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Diastereoselectivity Control in the $TiCl_4$-Mediated Addition Reaction of Allyltrimethylsilane to N,O-Protected (*L*)-Serinals

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Abstract: The $TiCl_4$- and $SnCl_4$-mediated addition reactions of allyltrimethylsilane (**1**) to protected (*L*)-serinals (**2-5**) were studied, and in the case of $TiCl_4$ a large influence of the N- and O-protecting groups on the stereochemical course was observed.

The past 10-15 years have seen an impressive expansion in the application of α-amino acids to the total synthesis of natural products, including amino sugars.[1-3] The subject of the total synthesis of amino sugars is covered in several general reviews.[4-9] Stereoselective elongation of the carbon skeleton is the central issue in the synthesis of amino sugars from α-amino acids and their derivatives.[10,11]

We have recently reported[12] the highly stereoselective synthesis of (2*R*,3*S*)-3-hydroxyproline, based on the addition reaction of allyltrimethylsilane (**1**) to (*N*)-Cbz-(*O*)-TBS-(*L*)-serinal (**2**). Addition of silane **1** to aldehyde **2**, in the presence of one equivalent of $SnCl_4$ at -78°C, afforded with very high diastereoselectivity (>95:5), the adduct *syn*-**6** (Scheme 1). Since control of the stereochemical course of such a C_3-elongation reaction is crucial from the standpoint of the synthesis of optically pure compounds,[13-16] we decided to study in detail the addition of silane **1** to N,O-protected (*L*)-serinals **2-5** under different reaction conditions (Scheme 1).

α-Amino aldehydes **2-5** were reacted with silane **1** in the presence of the chelating Lewis acids - $SnCl_4$ and $TiCl_4$. Additions were carried out at low temperature (-78°C) in methylene chloride as a solvent and under an argon atmosphere. After work-up, the crude reaction mixtures were subjected to HPLC to establish the *syn/anti* ratio of the adducts.[17] The results of our experiments are shown in Table 1.[18]

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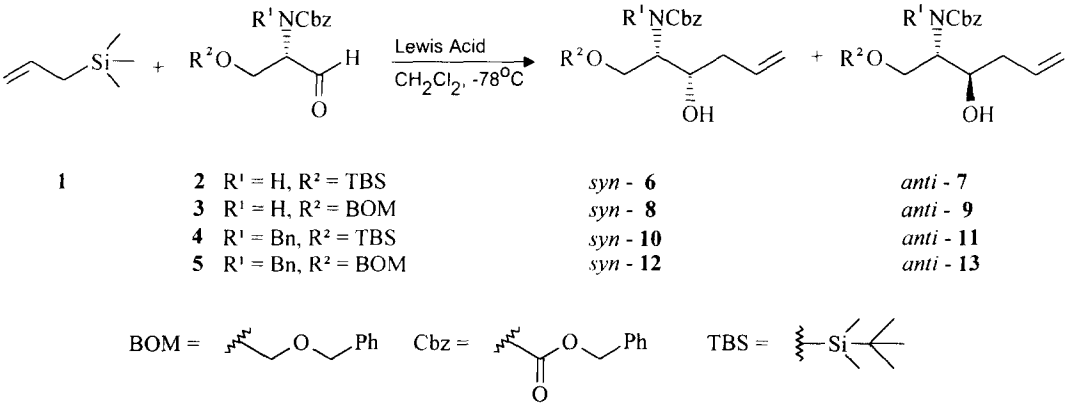


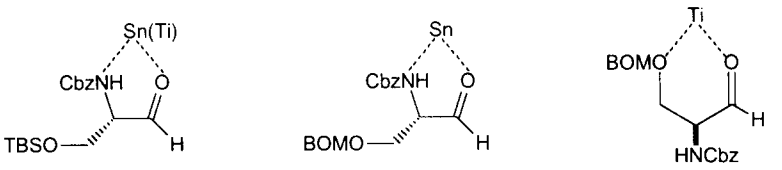
Scheme 1

Table 1. Results of reactions of **1** with **2-5**, carried out in the presence of one equivalent of Lewis acid in CH_2Cl_2 at -78°C

Entry	Aldehyde	Lewis Acid	Time [h]	Yield [%]	Diastereoisomer Ratio [*syn*:*anti*]
1	**2**	$SnCl_4$	1.0	88	98:2
2	**2**	$TiCl_4$	20.0	83	70:30
3	**3**	$SnCl_4$	1.5	68	82:18
4	**3**	$TiCl_4$	16.0	90	3:97
5	**4**	$SnCl_4$	1.5	75	45:55
6	**4**	$TiCl_4$	3.0	70	94:4
7	**5**	$SnCl_4$	3.0	73	21:79
8	**5**	$TiCl_4$	3.5	71	26:74

