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Lewis Acid-Catalyzed Ring-Opening Reactions of Semicyclic *N*,*O*-Acetals

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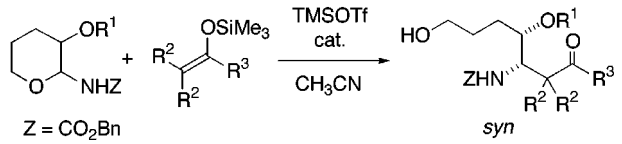
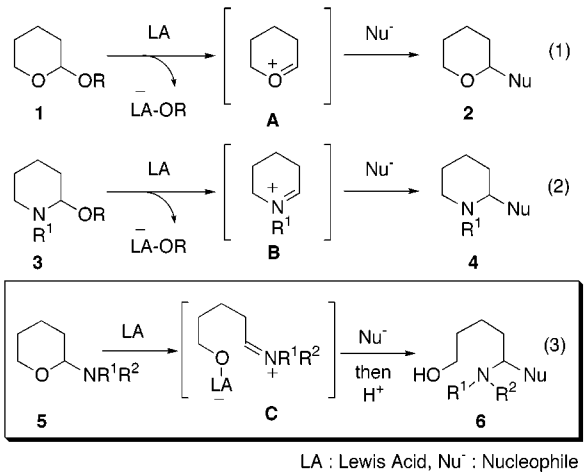
ABSTRACT



Ring-opening reactions of semicyclic *N*,*O*-acetals with various nucleophiles such as silyl enol ethers are effectively catalyzed by a Lewis acid (TMSOTf). Reactions of 3-substituted *N*,*O*-acetals showed high diastereoselectivities. Synthetic utility of this method has been demonstrated in the stereoselective synthesis of an *anti*-malarial agent, isofebrifugine.

In the presence of a Lewis acid, semicyclic acetals (**1**) such as *O*-glycosides are known to react with various nucleophiles to give cyclic ether products (**2**) via cyclic oxocarbenium ion intermediates **A** (eq 1).[1] Similarly, reactions of semicyclic[2] *N*,*O*-acetals (**3**) provide nitrogen-containing cyclic compounds (**4**) via cyclic iminium ion intermediates **B** (eq 2).[3] Meanwhile, reactions of *other* semicyclic *N*,*O*-acetals (**5**), where the positions of nitrogen and oxygen of **3** are inverted, are expected to proceed via formation of acyclic iminium ion intermediates **C** to afford ring-opened products (**6**) if an oxophilic Lewis acid is employed (eq 3). Although it has been reported that *N*,*N*-dialkylaminofuranosides or pyranosides reacted with excess Grignard reagents to give ring-opened alkylation products[4] and that *N*-galactosyl-*N*-homoallylamine undergoes aza-Cope rearrangement promoted by a stoichiometric amount of a Lewis acid,[5] this type of reaction has not been systematically explored. We have recently reported that the second-type reactions (eq 2) were effectively catalyzed by scandium trifluoromethanesulfonate.[6] Herein we report the third-type reactions shown in eq 3 using



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(3) For reviews, see: (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047−1082. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, 56, 3817.

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(6) Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989.

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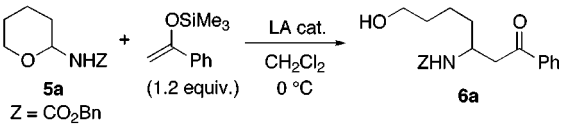
a catalytic amount of a Lewis acid, and their synthetic utility and high stereoselectivity are described.

At the outset, we chose benzyl *N*-(tetrahydropyran-2-yl)-carbamate (**5a**) as one of the simplest semicyclic *N*,*O*-acetals and the silyl enol ether derived from acetophenone as a nucleophile (Table 1). Pyran **5a** was readily prepared via

Table 1. Effect of Lewis Acids[a]



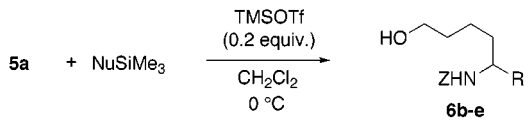
run	LA (equiv)	time	yield of **6a**/%
1	TMSOTf (0.2)	20 min	90
2[b]	TMSOTf (0.2)	20 min	94
3	$SnCl_4$ (0.2)	7 h	33
4	$BF_3{\cdot}OEt_2$ (0.2)	11 h	4
5	TfOH (0.1)	20 min	31
6	TMSCl−$AgClO_4$ (0.2)	15 min	48
7	$SnCl_4$−$AgClO_4$	15 min	71

