolyzed by acid to achieve 1,3-diamine **7a** in 95% yield without any purification (Table 3, Entry 1). The transformation for **7a** would be applied to investigate the possibilities for installing various kinds of alkyl groups stereoselectively at the C1 position of **6**. Nucleophilic alkylation at C1 position was implemented smoothly by reacting **6a** with methyl Grignard, deuterated methyl Grignard, and phenyl Grignard reagents, followed by the hydrolysis of the animal moiety to achieve the 1-alkyl-1,3-diamines, **7b**–**d**, in good yields with high diastereoselectivities (ca. 8: 1, Entries 2–4). Significantly, the deuterated chiral 1,3-diamine **7c** (Entry 3), which is the synthetic precursors to the natural polyamine derivatives,[51,52] was facile achieved via the new method. Moreover, synthesis of the deuterium-labeled polyamine precursors could be quite painful and tedious by other protocols,[52,53] further highlighting the advantage of the method (Table 3, Entries 9 and 13; Table 4, Entry 3). Likewise, treatment of the C3-substituted **6b** and **6c** by the identical protocol could stereoselectively obtain the chiral 3-methyl- and 3-ethyl-substituted 1,3-diamines **7e** and **7f** in 92% and 90% yields, respectively (Entries 5 and 6). We noted that the methyl stereochemistry at C3 of **7e** was the opposite of that obtained for **7b** (Entry 2). Thus, using appropriate unsaturated aldehydes **1** and nucleophiles could synthesize selectively different stereoisomers through the same chiral auxiliary. Alternatively, the direct treatment of **6b** with acid stereoselectively obtained the β-amino aldehyde dimethyl acetal **7 g** quantitatively (Entry 7), further highlighting the significance of the formal [4 + 2] cycloaddition for preparation of nonracemic β-amino acids and 1,3-amino alcohols. Finally, the 1,3-dialkyl substituted 1,3-diamines **7h–n** were facile achieved in 78%–84% yields through alkylating C3-substituted of **6b** and **6c** with various Grignard reagents, followed by subsequent acid hydrolysis (Entries 8–14). The disubstituted chiral 1,3-diamines produced by this protocol gave excellent diastereoselectivity at C3 (>99:1, obtained by the [4 + 2] cycloaddition), and high selectivity at C1 (ca. 6:1, obtained by alkylation).

Similarly, the eight-membered heterocycles **8f** and **8g** obtained by [4 + 2 + 2] cycloaddition were derivatized to substituted chiral 1,3-diamines by following the same procedures in Table 3. As a result, the reduction followed by hydrolysis of the methyl derivative **8f** give 2-methylpropane-1,3-diamine **9a** in 87% yield (Table 4,

TABLE 4 Synthesis of the substituted chiral linear 1,3-diamines from derivatization of 1,3,5-triazacyclooctanes



Entry	R^{α}	Reagent	Product		Yield (ratio of d.r.)
1	Me (**8f**)	$LiAlH_4$		**9a**	87%
2	Me (**8f**)	MeMgI		**9b**	78% (83:17 at C1) (99: 1 at C2)
3	Me (**8f**)	CD_3MgI		**9c**	78% (88:12 at C1) (99: 1 at C2)
4	Et (**8g**)	PhMgI		**9d**	72% (91:9 at C1) (99:1 at C2)

Entry 1). Furthermore, C1-alkylation of **8f** by methyl Grignard and deuterated methyl Grignard reagents, followed by hydrolysis, produced the chiral compounds **9b** and **9c** in 78% yields with excellent diastereoselectivity at C1 (6:1) and C2 (>99:1) (Entries 2 and 3). Likewise, the reaction of the ethyl congener **8g** with the phenyl Grignard reagent and subsequent hydrolysis stereoselectively yielded **9d** in 72% (Entry 4).

