

# Synthetic Strategy for Cyclic Amines: A Stereodefined Cyclic N,O-Acetal as a Stereocontrol and Diversity-Generating Element\*\*

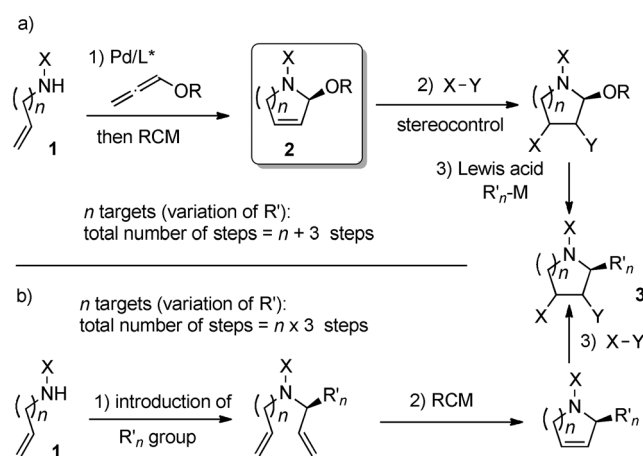
Haejin Kim, Wontaeck Lim, Donghong Im, Dong-gil Kim, and Young Ho Rhee\*

The diversity of natural products has attracted synthetic chemists over the past decades.<sup>[1]</sup> Also, it is important for the discovery of new lead compounds for pharmaceuticals. Thus, developing new synthetic methodologies which can introduce molecular diversity with high chemical efficiency represents a primary goal in synthetic organic chemistry. As a result of their high reactivity and chemoselectivity, organometal catalysts may play a unique role in this area. In this context, we recently reported the first synthesis of stereodefined acyclic allylic N,O-acetals and their utility as a stereodiversity-generating tool for the flexible synthesis of 2,6-substituted piperidines.<sup>[2]</sup> Herein, we report a conceptually new strategy for the synthesis of cyclic amines, one which employs stereo-defined cyclic allylic N,O-acetals such as **2** as the key moiety (Scheme 1a).<sup>[3,4]</sup> This substrate can be accessed by the intermolecular asymmetric addition of the aminoolefin **1** (hydroamination) to an alkoxyallene<sup>[5,6]</sup> and a subsequent ring-closing metathesis (RCM) reaction.<sup>[7]</sup> A salient feature of the proposed method is highlighted by the unprecedented use of an N,O-acetal moiety as a stereocontrol element in olefin

functionalization after the RCM reaction. Moreover, the N,O-acetal allows the iminium-ion-mediated C–C bond formation<sup>[8]</sup> at a late stage of the synthesis. In this regard, the proposed method is clearly distinguished from a well-established protocol for the cyclic amine synthesis, which introduces the alkyl group prior to the RCM reaction (Scheme 1b).<sup>[9]</sup> The unique advantage of the proposed strategy can be easily addressed by the overall synthetic efficiency, particularly when the synthesis of multiple targets are pursued. For example, installing  $n$  different alkyl groups  $R'_n$  in the synthesis of **3** would require  $3 + n$  overall steps according to the proposed strategy. In contrast, the conventional methods would require  $3 \times n$  overall steps, because the alkyl group is introduced at an early stage. Thus, the new method shown in Scheme 1a should give rapid access to diversely substituted and biologically important cyclic amines in a highly controlled and unified manner. In the meantime, this new strategy raises a number of challenging issues. For example, the stereoselectivity should be clearly determined in the olefin functionalization and alkyl substitution reaction. In addition, the racemization of the cyclic N,O-acetal moiety should be avoided. Thus, the chemoselectivity of the catalytic reactions becomes a major issue.

For the successful implementation of the proposed strategy, it is of crucial importance to secure the cyclic stereodefined N,O-acetals **2**. Thus, we were particularly interested in the plausibility of the unprecedented ring-closing metathesis reaction of the stereodefined acyclic N,O-acetals at the outset of the study because of the chemical instability of the N,O-acetal moiety.

