A Novel BF_3·OEt_2-Catalyzed [3 + 2] Annulation of *N*-Cbz-α-Amino Aldehydes with Allyltrimethylsilane. Highly Stereoselective Synthesis of Cis-2,3,5-Trisubstituted Pyrrolidines

Syun-ichi Kiyooka,* Yasuhiro Shiomi, Haruhide Kira, Yuichi Kaneko, and Shinji Tanimori[1]

Department of Chemistry, Kochi University, Akebono-cho, Kochi 780, Japan

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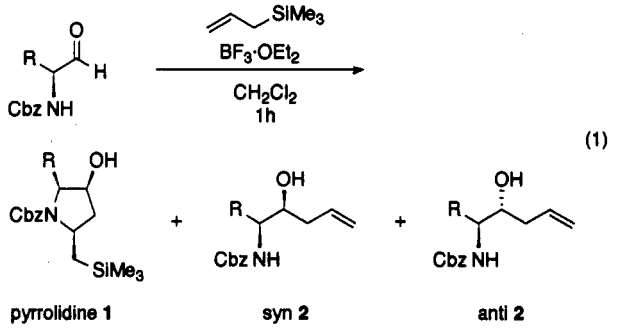
Summary: In the presence of BF_3·OEt_2 (0.2 molar equiv), the reactions (−10 °C, CH_2Cl_2) of *N*-Cbz-α-amino aldehydes with allyltrimethylsilane produced pyrrolidines in good yields (70–80%), with high all-cis stereoselectivity at the C-2, C-3, and C-5 positions, along with small amounts of the expected homoallylic alcohols.

The Sakurai–Hosomi reaction of allylsilanes[2] with carbonyl compounds in the presence of a Lewis acid to produce homoallylic alcohols has found extensive application in organic synthesis.[3] The reaction has been used for allylsilane- and allylstannane-based bond construction methodology, and its stereochemical outcome has occasionally been explained by considering Lewis acid–carbonyl complexation.[4] This type of complexation mainly occurs through two discrete pathways, chelation and non-chelation controlled, depending on the nature of the Lewis acid and on the steric and electronic requirements of the carbonyl ligand.[5,6]

Recently, as part of a stereoselective synthesis of hydroxyethylene dipeptide isosters, Taddei[7] reported that a high level of diastereoselectivity was surprisingly achieved in the BF_3·OEt_2-mediated reactions of *N*-Boc-α-amino aldehydes with 2-(chloromethyl)-3-(trimethylsilyl)-1-propene to yield the corresponding syn "chelation-type" products as single isomers. The rationalization of the stereochemical outcome with a Felkin–Anh model, however, appeared to be inadequate to explain the syn selectivity observed in the reaction. Questions about the role of BF_3·OEt_2, which is incapable of chelation, in the Lewis acid–carbonyl complexation prompted us to reinvestigate the related simpler reaction, that is, the BF_3·OEt_2-mediated reaction of *N*-protected α-amino aldehydes with allyltrimethylsilane.[8] We found a novel [3 + 2] annulation reaction catalyzed by BF_3·OEt_2 to afford pyrrolidines.

Under the usual conditions (−78 °C, 1 h), the reaction of *N*-Cbz-alaninal with allyltrimethylsilane in the presence of BF_3·OEt_2 (1.1 equiv) in CH_2Cl_2 produced the corresponding homoallylic alcohol with moderate syn diastereoselectivity along with the cyclic compound of interest (eq 1), whereas the reaction with $TiCl_4$ resulted in the



(1)

formation of only the homoallylic alcohol. The cyclic compound isolated from the reaction was determined to be one cis-2,3,5-trisubstituted pyrrolidine.[9] The relative stereochemistry at the C-2 and C-5 positions of the pyrrolidine corresponds to syn in the homoallylic alcohol. This result suggests that a "chelation-controlled" C–C bond formation took place with BF_3·OEt_2, which is normally thought of as a monodentate Lewis acid.