[a] Reactions were carried out using **5a** (0.2 mmol), the silyl enol ether (1.2 equiv), and a Lewis acid (0.1 or 0.2 equiv) in dichloromethane at 0 °C, unless otherwise noted. [b] Two equivalents of the silyl enol ether were used.

acid-catalyzed addition of benzyl carbamate to 3,4-dihydro-2*H*-pyran.[7] The reactions were carried out using a catalytic amount of a Lewis acid (0.1−0.2 equiv) at 0 °C in dichloromethane. Among the various Lewis acids tested (runs 1−5), trimethylsilyl trifluoromethanesulfonate (TMSOTf) was found to be the most effective (runs 1 and 2), and ring-opened alcohol **6a** was obtained in high yields. A combination of chlorotrimethylsilane or tin tetrachloride and silver perchlorate[8] was also effective (runs 6 and 7).

Under these optimal conditions for **5a**, reactions with various nucleophiles were also investigated (Table 2). Allyltrimethylsilane, trimethylsilyl cyanide, and other silyl enolates reacted smoothly to afford the desired adducts **6b**−**e** in excellent yields.

Table 2. Reactions with Various Nucleophiles[a]

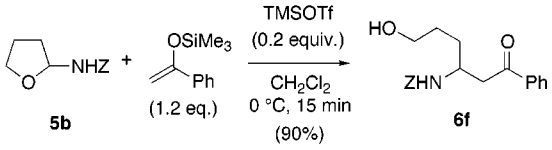


$NuSiMe_3$ (equiv)	time/ min	product (**6**)	yield/ %
$CH_2{=}CHCH_2SiMe_3$	120	**6b** (R = $CH_2CH{=}CH_2$)	91
Me_3SiCN (2)	15	**6c** (R = CN)	99
$CH_2{=}C(t\text{-Bu})(OSiMe_3)$ (1.5)	20	**6d** (R = $CH_2CO t$-Bu)	89
$Me_2C{=}C(OMe)OSiMe_3$ (1.5)	20	**6e** (R = CMe_2CO_2Me)	99

[a] All reactions were carried out using **5a** (0.2 mmol), a nucleophile, and TMSOTf (0.2 equiv) in dichloromethane at 0 °C.

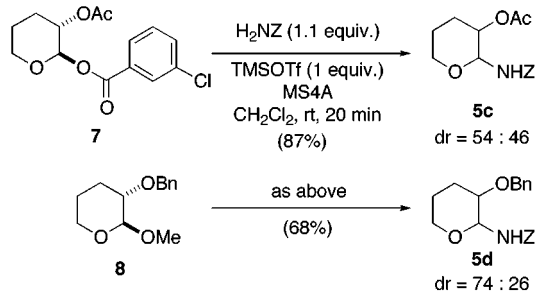
Furthermore, five-membered analogue **5b** was also shown to provide the ring-opened product **6f** in high yield (Scheme 1).

Scheme 1. THF System



We next focused on the elucidation of the stereochemical aspect of this reaction. For this purpose, 3-substituted semicyclic *N*,*O*-acetals **5c** and **5d** were prepared via TMSOTf-promoted substitution of ester **7** or ether **8** with benzyl carbamate (Scheme 2). Since benzyl carbamate is a weak

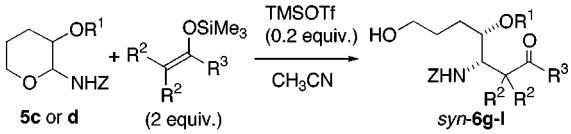
Scheme 2. Preparations of 3-Substituted THP Substrates



nucleophile, an addition of 4 Å molecular sieves was essential to prevent the formation of the hydrolyzed products.

