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Intramolecular Amidoalkylation of Chiral Iminium Ions: Stereoselective Synthesis of *syn*- 1, 3-Aminoalcohols

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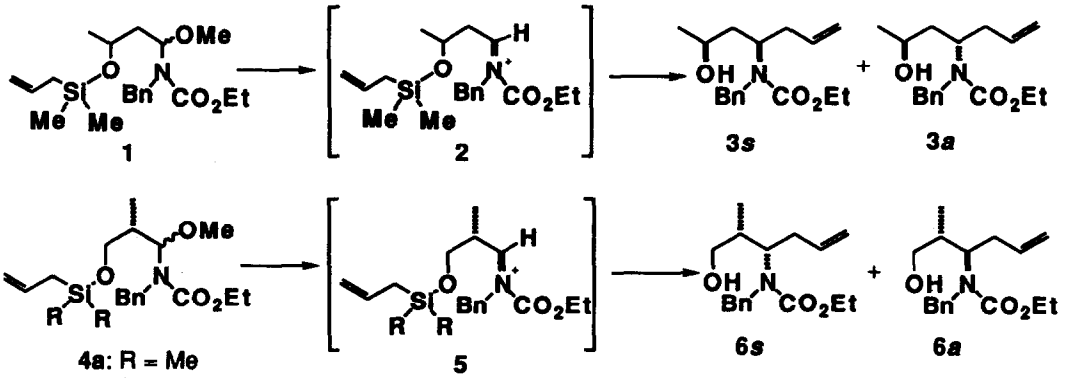
Abstract: The intramolecular Hosomi-Sakurai reaction of 3-siloxybutaniminium salts exhibited a *syn* selectivity of up to 51:1, while the same type of reaction of 2-methyl-3-siloxypropaniminium salts showed up to 290 :1 *syn* selectivity.

Compared to various methodologies developed in the last two decades for the synthesis of 1,2-diols or -aminoalcohols, those for the formation of 1,3-diols or -aminoalcohols are less satisfactory,[1] although they are equally as important for the construction of the structural units often found in many bioactive natural products. Thus, in order for the latter reactions to be equally appreciated in organic synthesis, more effective methodologies are desirable. We describe herein a highly stereoselective entry to the synthesis of two types of 1,3-aminoalcohols **3** and **6** by an intramolecular combination of the Hosomi-Sakurai reaction and the amidoalkylation of chiral iminium salts **2** and **5** (Scheme 1). Although applied to cyclic systems,[2] this methodology has not yet been reported for the stereocontrolled construction of an acyclic system. The closest analogy is Reetz's Lewis acid-mediated Hosomi-Sakurai reaction of chiral β-siloxyaldehydes to afford 1,3-diols;[3] the $TiCl_4$-induced reactions proceeded intramolecularly giving mostly *syn* products (*syn* : *anti* = 92 : 8), while those with $SnCl_4$ occurred intermolecularly to give mainly *anti* products (*syn* : *anti* = 8 : 92).[3b]

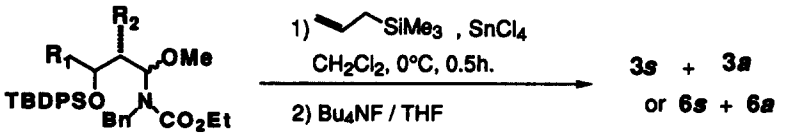
Scheme 1.



As the reactive iminium ions such as **2** and **5** are usually generated *in situ* by treating aminoacetals with Lewis acids, **1**, **4a** and **4b**[4] were treated with various Lewis acids in order to induce the amidoalkylation reaction. General procedure for the reaction is as follows. To the CH_2Cl_2 solution of a Lewis acid (2.2 equiv.), **1**, **4a**, or **4b** (1 equiv.) in the same solvent was added slowly with stirring at 0°C under argon atmosphere. After 30min in which the aminoacetals disappeared completely, the siloxy group was solvolyzed with methanol at

0°C for 10min. The products were collected by the standard procedure after neutralization by aq. $NaHCO_3$. The *syn* : *anti* ratio was determined by G.C. on the crude product, while the yield was established after silica gel column chromatography.[5] The results were compared with those of the intermolecular reactions (Scheme 2) and are listed in Table 1.

Scheme 2



7a: R_1 = Me, R_2 =H
7b: R_1 =H, R_2 = Me

Table 1. Amidoalkylation of 3-Siloxybutaniminium Ions.

