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Highly 2,3-*trans* Stereoselective Allylations of 2,3-*O*-Isopropylidene-Protected Pyrrolidines: Circumventing the *N*-Acyliminium Ion Chemistry?

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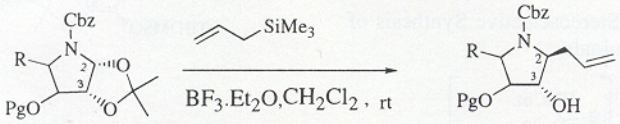
ABSTRACT



A remarkable *exo*-facial template effect exercised by a 2,3-*O*-isopropylidene protective group is the key for the entire 2,3-*trans* stereoselectivity observed in the allylsilane addition promoted by $BF_3 \cdot OEt_2$ to 2,3-*O*-isopropylidene-protected pyrrolidines.

The diastereoselective construction of 2,5 disubstituted pyrrolidines remains a topic of intense synthetic interest.[1] This may be attributed to their ubiquity in biologically interesting natural and nonnatural products.[2] Nucleophilic addition to *N*-acyliminium ions[3] constitutes one of the most important methods for the synthesis of these pyrrolidinic alkaloids. However, the diastereoselection levels are generally moderate,[4,5] with the stereochemical outcome of the nucleophilic attack[6] controlled by a balance of steric and stereoelectronic effects exercised by the asymmetric centers at C-5,C-3 and the functional group located at the nitrogen atom (Figure 1).

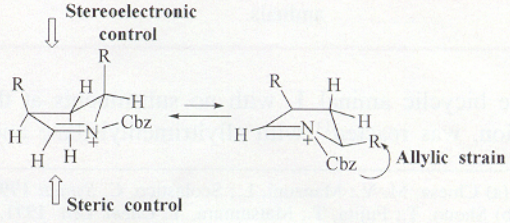


Figure 1. Postulated model used to explain the nucleophilic attack on the *N*-acyliminium ion.

In our practical total synthesis of (+)-preusine,[7] we installed the (*R*)-C-5 nonyl chain with a high degree of

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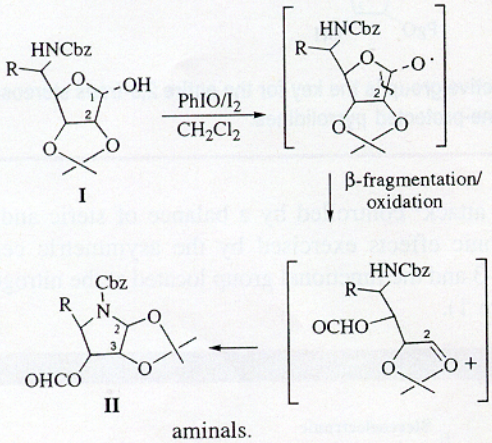
diastereoselection, by addition of allyltrimethylsilane to a pyrrolidinic bicyclic aminal activated by $BF_3{\cdot}OEt_2$. We thought that the high diastereoselectivity obtained in this addition was due to the bicyclic nature of this aminal favoring the *exo* attack. Encouraged by this result, we undertook a program to study the template effect that the bicyclic acetal can exert in the derivatives of 1,2-*O*-isopropylidene-protected furanosides on the diastereoselection levels in the formation of C-furanosides by addition of a π-nucleophile promoted by Lewis acid. We found[8] that the addition was uniformly diastereoselective, providing only the 1,2-*trans* compound and was independent of the nature of the bicyclic molecule.

Because of the importance of enantiomerically pure α-substituted cyclic amines and the difficulty in predicting the stereochemical course of the nucleophilic addition to *N*-acyliminium ion, we decided to explore whether the same template effect could be operative in the allylsilane addition to bicyclic aminals.