We then investigated the reaction of **5c** with the silyl enol ether derived from acetophenone (Table 3). Unlike **5a**, **5c**

Table 3. Reactions of 3-Substituted Substrates[a]



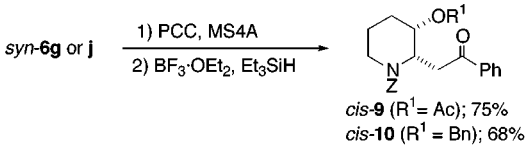
run	R^1	R^2	R^3	products (**6**)	conditions	yield/ %	*syn*/ *anti*
1[b]	Ac	H	Ph	**6g**	0 °C, 2 h	60	58/42
2[c]					0 °C, 2 h	77	82/18
3					0 °C, 2 h	76	91/9
4					−23 °C, 2 h	45	93/7
5		H	*t*-Bu	**6h**	0 °C, 5 h	61	94/6
6		Me	MeO	**6i**	0 °C, 30 min	87	94/6
7	Bn	H	Ph	**6j**	−23 °C, 1 h	67	94/6
8		H	*t*-Bu	**6k**	0 °C, 3 h	59	94/6
9		Me	MeO	**6l**	−23 °C, 40 min	94	94/6

[a] Reactions were carried out using **5c** or **5d** (0.1 mmol), a nucleophile (2 equiv), and TMSOTf (0.2 equiv) in acetonitrile, unless otherwise noted. [b] One equivalent of TMSOTf was used in dichloromethane as a solvent.[c] Nitromethane was used as a solvent.

required a stoichiometric amount of TMSOTf for complete consumption in dichloromethane, giving a ca. 1:1 diastereomeric mixture of product **6g** (run 1). A polar solvent such as acetonitrile or nitromethane, which was presumed to stabilize the iminium ion intermediate, was found to promote a catalytic reaction and to improve the yield and stereoselectivity (runs 2−4). Using the conditions in acetonitrile, reactions of **5c** with other silyl enolates provided alcohols **6h** and **6i** with high *syn*-diastereoselectivities (runs 5 and 6). In addition, reactions of 3-benzyloxypyran **5d** also proceeded catalytically in acetonitrile to give ring-opened products **6j**−**l** with high *syn*-diastereoselectivities (runs 7−9).

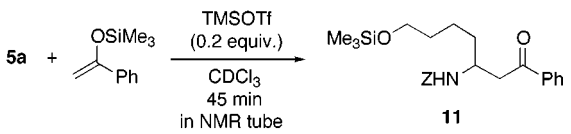
The configuration of the major diastereomers of **6g** and **6j** were determined, respectively, as *syn* after converting to *cis*-piperidines **9** or **10**[6] via PCC-oxidation and reductive cyclization (Scheme 3).

Scheme 3. Determination of Relative Stereochemistries



^{1}H NMR analysis of the TMSOTf-catalyzed reaction of **5a** in $CDCl_3$ showed that the initial product formed was *O*-trimethylsilylated ether **11** which was easily hydrolyzed to the alcohol **6a** by the addition of water (Scheme 4).[9] This

Scheme 4. Observation of the Initial Product



result strongly suggests a mechanism of this reaction involving coordination of the Lewis acid to the ring-oxygen followed by ring-opening activation to form an acyclic iminium ion intermediate (see, eq 3).

The stereochemical course of the present reaction can be rationalized as shown in Figure 1. In 3-acetoxy system **5c**, five-membered dioxocarbenium ion intermediate TS_1 could be involved in neighboring group participation of the 3-acetoxy group. This dioxocarbenium ion would have the *trans*-configuration due to steric reason, and then an S_N2-type attack of a nucleophile would provide the *syn*-product. This is a good contrast to the reaction of the 3-acetoxy cyclic piperidine system where the *cis*-fused bicyclic dioxocarbenium ion intermediate could be involved, giving a *trans*-product preferentially.[6] While the 3-benzyloxy substituent of **5d** could not participate as an iminium ion intermediate, TS_2 would be favorable between the two competitive transition states TS_2 and TS_3, since the conformation of TS_3 has a large allylic strain between the alkyl side chain and the proton bound to the iminium nitrogen.[10] It would be also possible that the hydrogen bonding between the proton bound to the iminium nitrogen and the 3-benzyloxy group could fix the conformation of the transition state (see, TS_4) and a nucleophile would attack from the less hindered side to give the *syn*-product.