The yield of the pyrrolidine was considerably improved when a catalytic amount of BF_3·OEt_2 (0.2 molar equiv) was used at −10 °C.[10] The results of this novel pyrrolidine synthesis are summarized in Table 1. The catalytic reactions produced the corresponding *cis*-2,3,5-pyrrolidines in good yields, and the corresponding homoallylic alcohols were also produced in small amounts (less than 6%) with syn preference (entries 1, 5, 6, and 7).

In the synthesis of Prelog–Djerassi lactonic acid, the formation of a "chelation-controlled" product from the

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(9) All new compounds exhibited acceptable ^1H NMR, ^{13}C NMR, and IR spectra (supplementary material).

(10) **General Procedure.** To a stirred solution of *N*-Cbz-α-amino aldehyde (1 mmol) in 5 mL of dry CH_2Cl_2 at −10 °C was added BF_3·OEt_2 (0.2 mmol). Allyltrimethylsilane (1.1 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise over a period of 5 min, and the mixture was stirred for 1 h at −10 °C. The reaction mixture was quenched with a buffer (pH 6.86) solution (10 mL), extracted with Et_2O (20 mL × 3), and dried ($MgSO_4$). After evaporation of the solvent, the pure products were isolated by flash column chromatography [SiO_2, AcOEt/*n*-hexane (1:4 v/v)].

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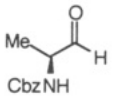
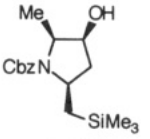
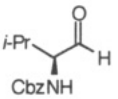
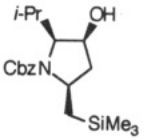
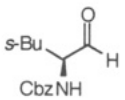
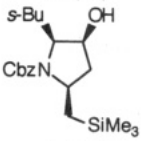
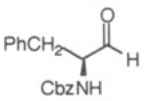
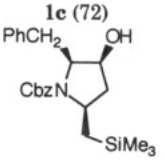
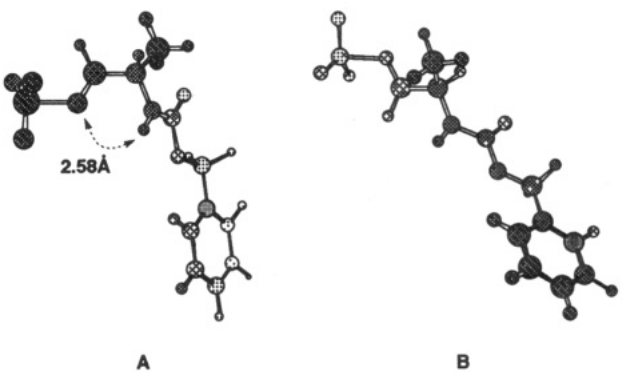
Table 1. Pyrrolidine Synthesis in the BF_3·OEt_2-Catalyzed Reactions of *N*-Cbz-α-amino Aldehydes with Allyltrimethylsilane

entry	α-amino aldehyde[a]	reaction condns LA, *T* (°C)	reaction products (% yield)[c] pyrrolidine[d]	homoallylic alcohol (ratio syn/anti)[e]
1		BF_3·OEt_2 (0.2 equiv), −10		
			1a (75)	**2a** (6) (1.2/1)
2		BF_3·OEt_2 (1.1 equiv), −10	**1a** (50)	**2a** (23) (3.5/1)
3		BF_3·OEt_2 (1.1 equiv), −78	**1a** (19)	**2a** (11) (4.3/1)
4		$TiCl_4$ (1.1 equiv), −10	–	**2a** (64) (2.2/1)
5		BF_3·OEt_2 (0.2 equiv), −10		
			1b (70)	**2b** (3) (1.6/1)
6		BF_3·OEt_2 (0.2 equiv), −10		
			1c (72)	**2c** (4) (1.5/1)
7		BF_3·OEt_2 (0.2 equiv), −10		
			1d (76)	**2d** (2) (1.2/1)

[a] *N*-Cbz-α-amino aldehydes were prepared by DIBAL reduction of the corresponding carboxylic esters. [b] All reactions with 1.1 equiv of allyltrimethylsilane were carried out in CH_2Cl_2 (0.2 M) for 1 h at the indicated temperature under Ar (see ref 9). [c] All yields are based on pure materials isolated by silica gel chromatography. [d] The stereochemistry is assigned on the basis of spectral data (see supplementary material). [e] Ratios of syn/anti isomers were determined by HPLC and capillary GLC.