We initiated our studies using the Ts-protected allylic amine **4** (Table 1). Employing Pd(OAc)<sub>2</sub> (5 mol %) and the bis(phosphane) ligand (*R,R*)-**L1** (6.5 mol %) in combination with excess *n*-pentoxyallene (70 equiv) and triethylamine (1.5 equiv), as based upon the previous study,<sup>[2]</sup> gave the enantioenriched acyclic N,O-acetal **5** in 97% yield. Because the measurement of enantiomeric purity of this compound was troublesome, we directly moved to the RCM step. Using the first-generation Grubbs catalyst (5 mol %) gave the cyclic amine **6** in 88% yield. Notably, approximately 92% *ee* was observed for this compound (entry 1). At this stage, the absolute configuration of the N,O-acetal carbon atom was assigned to be *S* by analogy to our previous study.<sup>[2]</sup> Interestingly, switching to the ligand (*R,R*)-**L2**<sup>[10,11]</sup> gave **6** in greater than 99% *ee* in near quantitative yield (entry 2). This excellent *ee* value confirms the conservation of the stereochemical integrity of the N,O-acetal in the RCM reaction, thus verifying the plausibility of the proposed concept. Interestingly, decreasing the amount of *n*-pentoxyallene to 10 equivalents still maintained the conversion and the enan-



**Scheme 1.** a) New concept in cyclic amine synthesis exploiting stereo-defined cyclic N,O-acetals. b) Conventional route. R = *n*-alkyl, R' = allyl or homopropargyl or cyano.

[\*] H. Kim, W. Lim, D. Im, D.-g. Kim, Prof. Y. H. Rhee  
Department of Chemistry  
POSTECH (Pohang University of Science and Technology)  
Pohang, 790-784 (Korea)  
E-mail: yhrhee@postech.ac.kr  
Homepage: <http://yhrhee.postech.ac.kr>

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**Table 1:** Optimization for the reaction conditions.

Entry	Allene (equiv)	Ligand	5/6 Yield [%] <sup>[a]</sup>	6 <i>ee</i> [%] <sup>[b]</sup>
1	70	<b>L1</b>	97:88	92
2	70	<b>L2</b>	99:99	> 99
3	10	<b>L2</b>	99:90	> 99
4	5	<b>L2</b>	99:99	> 99
5 <sup>[c]</sup>	2	<b>L2</b>	30:–	n.d.

[a] Yield of isolated product. [b] Determined by HPLC using a chiral stationary phase. [c] The reaction was run for two days. n.d. = not determined. Ts = 4-toluenesulfonyl.

tiomeric excess when the latter ligand was used (entry 3). Additional reduction in the amount of *n*-pentoxyallene to 5 equivalents still showed high reactivity and *ee* (entry 4), while using 2 equivalents showed poor conversion in the hydroamination reaction (entry 5), even after a prolonged reaction time. Notably, formation of the pyrrole product **6'** was not observed, as indicated by the high yield of the desired product.<sup>[12]</sup>

With the optimized two-step protocol for the synthesis of the cyclic N,O-acetal **6** in hand, we explored the scope of this sequential catalytic processes (Table 2). Synthesis of the six-membered and seven-membered analogue (**8** and **10**) also showed excellent yield and enantioselectivity (entries 1 and 2). In the case of allylic amines possessing alkyl groups at the olefin moiety, the asymmetric hydroamination reaction worked invariably well (entries 3–5). However, the RCM reaction showed some discrepancy between the substrates. For example, the methallyl amine substrate **11** gave the cyclic product **12** in fair 84% yield (over two steps) when 5 mol% of first-generation Grubbs catalyst was employed (entry 3). Introducing the bulkier *n*-butyl and benzyl groups, however, considerably slowed the reaction (entries 4 and 5). In this case, formation of a significant amount of the pyrrole compounds analogous to **6'** was also noted. Interestingly, switching to the second-generation Grubbs catalyst (20 mol%) improved the reactivity, thus producing the cyclic N,O-acetal **14** and **16** in high yield and *ee*.<sup>[13]</sup> Also, the piperidine ring **18** could be obtained from homoallylic amine substrate **17** in good yield and *ee*, even when 5 mol% of second-generation Grubbs catalyst was used (entry 6). In addition, the chiral homoallylic amine **19** proved

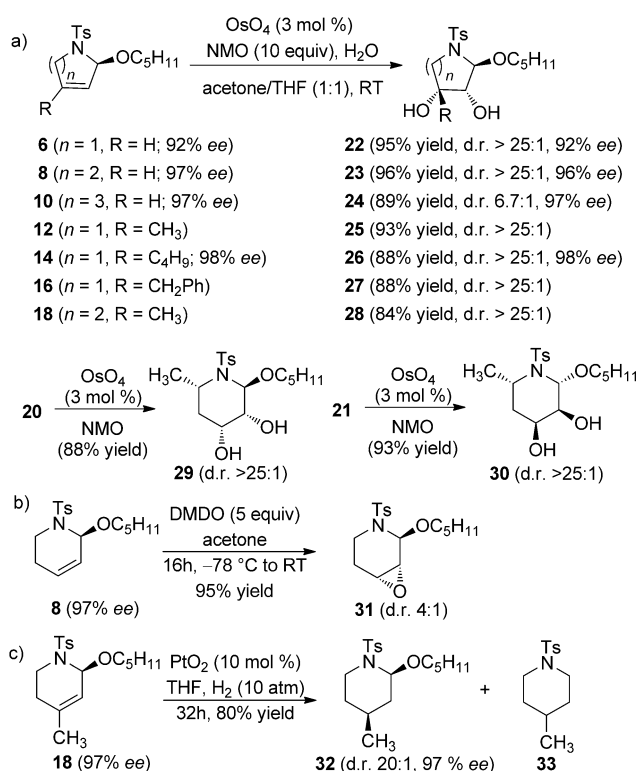
comparably efficient for the two-step sequence, thus generating the diastereomeric acyclic N,O-acetals **20** and **21** in high yield (entries 7 and 8) and high diastereoselectivity in both cases.