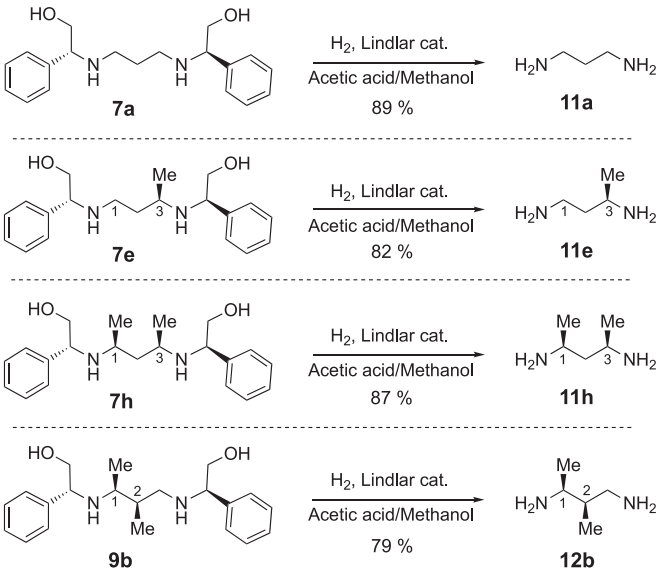
Finally, the chiral auxiliary, phenylethanol group, in Tables 3–4, also could be removed without incident by using the identical protocol in Table 2. Hydrogenolysis of **7a**, **7e**, **7 h**, and **9b** gave the corresponding chiral 1,3-diamine **11a**, **11e**, **11 h**, and **12b** in 79%–89% yields. (Scheme 3).

5 | CONCLUSION

As mentioned previously, it is difficult to control the reactivities of *N*-alkyl unsaturated imines because of their inherent properties. However, we found these formal [4 + 4], [4 + 2], and [4 + 2 + 2] cycloaddition could efficiently implement the stereo-controlled synthesis of substituted chiral 1,5-diazacyclooctanes, hexahydropyrimidines, and 1,3,5-triazacyclooctanes through using simple substrates, namely, substituted unsaturated aldehydes, chiral phenyl glycinol, or paraformaldehyde. Moreover, the different substituted positions in aldehyde could control the reaction pathways to achieve six- or eight-membered heterocycles under thermodynamic conditions. Also, we could perform functional group manipulation toward these heterocyclic products into various substituted chiral cyclic and linear 1,3-diamines derivatives.

The usage of phenylglycinol auxiliary and formaldehyde is of great benefit to (i) facilitate the treatment of the unstable *N*-alkyl unsaturated imines and facile preparation of six- and eight-membered compounds for further modifications and (ii) provide various stereoselective reactions by the thermodynamic and auxiliary effects of the conformationally restricted heterocycles. The simple procedure and good stereoselectivity of the asymmetric reaction are advantageous for the synthesis of chiral monosubstituted and disubstituted and even 1,5-diazacyclooctanes a class of compounds that is ubiquitous in a wide range of bioactive natural products and metal chiral ligands. Also, the deuterium-labeled polyamine precursors are challenging to synthesize using any other method, hence highlighting the importance of this new protocol.

Alternatively, we also noted that aside from alkylamine and unsaturated aldehyde, formaldehyde is ubiquitous biogenic substances in living systems. Our attempts to these unexplored reactivities of *N*-alkyl unsaturated imines potentially provide new access towards identifying new organic transformations and new biofunctions in biological systems.



SCHEME 3 Preparation of the chiral 1,3-diamine **11a**, **11e**, **11 h**, and **12b** by removal of the chiral auxiliary

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In memory of Professor Koji Nakanishi. We are so grateful to Prof Nakanishi for all that he had contributed in the areas of organic chemistry of bioactive natural products and bioorganic science. His group determined the structures of more 200 biologically active compounds, many of which occur in minuscule quantities, investigated and delineated the mechanism of action of the new natural products. His group also innovated and developed the ^{1}H NMR NOE and CD exciton chirality methods that are useful for the structural elucidation.

ORCID

Tsung-Che Chang https://orcid.org/0000-0001-8445-2810

Ambara R. Pradipta https://orcid.org/0000-0002-9056-447X

Katsunori Tanaka https://orcid.org/0000-0001-6932-4802

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