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A new entry to functionalized cycloalkylamines: diastereoselective intramolecular amidoalkylation of *N*,*O*-acetal TMS ether possessing allylsilane

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Abstract—Highly diastereoselective cyclization (>20:1) as a new entry to functionalized cycloalkylamines has been conducted with acyclic *N*,*O*-acetal TMS ethers possessing an allylsilane moiety.

The *N*-acyliminium ion reaction with various carbon nucleophiles (e.g., allylsilane) is one of the most powerful methodologies for the synthesis of α-substituted amines, due to their facile susceptibility to a variety of nucleophilic attacks.[1] In addition, the intramolecular version of amidoalkylation have been applied to the syntheses of bicyclic and/or polycyclic amines from readily available cyclic imides or lactams as *N*-acyliminium ion precursors.[1,2] However, there have been few reports concerning monocyclization from the acyclic *N*-acyliminium ion precursor, mainly due to the limited methodologies for efficient preparations of the acyclic precursors as well as their propensity to readily hydrolyze. To the best of our knowledge, Hiemstra et al.[3] have made the only notable progress with regard to the intramolecular version of linear *N*-acyliminium ion precursors; nonetheless, challenges have not yet been effectively addressed.

Recently, we reported the intermolecular amidoalkylation of *N*,*O*-acetal TMS ether as an excellent *N*-acyliminium ion equivalent,[4a,b] as well as its application to the asymmetric synthesis of β-amino acids.[4c] In the context with our work on *N*-acyliminium ion chemistry, we have recently developed an intramolecular amidoalkylation of acyclic *N*-acyliminium ion precursors, which provides a rapid access to functionalized five-membered cycloalkylamines[5] such as *trans*-aminocyclopentane carboxylic acid (*trans*-ACPC, **3**),[6] of which foldamer were reported to display promising antimicrobial activity.[7] Herein, we report the highly diastereoselective intramolecular amidoalkylation of acylic *N*,*O*-acetal TMS ethers, as well as preliminary studies on its asymmetric version. The synthetic utility of this procedure is also demonstrated via concise syntheses of useful chiral building blocks (e.g., **3** and **4**), which are not accessible by the conventional method (Fig. 1).

We envisioned an objective intramolecular amidoalkylation via efficient preparation of the requisite cyclization precursors **1** by cross metathesis (CM)[8] of the *N*,*O*-acetal TMS ether **6**, which was prepared from the corresponding amide in an excellent yield according to our standard procedure.[4a,b] Cross metathesis between **6**

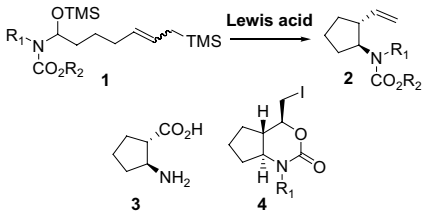

Figure 1.

Keywords: Cycloalkylamine; Intramolecular amidoalkylation; *N*,*O*-Acetal TMS ether.
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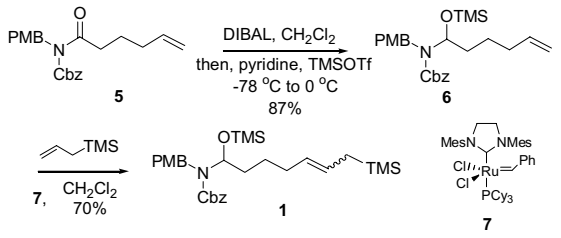
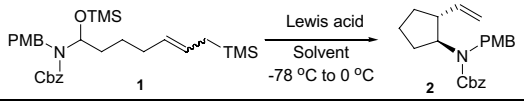


Scheme 1. Synthesis of cyclization precursor **1**.

and allylsilane in the presence of the Grubbs' catalyst **7** proceeded smoothly, to give the cyclization precursor **1** as an inseparable *E*/*Z* mixture (~1:1). It is noteworthy that under the metathesis conditions, the labile *N*,*O*-acetal TMS ether remains intact (Scheme 1).