Having established the generality of the two-step protocol to access stereodefined cyclic N,O-acetals, we explored the use of these moieties as a stereocontrol element. We first considered the diastereoselective dihydroxylation of the cyclic N,O-acetals (Scheme 2a). A preliminary reaction of the compound **6** using catalytic OsO<sub>4</sub> (3 mol%) indeed gave the diol product **22** in 95% yield with a ratio of over 25:1 and with no deterioration of the *ee* value. The relative stereochemistry between the substituents on C2 and C3 in **22** was tentatively assigned as *trans* based upon the presumed steric effect of the N,O-acetal. For the complete assignment of the stereochemistry of the diols, see below. The N,O-acetal in the piperidine ring **8** also showed excellent stereodirecting effect, as the diol **23** was obtained as the predominant isomer in 96% yield. In contrast, the larger seven-membered ring compound **24** was obtained with somewhat lower 7:1 stereoselectivity from **10**. The N,O-acetal substrates possessing alkyl substitution on the olefin (compounds **12**, **14**, **16**, and **18**) also showed high yield and selectivity for the dihydroxylation. In the case

**Table 2:** Scope of the formation of cyclic stereodefined N,O-acetals.<sup>[a]</sup>

Entry	Substrate	Product	Yield [%] <sup>[b]</sup>		<i>ee</i> <sup>[c]</sup> [%]
			1st step (method)	2nd step (method)	
1	<b>7</b> ( <i>n</i> = 2, R = H)	<b>8</b>	99 (A1)	91 (B1)	> 99
2	<b>9</b> ( <i>n</i> = 3, R = H)	<b>10</b>	99 (A1)	93 (B1)	> 99
3	<b>11</b> ( <i>n</i> = 1, R = CH <sub>3</sub> )	<b>12</b>	99 (A2)	85 (B1)	94
4	<b>13</b> ( <i>n</i> = 1, R = <i>n</i> -C <sub>4</sub> H <sub>9</sub> )	<b>14</b>	93 (A2)	81 (B2)	97
5	<b>15</b> ( <i>n</i> = 1, R = Bn)	<b>16</b>	99 (A2)	89 (B2)	94
6 <sup>[d]</sup>	<b>17</b> ( <i>n</i> = 2, R = CH <sub>3</sub> )	<b>18</b>	99 (A2)	88 (B2)	97
7	<b>19</b>	<b>20</b>	99 (A2)	95 (B1)	> 25:1 <sup>[e]</sup>
8 <sup>[f]</sup>	<b>19</b>	<b>21</b>	99 (A2)	98 (B1)	> 25:1 <sup>[e]</sup>

[a] Method A1: Pentoxyallene (5 equiv) and (*R,R*)-**L2** were used. Method A2: Pentoxyallene (70 equiv) and (*R,R*)-**L1** were used. Method B1: The first-generation Grubbs' catalyst (5 mol%) was used. Method B2: The second-generation Grubbs' catalyst (20 mol%) was used. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. [d] The second-generation Grubbs' catalyst (5 mol%) was used at 60 °C. [e] Diastereomeric ratio determined by the integration of signals in the <sup>1</sup>H NMR spectra of the crude reaction mixture. [f] (*S,S*)-**L1** was used instead of (*R,R*)-**L1**.