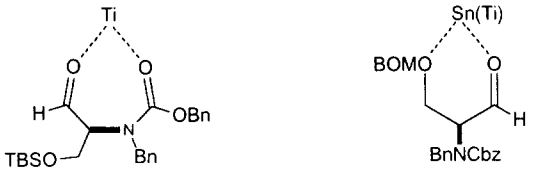
The data show that (*N*)-Cbz-(*O*)-TBS-(*L*)-serinal (**2**) gives, *via* α-chelated conformer A (Scheme 2), the adduct *syn*-**6**[19] as a main product, in the presence of both catalysts $SnCl_4$ and $TiCl_4$ (entries 1 and 2, respectively). Similar diastereoselectivity, as a result of the predominance of α-chelated conformer B, was observed for (*N*)-Cbz-(*O*)-BOM-(*L*)-serinal (**3**) when it was reacted with silane **1** in the presence of $SnCl_4$ (entry 3). The adduct *anti*-**9**[20] was the major product of the reaction of silane **1** with aldehyde **3**, catalyzed by $TiCl_4$ (entry 4). In this case β-chelated conformer C clearly predominates (Scheme 2). Surprisingly, *syn*-diastereoselectivity was obtained in the reaction of **1** with (*N*)-Bn-(*N*)-Cbz-(*O*)-TBS-(*L*)-serinal (**4**) mediated by $TiCl_4$, giving the adduct *syn*-**10**[21] (entry 6), which is easily explained by the γ-chelated conformer D (Scheme 3). Similar seven-membered chelates were observed by Garner and Ramakanth,[22] and by Kunz *et al.*[23] for related compounds possessing the (*N*)-Cbz protecting group. Finally, we found that (*N*)-Bn-(*N*)-Cbz-

(*O*)-BOM-(*L*)-serinal (**5**) affords, *via* β-chelated conformer E (Scheme 3), the adduct *anti*-**13**[24] as a main one, in the presence of both catalysts $SnCl_4$ and $TiCl_4$ (entries 7 and 8, respectively).



A B C

Scheme 2. Preferred complexes of **2** with $SnCl_4$ or $TiCl_4$ (A), of **3** with $SnCl_4$ (B) and $TiCl_4$ (C)



D E

Scheme 3. Preferred complexes of **4** with $TiCl_4$ (D) and of **5** with $SnCl_4$ or $TiCl_4$ (E)

The results presented demonstrate that it is possible to control the diastereoselectivity of Lewis acid promoted addition of allyltrimethylsilane (**1**) to N,O-protected (*L*)-serinals by means of changing the N- and O-protecting groups as well as Lewis acids used. Enlargement upon these findings and the application of this approach to the total synthesis of complex amino sugars are matters of continuing interest in this laboratory.

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17. HPLC experiments were performed using a Lichrospher 100-NH_2 column with a mixture of n-hexane and isopropanol (97.5:2.5 v/v) as eluent.
18. Relative configuration for the major product of the reaction **1** + **2** → *syn*-**6** was determined by a chemical correlation with (2*R*,3*S*)-3-hydroxyproline.[12] Relative configurations of adducts formed in other reactions were established on the basis of their chemical correlations with *syn*-**6** and *anti*-**7**.
19. Data for *syn*-**6**: oil; $[\alpha]_D^{20}$= +20.5 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, toluene-d_8, δ): 7,17-6.90 (m, 5H), 5.68 (ddt, J_1=6.5, J_2=17.9, J_3=10.6 Hz, 1H), 5.04-4.84 (m, 5H), 3.73 (dt, J_1=5.3, J_2=3.3 Hz, 1H), 3.66-3.60 (m, 2H), 3.60-3.50 (m, 2H), 2.12-2.05 (m, 2H), 0.80 (s, 9H), -0.08 (s, 6H).
20. Data for *anti*-**9**: oil; $[\alpha]_D^{20}$ = -2.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, toluene-d_8, δ): 7.15-6.90 (m, 10H), 5.66 (ddt, J_1=6.9, J_2=17.2, J_3=10.3 Hz, 1H), 4.95 (s, 2H), 4.93-4.85 (m, 4H), 4.39 (s, 2H), 4.32 (s, 2H), 3.67-3.46 (m, 4H), 2.12-2.04 (m, 2H).
21. Data for *syn*-**10**: oil; $[\alpha]_D^{20}$= +13.9 (*c*, 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, toluene-d_8, δ): 7.19-6.89 (m, 10H), 5.81-5.67 (m, 1H), 4.98 (s, 1H), 4.97 (s, 1H), 4.90 (m, 1H), 4.86 (s, 1H), 4.56 (d, J=15.6 Hz,1H), 4.48 (d, J=15.6 Hz, 1H), 3.89-3.75 (m, 3H), 3.73-3.62 (m, 2H), 2.11-2.03 (m, 2H), 0.81 (s, 9H), -0.10 (s, 6H).
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24. Data for *anti*-**13**: oil; $[\alpha]_D^{20}$ = -10.1 (*c*, 1.8, $CHCl_3$); ^{1}H NMR (500 MHz, toluene-d_8, δ): 7.25-7.00 (m, 15H), 5.58 (ddt, J_1=7.0, J_2=17.2, J_3=10.3 Hz, 1H), 5.06 (s, 2H), 4.92-4.88 (m, 2H), 4.87 (m, 1H), 4.69 (d, J=15.4 Hz, 1H), 4.51 (dd, J_1=19.8, J_2=6.3 Hz, 2H), 4.42 (d, J=4.5 Hz, 2H), 4.38 (d, J=5.1 Hz, 1H), 4.06 (m, 1H), 3.97 (dd, J_1=10.3, J_2=4.0 Hz, 1H), 3.89 (m, 1H), 3.76-3.65 (m, 1H), 2.14 (m, 2H).