With the desired *N*,*O*-acetal TMS ether **1** in hand, the intramolecular amidoalkylations of **1** were examined under various reaction conditions. As illustrated in Table 1, the *N*-acyliminium ion precursor, **1** revealed excellent reactivity to most of the Lewis acids to afford the cyclization adduct **2** in good yields. $SnCl_4$ was proved most effective, yielding the desired β-vinylcyclopentylamine **2** as a sole product, with the *trans* relationship between the amine and the newly formed terminal olefin (entry 8). The relative stereochemistry of **2** was confirmed by extensive NMR studies and its conversion to the known *trans*-ACPC derivative (Scheme 3). The cyclization with the high diastereoselectivity would proceed through the more favorable transition state **B** as shown in Figure 2. In addition, the stereochemical outcome implies the high diastereoselectivity of this cyclization regardless of olefin geometry of the allylsilane. Considering the precedents dealing with the Lewis acid mediated type II cyclization

Table 1. Optimization of intramolecular amidoalkylation of **1**



Entry	Lewis acid	Solvent	Yields[a] (%)	dr[b]
1	BF_3OEt_2	CH_2Cl_2	74	92:8
2	BF_3OEt_2	Et_2O	72	91:9
3	BF_3OEt_2	THF	—	—
4	BF_3OEt_2	$PhCH_3$	69	84:16
5	BF_3OEt_2	CH_3CN	62	90:10
6	TMSOTf	CH_2Cl_2	—	—
7	$TiCl_4$	CH_2Cl_2	70	93:7
8	$SnCl_4$	CH_2Cl_2	72	>95:5

[a] Isolated yields after column chromatography.
[b] Determined by the ^1H NMR spectra of the diastereomeric mixture or the isolation yield of each isomer.

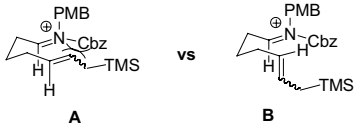
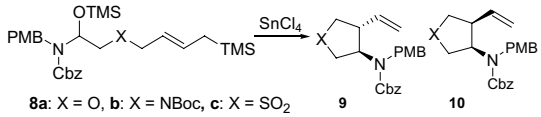


Figure 2. Proposed transition state.

of carbonyl derivatives, the highly diastereoselective amidoalkylation of **1** is quite noteworthy.[9]

Having successfully addressed the synthesis of β-vinylcyclopentylamine **2**, the intramolecular amidoalkylation was extended to the synthesis of the medicinally useful heterocycloalkylamines, for validation of generality and wide range of synthetic utility of this methodology. The *N*,*O*-acetal TMS ethers as intramolecular amidoalkylation substrates, involving oxygen (**8a**), nitrogen (**8b**), and sulfone (**8c**), were readily prepared from the known α-bromo-*N*-*p*-methoxybenzyl acetamide[10] by analogy of the precursor **1**. Cyclization of **8a** under the optimized conditions afforded a 5.7:1 diastereomeric mixture of **9a** and **10a**, in favor of the *trans*-isomer **9a** (entry 1). On the other hand, $SnCl_4$ treatment of **8b** and **8c** resulted in the exclusive formation of the desired *trans*-isomers **9b** and **9c** in moderate yields, respectively (entries 2 and 3).[11] The reason for the lower diastereoselectivity in the amidoalkylation of **8a** is not clear. However, it is likely due to the conformational change of the corresponding transition states, which is induced by the unshared oxygen electrons (Table 2).

Table 2. Cyclization of heteroatom-containing substrate **8**

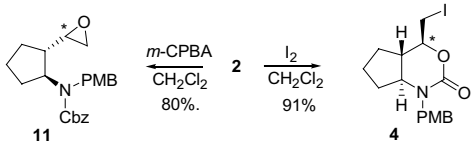


8a: X = O, **b**: X = NBoc, **c**: X = SO_2

Entry	Substrate	Yields[a] (%)	Ratio (**9**:**10**)[b]
1	**8a**	65	5.7:1
2	**8b**	61	>20:1
3	**8c**	48	>13:1

[a] Isolated yields after column chromatography.
[b] Determined by analyses of the ^1H NMR (500 MHz) spectra of the diastereomeric mixture.

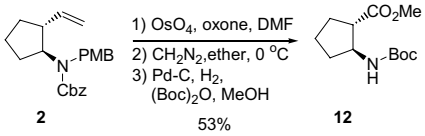
We have also extended synthetic utility of this methodology by simple oxidations of **2** as shown in Scheme 2. Halolactonization and epoxidation of **2** proceeded stereoselectively to give the cyclic carbamate **4** and the epoxide **11** as a single diastereomer, respectively. A structural confirmation of the cyclic carbamate **4** has been made by extensive NOE studies.



Scheme 2. Conversion of **2** to key building blocks.