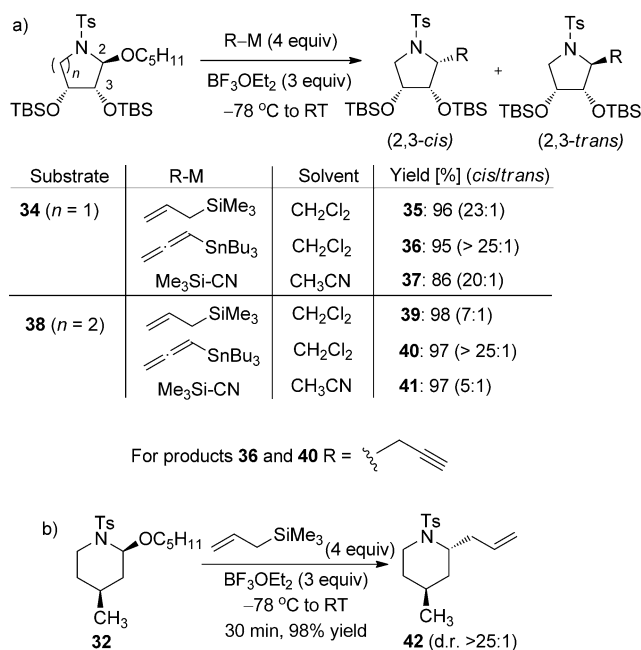


**Scheme 2.** Examples for the use of cyclic N,O-acetals as a stereocontrol element. a) For dihydroxylation. b) For epoxidation. c) For hydrogenation. NMO = *N*-methylmorpholine-*N*-oxide, THF = tetrahydrofuran.

of the isomeric piperidine N,O-acetal substrates **20** and **21**, the dihydroxylation showed complete diastereoselectivity, which was directed solely by the stereochemistry of cyclic N,O-acetal moiety to give the diastereomeric products **29** and **30** in good yield.<sup>[14]</sup>

In addition to the dihydroxylation, the reaction of **8** with dimethyldioxirane (DMDO) gave the epoxide **31** in high yield with 4:1 selectivity (Scheme 2b). Also, stereoselective hydrogenation of **18** using catalytic PtO<sub>2</sub> (5 mol %) generated the *cis*-piperidine acetal **32** in 80% yield with an approximate diastereoselectivity of 20:1 and no erosion of the enantioselectivity (Scheme 2c).<sup>[14,15]</sup>

Having confirmed the role of the N,O-acetal as the stereocontrol element, we finally investigated the iminium-mediated carbon–carbon bond formation to install a variety of alkyl groups at the C2-position (Scheme 3a). After extensive investigation, we discovered that the bis(TBS ether) **34** generated from **22** gave the allylated *cis*-product **35** in 96% yield with an approximate diastereoselectivity of 23:1 upon treatment with trimethylallylsilane and BF<sub>3</sub>OEt<sub>2</sub>.<sup>[14,16,17]</sup> Employing allenyltributylstannane and trimethyl cyanide also gave the product **36** and **37** in high yield and high diastereoselectivity, respectively. The absolute structure of **37** was unambiguously determined by the X-ray crystallographic study.<sup>[18]</sup> This structural analysis further confirms the stereochemical assignment suggested in the dihydroxylation (Scheme 2) and the asymmetric hydroamination (Table 1).



**Scheme 3.** Examples for the use of cyclic N,O-acetals as a diversity-generating element. TBS = *tert*-butyldimethylsilyl.

In addition, the above examples complete the study on the role of N,O-acetals as the diversity-generating element for the alkyl substitution at the C2-position of pyrrolidines.

In addition to the pyrrolidine substrate **34**, the bis(TBS ether) **38** generated from the piperidine diol **23** also showed high yield and diastereoselectivity for the alkyl substitution. For example, using allyltrimethylsilane proceeded smoothly to give the product **39** in 98% yield with 7:1 diastereoselectivity. Interestingly, employing allenyltributylstannane gave the product **40** in 97% yield with a significantly improved stereoselectivity of greater than 25:1, whereas using trimethylsilyl cyanide gave the product **41** in similar yield with a somewhat lower selectivity (5:1). The utility of the N,O-acetal is further demonstrated by the reaction of **32** with allyltrimethylsilane, which produced the *trans*-2,4-disubstituted piperidine **42** in high yield and excellent diastereoselectivity (Scheme 3b).<sup>[14,19]</sup>

From a synthetic viewpoint, the unprecedented strategy introduced here firmly establishes a highly efficient and unified protocol for the synthesis of bioactive natural products such as azasugars<sup>[20]</sup> and various alkaloids.<sup>[21]</sup> Moreover, the combined role of cyclic N,O-acetals as a stereocontrol and diversity-generating element makes this method particularly attractive for preparing cyclic amines possessing diverse stereochemical and substitution patterns.

In summary, we have developed a new synthetic strategy towards cyclic amines based upon the stereodefined cyclic N,O-acetals. Our future studies are aimed at expanding the scope of the allenes in the hydroamination reaction as well as exploring the biological effect of various cyclic amines.

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