

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

Janusz Jurczak^{a,b,*} and Piotr Prokopowicz^a

^aInstitute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw

^bDepartment of Chemistry, Warsaw University, 02-093 Warsaw, Poland

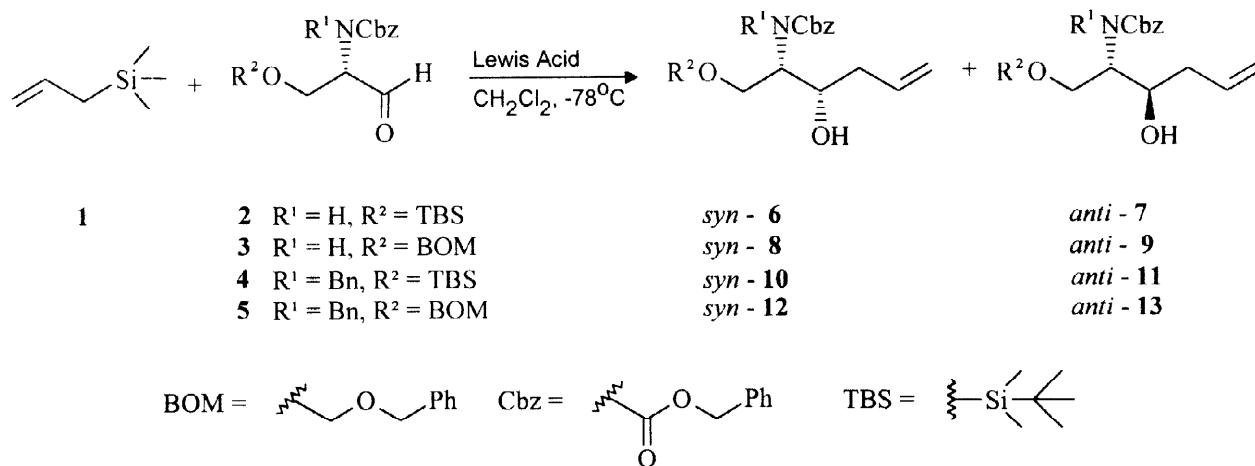
Received 3 September 1998; accepted 19 October 1998

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. © 1998 Published by Elsevier Science Ltd. All rights reserved.

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 reported¹² 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



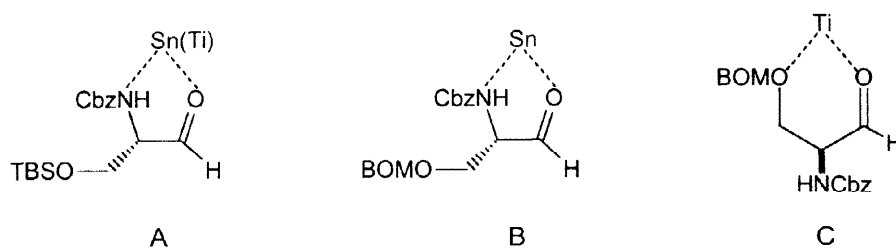
Scheme 1

Table 1. Results of reactions of **1** with **2-5**, carried out in the presence of one equivalent of Lewis acid in CH₂Cl₂ at -78°C

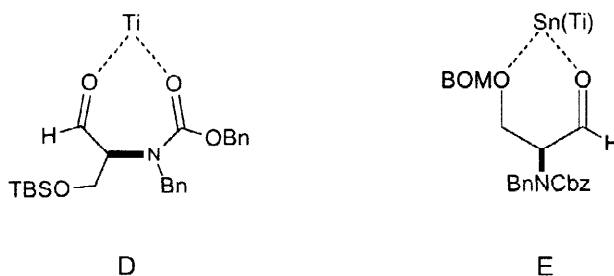
| Entry | Aldehyde | Lewis Acid | Time [h] | Yield [%] | Diastereoisomer Ratio [<i>syn</i> : <i>anti</i>] |
|-------|----------|-------------------|----------|-----------|--|
| 1 | 2 | SnCl ₄ | 1.0 | 88 | 98:2 |
| 2 | 2 | TiCl ₄ | 20.0 | 83 | 70:30 |
| 3 | 3 | SnCl ₄ | 1.5 | 68 | 82:18 |
| 4 | 3 | TiCl 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 SnCl₄ and TiCl₄ (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 SnCl₄ (entry 3). The adduct *anti*-**9**²⁰ was the major product of the reaction of silane **1** with aldehyde **3**, catalyzed by TiCl₄ (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 TiCl₄, 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 SnCl₄ and TiCl₄ (entries 7 and 8, respectively).



