Lewis Acid-Mediated Addition of Amino Acid-Substituted α-Allylsilanes to Aromatic Acetals

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Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

Unnatural amino acids extend the pharmacological formulator's toolkit. Strategies to prepare unnatural amino acid derivatives using *Lewis* acid-activated allylsilane reactions are few. In this regard, we examined the utility of allylsilanes bearing an amino acid substituent in the reaction. Diastereoselective addition of methyl 2-(*N*-PG-amino)-3-(trimethylsilyl)pent-4-enoate and methyl (*E*)-2-(*N*-PG-amino)-3-(trimethylsilyl)hex-4-enoate (PG = protecting group), **2** and **13**, respectively, to aromatic acetals in the presence of *Lewis* acids is described. Of those examined, $TiCl_4$ was found to be the most effective *Lewis* acid for promoting the addition. At least 1 equiv. of $TiCl_4$ was required to achieve high yields, whereas 2 equiv. of $BF_3 \cdot OEt_2$ were required for comparable outcomes. Excellent selectivity (> 99% *syn*/*anti*) and high yield (up to 89%) were obtained with halo-substituted aromatic acetals, while more electron-rich electrophiles led to both lower yields and diastereoselectivities.

Introduction. – Given their special place in biology [1], it is no surprise that all aspects of amino acid chemistry hold a strong interest for organic and biological chemists of all stripes [2]. While the readily available amino acids combine to make a fascinating myriad of key oligopeptides and proteins, there remains an enthusiasm to expand Nature's palette by the use of new compounds that mimic the behavior of amino acids and their derivatives while improving their stability against degradation [3], particularly from enzymes. In addition, medicinal chemists [4] remain curious about the ability to tune the biological behavior of proteinaceous materials by adding new side chains to amino acids [5]. As examples, strategic approaches to β-amino acids [6] and tetrapeptides [7] have been authoritatively reviewed by *Seebach et al.*

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[1]) It is a pleasure to celebrate the 75th birthday of Prof. *Dieter Seebach*. In addition to his prodigious contributions to the art of synthetic organic chemistry, *Seebach* is known for his ability to assimilate enormous amounts of literature and to codify the trends therein for the rest of us. A teacher leaves his legacy through his students and his writings, and, on that basis, *Seebach* has an enormously strong legacy. Prof. *Seebach* taught me many things about being a scientist, most important among them was to always put one's current work in the context of the field, to look for trends, and to follow up exceptions to the rule. I am grateful to have been a small part of the team: it had a profound and positive effect on my scientific career.

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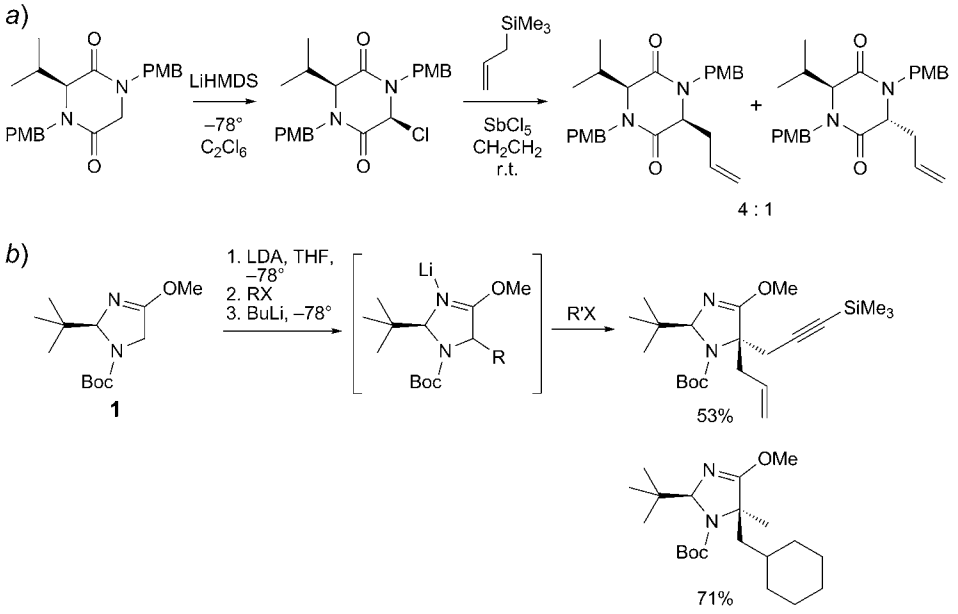
Many groups have endeavored to develop generic routes to amino acids. For example, diketopiperazines have proven to be fruitful substrates that can be used to generate new amino acids. Preparation from glycine and another amino acid allows the stereogenic center in one amino acid to induce stereoselective functionalization/alkylation of the glycine (*Scheme 1,a*) [8]. One disadvantage of this method is that two amino acids (and isomers in some cases) must be separated after workup.