BF_3·OEt_2-mediated reaction of *meso*-dimethylglutaric hemialdehyde and crotylstannane has been explained by postulating an 8-membered cyclic transition state involving the Lewis acid.[11] However, Yamamoto[12] recently concluded that the hemialdehyde takes a rigid cyclic conformation in solution without any assistance from chelating reagents. Therefore, an explanation of the "chelation-controlled" selectivity in BF_3·OEt_2-mediated reactions should consider the inherent conformational characteristics of the substrate aldehydes. An α-chelation-controlled process observed during the [4 + 2] cycloaddition of *N*-monoprotected α-amino aldehydes was suggested to result from the formation of a hydrogen bond between the NH proton and the carbonyl group.[13] Our AM1 calculations[14,15] of the BF_3–*N*-Cbz-alaninal complex suggest that conformation **A** is 0.32 Kcal mol^{-1} more stable than conformation **B**, as illustrated in Scheme 1. Thus, it is possible that the syn selectivity results from a transition state that arises from a conformation like **A**.

Scheme 1



On the basis of the conformational features of the BF_3–*N*-Cbz-α-amino aldehyde complex, *si* face addition of allyltrimethylsilane to the *N*-Cbz-α-amino aldehyde leading to syn selectivity at the C-2 and C-5 positions of the pyrrolidine can proceed via a synclinal or an antiperiplanar transition state[16] to a nonclassical pentavalent silicon cation (Scheme 2).[17] A subsequent highly stereoselective cyclization involving the nitrogen lone pair and the silicon

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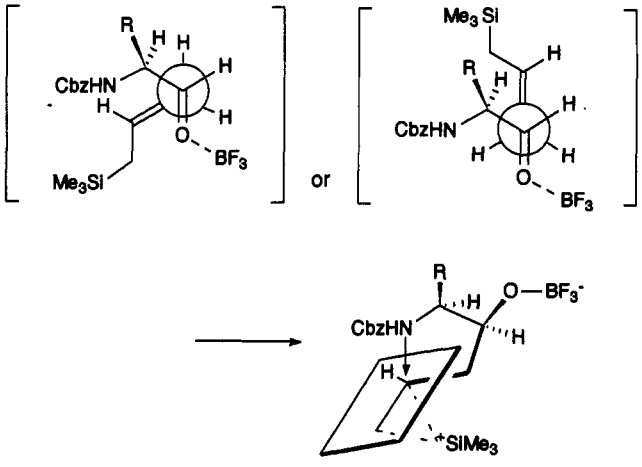
Scheme 2



cation occurs and minimizes the destabilizing steric interactions between the silicon moiety and the *N*-(carbobenzyloxy) group. The minor reaction intermediate produced via *re* face addition may lead to the corresponding anti homoallylic alcohol, which does not cyclize to the pyrrolidine because of steric hindrance.

In conclusion, the *si* face selection with BF_3·OEt_2 may result from the inherent conformational arrangement of the aldehyde–BF_3 complex and lead to the "chelation-controlled" stereochemistry. The cyclization of the resulting silicon cationic intermediate exclusively and stereoselectively yields the pyrrolidine derivatives. A further mechanistic study on the one-pot cyclization using the BF_3·OEt_2–allyltrimethylsilane system and its application to synthesis of pyrrolidine natural products is underway in our laboratory.

Supplementary Material Available: Spectroscopic data for the pyrrolidine derivatives and AM1 calculation data (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; ordering information is given on any current masthead page.