Scheme 2. Preferred complexes of **2** with SnCl₄ or TiCl₄ (A), of **3** with SnCl₄ (B) and TiCl₄ (C)



Scheme 3. Preferred complexes of **4** with TiCl₄ (D) and of **5** with SnCl₄ or TiCl₄ (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.

Acknowledgement: This work was supported by the Polish Academy of Sciences and by the University of Warsaw (BST-562/18/97)

REFERENCES AND NOTES

1. G. M. Coppola, H. H. Schuster, *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*, Wiley, New York, **1987**.
2. J. Jurczak, A. Gołębowski, *Chem. Rev.* **1989**, *89*, 149.
3. M. T. Reetz, *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.
4. I. F. Pelyves, C. Monneret, P. Herczegh, *Synthetic Aspects of Aminodeoxy Sugars of Antibiotics*, Springer, Heidelberg, **1988**.
5. J. Jurczak, A. Gołębowski in *Studies in Natural Products Chemistry, Vol. 4* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1989**, 111.
6. A. Gołębowski, J. Jurczak, in *Recent Progress in the Chemical Synthesis of Antibiotics* (Eds.: G. Lukacs, M. Ohno), Springer, Heidelberg, **1990**, 365.

7. A. Dondoni in *Modern Synthetic Methods* (Ed.: R. Scheffold), Verlag Helvetica Chimica Acta, Basel, **1992**, 377.
8. J. Jurczak, A. Gołębowski in *Antibiotics and Antiviral Compounds. Chemical Synthesis and Modification* (Eds.: K. Krohn, H. Kirst, H. Maag), VCH, Weinheim, **1993**, 343.
9. K. Kiciak, U. Jacobsson, A. Gołębowski, J. Jurczak, *Polish J. Chem.* **1994**, *68*, 199.
10. A. Gołębowski, J. Jurczak, *Synlett* **1993**, 241.
11. J. Jurczak, in *Preparative Carbohydrate Chemistry* (Ed.: S. Hanessian), Dekker, New York, **1997**, 593.
12. J. Jurczak, P. Prokopowicz, A. Gołębowski, *Tetrahedron Lett.* **1993**, *34*, 7107.
13. J. V. N. Vara Prasad, D. H. Rich, *Tetrahedron Lett.* **1990**, *31*, 1803.
14. S. Kiyooka, M. Nakano, F. Shiota, R. Fujiyama, *J. Org. Chem.* **1989**, *54*, 5409.
15. S. Kiyooka, Y. Shiomi, H. Kira, Y. Kaneko, S. Tanimori, *J. Org. Chem.* **1994**, *59*, 1958.
16. J. B. Springer, B. DeBoard, R. C. Corcoran, *Tetrahedron Lett.* **1995**, *36*, 8733.
17. HPLC experiments were performed using a Lichrospher 100-NH₂ 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, CHCl₃); ¹H NMR (400 MHz, toluene-d₈, δ): 7.17-6.90 (m, 5H), 5.68 (ddt, J₁=6.5, J₂=17.9, J₃=10.6 Hz, 1H), 5.04-4.84 (m, 5H), 3.73 (dt, J₁=5.3, J₂=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, CHCl₃); ¹H NMR (400 MHz, toluene-d₈, δ): 7.15-6.90 (m, 10H), 5.66 (ddt, J₁=6.9, J₂=17.2, J₃=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, CHCl₃); ¹H NMR (400 MHz, toluene-d₈, 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).
22. P. Garner, S. Ramakanth, *J. Org. Chem.* **1986**, *51*, 2609.
23. T. Kunz, A. Janowitz, H. Reissig, *Chem. Ber.* **1989**, *122*, 2165.
24. Data for *anti*-**13**: oil; $[\alpha]_D^{20} = -10.1$ (*c* 1.8, CHCl₃); ¹H NMR (500 MHz, toluene-d₈, δ): 7.25-7.00 (m, 15H), 5.58 (ddt, J₁=7.0, J₂=17.2, J₃=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, J₁=19.8, J₂=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, J₁=10.3, J₂=4.0 Hz, 1H), 3.89 (m, 1H), 3.76-3.65 (m, 1H), 2.14 (m, 2H).