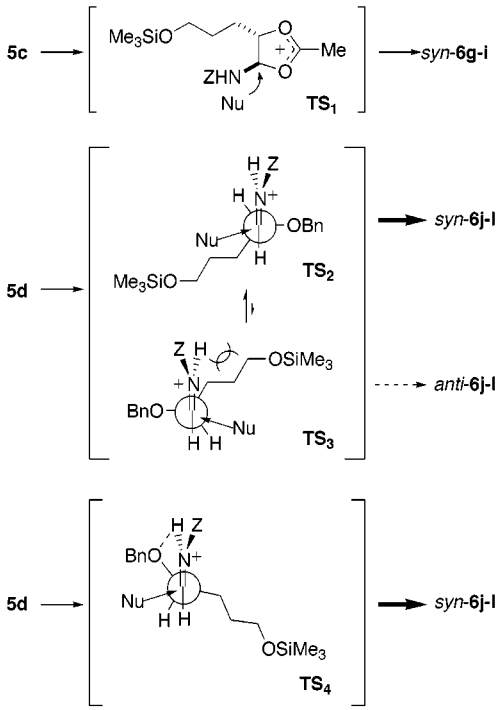
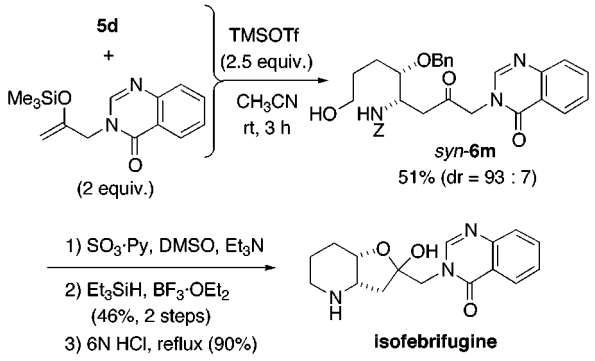


Figure 1.

Synthetic utility of the present reaction has been demonstrated in a facile synthesis of an *anti*-malarial alkaloid, isofebrifugine[11] (Scheme 5). Using a quinazoline-containing

Scheme 5. Synthesis of Isofebrifugine



(7) Related reactions of benzamides have been reported: Chen, J.; Crooks, P. A.; Hussain, A. *Int. J. Pharm.* **1995**, *123*, 95.

(8) For a leading reference: Mukaiyama, T.; Takashima, T.; Katsurada, M.; Aizawa, H. *Chem. Lett.* **1991**, 533.

(9) Although the ^{1}H NMR spectra of **11** and **6a** are quite similar, the chemical shifts for the methylene proton adjacent to the silyloxy group or the hydroxyl group are distinguishable, i.e., 3.55 ppm (t) for **11** and 3.60 ppm (t) for **6a**.

silyl enol ether[11a] as a nucleophile, 3-benzyloxy *N*,*O*-acetal **5d** was converted to acyclic alcohol **6m** in good yield. A slight excess of TMSOTf was required presumably due to the basicity of the quinazoline nitrogen. Further transformations of **6m** accomplished a diastereoselective synthesis of isofebrifugine.

In summary, we have demonstrated that ring-opening reactions of semicyclic *N*,*O*-acetals **5** with silicon-based nucleophiles were effectively catalyzed by a Lewis acid to afford acyclic alcohols **6** with high diastereoselectivities. The stereoselective synthesis of isofebrifugine provided an example of their synthetic utility. Further applications and mechanistic studies are now in progress.

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Supporting Information Available: Experimental procedures and physical data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Nagai et al. suggested a similar transition state model for α-alkoxy-*N*,*N*-dibenzyliminium ion system (see, ref 4a).

(11) For recent syntheses of isofebrifugine and/or febrifugine, see: (a) Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* **1996**, *37*, 3255. (b) Kobayashi, S; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175. (c) Kobayashi, S; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* **1999**, *64*, 6833. (d) Takeuchi, Y.; Abe, H.; Harayama, T. *Chem. Pharm. Bull*. **1999**, *47*, 905. (e) Takeuchi, Y.; Hattori, M.; Abe, H.; Harayama, T. *Synthesis* **1999**, 1814. (f) Takeuchi, Y.; Azuma, K.; Takakura, K.; Abe, H.; Harayama, T. *Chem. Commun.* **2000**, 1643. (g) Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3193.