To this end we synthesized different 1,2-*O*-isopropylidene-protected pyrrolidinic bicyclic aminals, which are obtained in enantiomerically pure form and in high yield through the Suárez protocol.[6,9] This protocol entails (1) formation of the anomeric alkoxy radical by exposure of the lactol **I** to PhIO/I_2 in wet CH_2Cl_2, (2) β-fragmentation of this alkoxy radical to produce the C-2 radical which is oxidized[10] to an oxonium ion intermediate, and (3) intramolecular trapping of this oxonium ion by the carbamate group to give the bicyclic aminal **II** (Scheme 1).

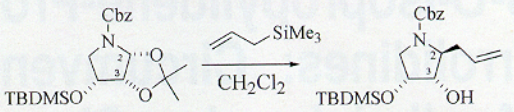
Scheme 1. Facile Route to the Stereoselective Synthesis of Bicyclic Aminals



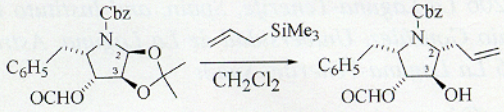
aminals.

The bicyclic aminal **1**, with no substituents at the C-5 position, was reacted[11] with allyltrimethylsilane and $BF_3{\cdot}OEt_2$ in anhydrous CH_2Cl_2 at −78 °C to room temperature, to give the 1,2 *trans* diastereomer **2** in moderated yield (52%) as the only compound isolated (Scheme 2).[12] Other Lewis acids screened [$MgBr_2$, $SnCl_2$, $(^iPrO)_2TiCl_2$, $Yb(OTf)_3$] were inactive under these conditions, and only starting material was recovered. The high diastereoselectivity obtained is in sharp contrast with those reported[4f] for the allylsilane addition to monosubstituted C-3 *N*-acyliminium ions. To evaluate the effect of the C-5 substituents on the diastereoselectivity, we carried out the allylation reaction with the aminals **3** and **5** (Scheme 2). We found that in both cases only the 1,2 *trans*

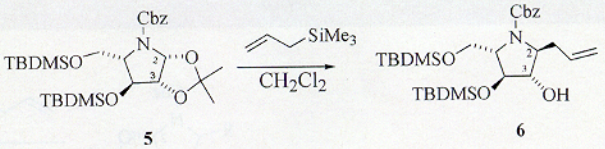
Scheme 2. Diasteroselective Allylsilane Addition to 2,3-*O*-Isopropylidene-Protected Pyrrolidines



	α/β	yield
$BF_3.Et_2O$	0/100	52%
$BF_3.Et_2O$/TMSOTf	36/64	47%



	α/β	yield
$BF_3.Et_2O$	100/0	62%
$BF_3.Et_2O$/TMSOTf	70/30	92%



	α/β	yield
$BF_3.Et_2O$	0/100	60%

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(6) For a deep study on the stereolectronic effects in the reactions with the five-membered-ring oxocarbenium ions analogue, see: Larsen, C. H.; Ridway, B. H.; Shaw, J. T.; Woarpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209.

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(10) For a mechanistic discussion, see: Armas, P.; García-Tellado, F.; Marrero-Tellado, J. J.; Robles, J. *Tetrahedron Lett.* **1997**, *38*, 8081−8084.

addition compound was isolated. The allylation of the aminal **5** to give **6** is illustrative: The 2,5 *trans* selectivity obtained is in sharp contrast with the *cis*-preference reported for C-5 *N*-acyliminium ions.[4a,b] The results obtained with aminals **3** and **5** prove that the C-5 substituents have no influence on the stereochemical outcome. Similar to that for the furanic bicyclic acetals,[7] the C-4 substituents behave like a mere spectator in contrast to the reported[13] influence on the diastereoselectivity of a silyloxy substituent at C-4.

The above results make it clear that the allylsilane always adds from the *exo*-face of the bicyclic aminal and the stereoselectivity of the reaction does not depend on the configuration of the substituents on the ring.