Entry	Substrate	Lewis acid	Isolated yield (%)	Ratio *syn* : *anti*
1	**7a**[a]	$SnCl_4$	74	1 : 1.1
2	**1**	$SnCl_4$	93	45 : 1
3	"	" (1.0 eq)	86	46 : 1
4	"	$TiCl_4$	86	48 : 1
5	"	$BF_3{\cdot}OEt_2$	86	51 : 1
6	**7b**[a]	$SnCl_4$	30	2 : 1
7	**4a**	$SnCl_4$	95	110 : 1
8	"	$BF_3{\cdot}OEt_2$	67	130 : 1
9	**4b**	$SnCl_4$	87	240 : 1
10	"	$BF_3{\cdot}OEt_2$	77	290 : 1

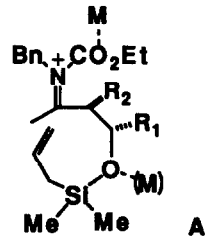
a. To the CH_2Cl_2 solution of $SnCl_4$ (2.2 equiv.) the precursor (1 equiv.) and allyltrimetylsilane (1.5 equiv.) was added at 0°C. After 0.5h, the reaction was quenched by aq. $NaHCO_3$ and the silyl guoup in the products was eliminated by Bu_4NF in THF.

Compared with the intermolecular reactions (entries 1 and 6) which show only poor stereoselectivity, all the intramolecular amidoalkylations exhibited much higher yields and excellent *syn* selectivity both in 1,2- and 1,3-chiral inductions regardless of the Lewis acids employed, implying the intramolecular nature for all Lewis acids used[6] and providing an excellent entry to the stereoselective synthesis of *syn*-1,3-aminoalcohols. The following trends are also noted in Table 1. The 1,2-chiral induction in **5** (entries 7 and 8) is about 2.5 times larger than the corresponding 1,3-induction in **2** (entries 2 and 5).[1] The 2.2 equivalents of $SnCl_4$ afford more product than the 1.0 equivalent, though the ratio remains the same (entries 2 and 3). Among Lewis acids, $SnCl_4$ gives the best yield for a given substrate (*e.g.* entries 2 vs 4 and 5), while $BF_3{\cdot}OEt_2$ shows the highest *syn* : *anti* ratio (*e,g,* entries 5 vs 2 and 4).[7]

We suggest the mechanism of the present reactions as follows: The Lewis acids would not coordinate with the iminium nitrogen but with the oxygens of ester group and siloxy group. While the coordination with siloxy group would retard the reaction, that with ester group would accelerate it. The excellent *syn* selectivity observed would originate from the intramolecular attack of the allyl group on the iminium carbon from the side

opposite to the methyl group at C-2 or C-3 (R_2 or R_1 in A). It is difficult to estimate the non-bonded repulsive interaction controlling the conformation of the transition state, but those between the methyl (R_1 or R_2) and the incoming allyl group, (Lewis acid and the C-2 methyl), two methyl (Si-Me and C-2) groups, and C-2 methyl and benzyl or ethoxycarbonyl group, can be envisaged. The chelation of Lewis acid with the silyl oxygen and an ester oxygen to form an 8-membered cyclic transition state is less likely, because 1) BF_3 which is incapable of chelation exhibited similar *syn* selectivity, and 2) the amidoalkylation of the corresponding imines **8a** and **8b**, which would certainly form a more stable 6-membered chelate, *e.g.* **B**, with $SnCl_4$, showed very poor diastereoselectivity.[3]

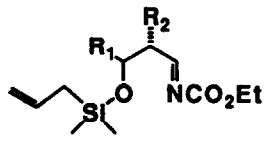
Thus, the amidoalkylation was proved to be an excellent means of constructing a 1,3-aminoalcohol unit.



A

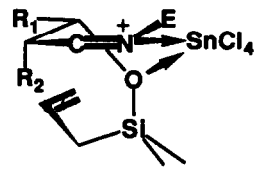
M = Lewis acid

R_1 = Me, R_2 = H or R_1 = H, R_2 = Me



8a: R_1 = Me, R_2 = H

8b: R_1 = H, R_2 = Me



B: E = CO_2Et

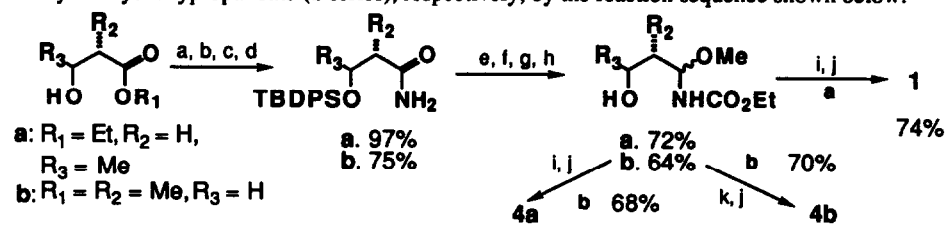
REFERENCES AND NOTES

1. For example, the stereoselectivity in the *syn*-1,3-aminoalcohol synthesis by the intramolecular conjugate carbamination is ca 5 times (Hirama, M.; Shigemoto. T.; Yamazaki, Y.; Itô, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797-1798) and that in the *syn*-1,3-diol synthesis by the intermolecular Hosomi-Sakurai reaction of 3-alkoxyaldehydes is ca 3 times (Kiyooka, S.; Heathcock, C. H. *Tetrahedron Letters* **1983**, *24*, 4765-4768) less effective than those observed in the synthesis of 1,2-diols.

2. Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *ibid.* **1985**, *26*, 3155-3158. Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014-4020. Mooiweer, H. H.; Hiemstra, H. Speckamp W. N. *Tetrahedron* **1991**, *47*, 3451-3462.

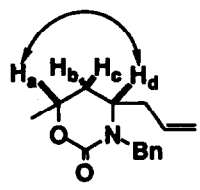
3. a. Reetz, M. T. *Pure Appl. Chem.* **1985**, *57*, 1781-1788. b. Reetz, M. T.; Jung, A.; Bolm, C. *Tetrahedron* **1988**, *44*, 3889-3898.

4. The precursors, **1**, **4a** and **4b**, were prepared from ethyl 3-hydroxybutanoate (a series) or methyl 2-methyl- 3-hydroxypropanoate (b series), respectively, by the reaction sequence shown below.



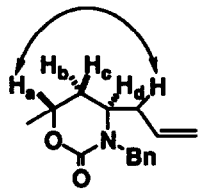
a. TBDPSCl, imidazole / DMF, r.t.,1.5h. b. 6N NaOH / MeOH, r.t. c. $ClCO_2Et$, Et_3N / CH_2Cl_2, 0°C, d. NH_3 aq. e. Me_3OBF_4 / CH_2Cl_2, r.t., 6h. f. $ClCO_2Et$, DMAP (0.1 equiv) / Py, r.t. 1 h. g. $NaBH_4$ (7 equiv.) / EtOH, r.t., 1h. h. Bu_4NF / THF, r.t., 24h. i. $SiMe_2Cl$, imidazole / DMF, 0°C, 1.5h. j. BnBr (10 equiv.), NaH (5 equiv.) / DMF, 0 °C, 30min. k. $SiPh_2Cl$, imidazole / DMF, 0°C, 30min.

5. For the structure determination of the products, each isomer, **3*s*** and **3*a***, and **6*s*** and **6*a***, was treated separately with NaH in THF at 0°C to give cyclic carbamates, **9*s*** and **9*a***, and **10*s*** and **10*a***, respectively. Their relative configuration was established by the magnitude of their H-H coupling constants and NOE experiments (see arrows).



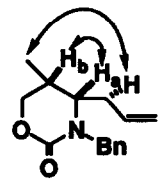
9*s*

J_{ab} = 11.2, J_{bd} = 11.2
J_{ac} = 2.0, J_{cd} = 6.1



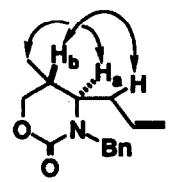
9*a*

J_{ab} = 11.7, J_{bd} = 5.9
J_{ac} = 2.0, J_{cd} = 2.0



10*s*

J_{ab} =5.4



10*a*

J_{ab} = 3.4

6. The intramolecular nature was established for the $SnCl_4$-induced reaction of **1** and **4a**. An equimolar mixture of **1** and the corresponding *t*-butyldimethylsiloxy aminoacetal was reacted with $SnCl_4$ under the standard conditions. A 41:1 mixture of **3*s*** and **3*a*** was obtained in 94% yield in addition to $BnNHCO_2Et$ (88%), the elimination product. The yield and the ratio of **3*s*** and **3*a*** are almost identical with those of the intramolecular reaction (entry 2, Table 1). A similar reaction using **4a** and **7b** afforded a 120 : 1 mixture of **6*s*** and **6*a*** (83% yield) and $BnNHCO_2Et$ (90% yield), a yield and ratio similar to entry 7, Table 1.

7. The reaction of **1** in the presence of $MgCl_2$ was very slow (60% recovery under standard conditions) and resulted in complete decomposition after 2 days. TMSOTf gave under the standard conditions a complex mixture from which **3** was isolated in only 2% yield, though the *syn* : *anti* ratio was adequate (40 : 1).

8. The results of the intramolecular Hosomi-Sakurai reaction of **8a** and **8b** as well as their intermolecular versions (debenzyl-**7a** and debenzyl-**7b**) are listed in Table 2, which again shows that BF_3 exhibited slightly better *syn* selectivity than $SnCl_4$.

Table 2. Amidoalkylation of **8a** and **8b**.[a]

Entry	Substrate	Lewis acid	Isolated yield (%)	Ratio *syn* : *anti*
1	debenzyl**7a**	$SnCl_4$	64	2 : 1
2	**8a**	$SnCl_4$	86	2.7 : 1
3	〃	$BF_3{\cdot}OEt_2$	85	7.5 : 1
4	debenzyl **7b**	$SnCl_4$	84	1 : 1.3
5	**8b**	$SnCl_4$	97	1 : 1
6	〃	$BF_3{\cdot}OEt_2$	80	2.4 : 1

a. Reaction was carried out under the standard conditions described in the text and the footnote of Table 1.

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