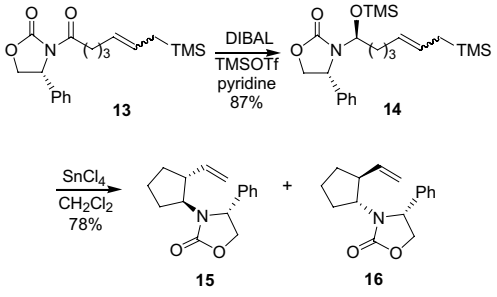
We confirmed synthetic utility of this versatile intramolecular amidoalkylation by conversion of the cyclopentylamine **2** to the methyl ester **12** of the Boc-protected *trans*-ACPC. The terminal olefin of **2** was initially transformed into the methyl ester by OsO_4 and oxone treatment, followed by esterfication (Scheme 3). Concurrent

deprotection of both the PMB and Cbz groups in the presence of Boc_2O provided the β-aminoester **12**, which is identical in all aspects to the reported β-aminoester.[12]



Scheme 3. Synthesis of *trans*-ACPC derivative **12**.

Encouraged by the successful cyclizations of various amidoalkylation substrates, we attempted to investigate the extension of this methodology to the asymmetric variants[4c] for the optically enriched cycloalkylamines. Thus, the *N*,*O*-acetal TMS ether **14**, prepared from the *N*-acyl-oxazolidinone **13**, was subjected to the standard intramolecular amidoalkylation condition. $SnCl_4$ treatment of **14** provided more than 20:1 diastereoselectivity in favor of the *trans*-isomer with 60% de.[13] The excellent diastereoselectivity was compatible with that of the achiral case, while the observed facial selectivity was lower than expected. However, this preliminary work on the asymmetric variant envisions its synthetic potential for the optically active cycloalkylamines, although the enantioselectivity is not satisfactory yet (Scheme 4).



Scheme 4. Asymmetric variant of intramolecular amidoalkylation.

In conclusion, we have developed a novel and versatile intramolecular amidoalkylation of acyclic *N*-acyliminium ion precursors for a variety of cycloalkylamines. This procedure appears to be quite useful for synthetic and medicinal chemists, in terms of synthetic efficiency and functional diversity. Currently, the studies on asymmetric variants of intramolecular amidoalkylation, based on our preliminary work, are in good progress. A report on the successful results as well as the advances in synthetic applications is forthcoming.

Acknowledgements

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References and notes

1. For excellent reviews on the chemistry of *N*-acyliminium ions and the related intermediates, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856; (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047–1082.
2. For selected recent reports, see: (a) Kamatani, A.; Overman, L. E. *Org. Lett.* **2001**, *3*, 129; (b) Overman, L. E.; Wolfe, J. P. *J. Org. Chem.* **2001**, *66*, 3167; (c) Heredia, M. L.; Cuesta, E. de la; Avendano, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2883; (d) Chao, W.; Waldman, J. H.; Weinreb, A. M. *Org. Lett.* **2003**, *5*, 2915.
3. (a) Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1985**, *26*, 3155; (b) Mooiweer, H. F.; Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1987**, *28*, 3285.
4. (a) Suh, Y.-G.; Shin, D.-Y.; Jung, J.-K.; Kim, S.-H. *Chem. Commum.* **2002**, 1064; (b) Suh, Y.-G.; Kim, S.-H.; Jung, J.-K.; Shin, D.-Y. *Tetrahedron Lett.* **2002**, *43*, 3165; (c) Shin, D.-Y.; Jung, J.-K.; Seo, S.-Y.; Lee, Y.-S.; Paek, S.-M.; Chung, Y. K.; Shin, D. M.; Suh, Y.-G. *Org. Lett.* **2003**, *5*, 3635.
5. For reviews on cyclic β-amino acids, see: (a) Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629; (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991.
6. Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 4976.
7. (a) Gademann, K.; Hintermann, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905; (b) Porter, E. A.; Wang, X.; Lee, H.-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565; (c) Wang, X.; Espinosa, J. F.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 4821, and the related references cited therein.
8. Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.
9. Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC, 1996; pp 91–177.
10. Wasserman, H. H.; Rotello, V. M.; Krause, G. B. *Tetrahedron Lett.* **1992**, *33*, 5419. The initial introduction of allylic moiety was conducted by reaction of α-bromo-*N*-*p*-methoxybenzyl acetamide with allyl mercaptan/NaH, allyl alcohol/NaH and allyl amine, respectively.
11. The enamide formation by β-elimination of the acylimium ion rather than allylsilane addition was consistently observed.
12. For the *trans*-ACPC derivative, see: Yokota, Y.; Cortez, G. S.; Romo, D. *Tetrahedron* **2002**, *58*, 7075. See also Ref. 6.
13. The isomer **15** is considered as the major product on the basis of our previous work. Refer to Ref. 4c.