The combination of trimethylsilyl triflate and boron trifluoride etherate as the Lewis acid deserves a separate comment. The stronger Lewis acid character decreased the stereoselectivity by about 30%. If the starting bicyclic aminal is cleaved in the medium before the nucleophilic attack, no template effect can be exercised and the stereochemical outcome is controlled by stereoelectronic or steric factors on the more favorable *N*-acyliminium ion conformation. We believe this is the case, the stereoselectivity level being in good accordance with the low stereoselectivities observed by some C-3,C-5 disubstituted *N*-acyliminium ions.[4e,h]

In summary, we have shown that the template effect of the 2,3-*O*-isopropylidene protective group used to activate the C-2 position of pyrrolidines directs the stereochemical outcome of the addition reaction on this center, and this effect is general. From a synthetic point of view, the easy access to these 2,3-*O*-isopropylidene-protected pyrrolidines and the intrinsic and complete 1,2 *trans* stereoselectivity of the reaction make this strategy a very interesting and solid alternative to the established synthetic methods for the synthesis of C-2,C-5 disubstituted pyrrolidines.

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Supporting Information Available: Experimental procedure and analytical and spectroscopic data for compound **2**, **4**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **Experimental procedure for the synthesis of 2:** To solution of **1** (100 mg, 0.23 mmol) was added allyltrimethylsilane (0.14 mL, 0.92 mmol) in CH_2Cl_2 (3 mL) in a dry flask nitrogen atmosphere. The mixture was cooled to −78 °C, and $BF_3{\cdot}Et_2O$ (0.06 mL, 0.47 mmol) was slowly added. After 5 min, the cooling bath was removed, and the mixture was stirred for 50 min. The organic phase was washed once with water and dried over $MgSO_4$. Concentration and purification by flash chromatography (EtOAc/*n*-hexane 15/85) gave **2** (52 mg, 52% yield) as a colorles oil. Selected physical data for **2** (acetate): $[\alpha]^{25}_D = +15°$ (c = 0.3 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.0 (s, 3H; *Me*Si), 0.05 (s, 3H; *Me*Si), 0.93 (s, 9H; t-*Bu*Si), 1.8 (s, 3H; AcO), 2.66 (m, 2H; CH_2−CH=CH_2), 3.4 (dd, J = 11 and 5.5 Hz, 2H; H-5), 4.02 (app q, J = 5.5 Hz; C4−H), 4.09 (app dd, J = 5 and 4.5 Hz, 1H; C-2), 5.1−5.01 (m, 3H; CH_2=CH−, H-3), 5.18 (d, J = 12.5 Hz, 1H; CH_2Obn), 5.23 (d, J = 12.5, 1H; CH_2OBn), 5.8 (m, 1H; −*CH* = CH_2), 7.12 (t, J = 7.5 Hz, 1H; Ar), 7.18 (t, J = 7.5 Hz, 2H; Ar), 7.34 (d, J = 7.5 Hz, 2H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ = −5.5 × 2C, 17.7, 19.9, 25.2 × 3C, 34.0, 51.6, 58.1, 66.7, 70.1, 73.1, 116.0, 127.4, 127.9, 128.2, 135.2, 137.2, 154.5, 168.6; IR (chloroform) ν = 3026, 2956, 2360, 2341, 1741, 1695, 1418, 1357 cm^{-1}; HMRS calcd for $C_{20}H_{30}NO_5Si$ [(M^+ − CH_2CH=CH_2)] 392.516, found 392.250. The configuration assigned at C-1 was unambiguously determined from ^{1}H−^{1}H decoupling experiments to show a ^3J(H-2, H-3) ≈ 0 Hz, confirming a 2,3-*trans* relationship[4f,i] and a NOESY experiment showed NOE's between H-3 and allylic protons and H-4 and between H-2 and H-5.

(12) After workup and percolation through a pad of silica gel, only one isomer was detected by ^{1}H NMR experiment. To obtain uniform 2,3 *trans* selectivity the $BF_3{\cdot}OEt_2$ needed to be used freshly distilled.

(13) Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1764−1769. We appreciate the suggestion of one of the reviewers for the following reference: Veerman, J. J. N.; Rutjes, F. P. J. T.; van Maarseveen, J. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 6079−6082.