Scheme 1. a) *Diketopiperazine and* b) *Chiral Glycine Strategies to Unnatural Amino Acids* (LiHMDS, Lithium hexamethyldisilazide; LDA, lithium diisopropylamide)



Seebach and *Hoffmann* had a different approach (*Scheme 1,b*) [9]. 'Chiral[3]) glycine' could be formed by excising the substituent of serine or other amino acids after formation of an oxazolidinone. A wide variety of elaboration strategies could then be exploited to make new amino acids [10]. An important lesson I learned at that time was to carefully balance elegance with practicality of a synthetic method. While compound **1** could be prepared in enantiomerically pure form by starting with serine – the elegant method – yields were modest. In this case, the practical route was a traditional, but less aesthetically appealing, resolution with chiral acids. I clearly recall the day that Prof. *Seebach* delightedly declared, '*now instead of 5 mg, we can have 5 kg of the compound!*'

We previously prepared interesting functional, unnatural amino acids using the *Ireland–Claisen* rearrangement, including **2** [11]. Allyl ethers with a terminal vinylsilane group could be transformed under anionic conditions in an *lk* [12] addition process to *syn-β*-silylamino acids with reasonable stereoselectivity (*Scheme 2*).

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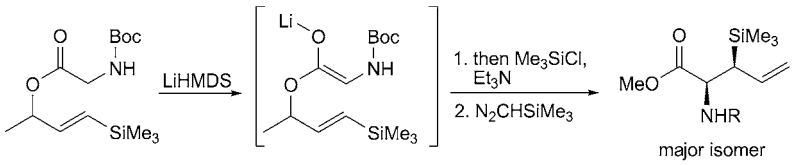
[3]) Throughout the manuscript, only one of the *rac*-structures is shown, *i.e.*, each structure represents an enantiomeric pair.

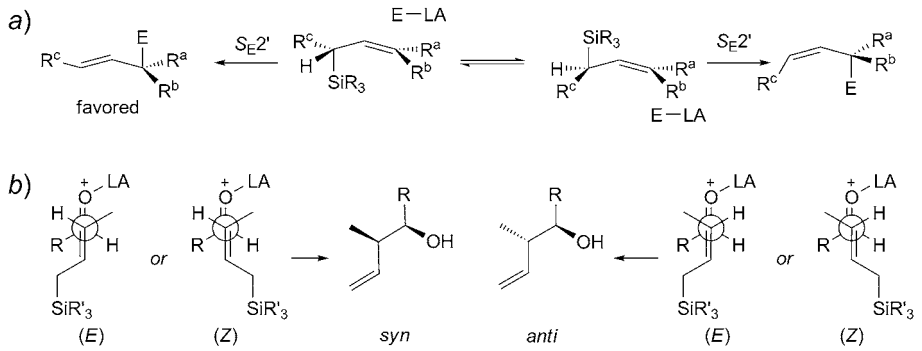
Scheme 2. *Stereocontrolled* Ireland–Claisen *Synthesis of Amino Acid-Modified Allylsilanes*



These compounds have the potential for further elaboration, particularly through the predictable reactivity of the allylsilane with a variety of electrophiles in the presence of *Lewis* acids [13]. Two control elements are important: the face with respect to Si from which the allylsilane attacks the electrophile, and the facial approach – *ul* or *lk* – when both allylsilane and electrophile are appropriately substituted.

Normally in acyclic systems, S_E2' attack of the electrophile occurs with respect to the silyl group. This allows development of the highly stabilizing β-silyl cation with very little molecular rearrangement required during/following bond-formation [14]. The reaction of α-substituted allylsilanes leads predominantly to products with (*E*)-C=C bond geometry (*Scheme 3*, *a*) unless the electrophile is particularly bulky, in which case the (*Z*)-alkene can result [15].

Scheme 3. S_E2' *Reaction of Allylsilanes* a) *Favoring (*E*)-Alkene Product and* b) syn-*Products Resulting from* ul *Addition*

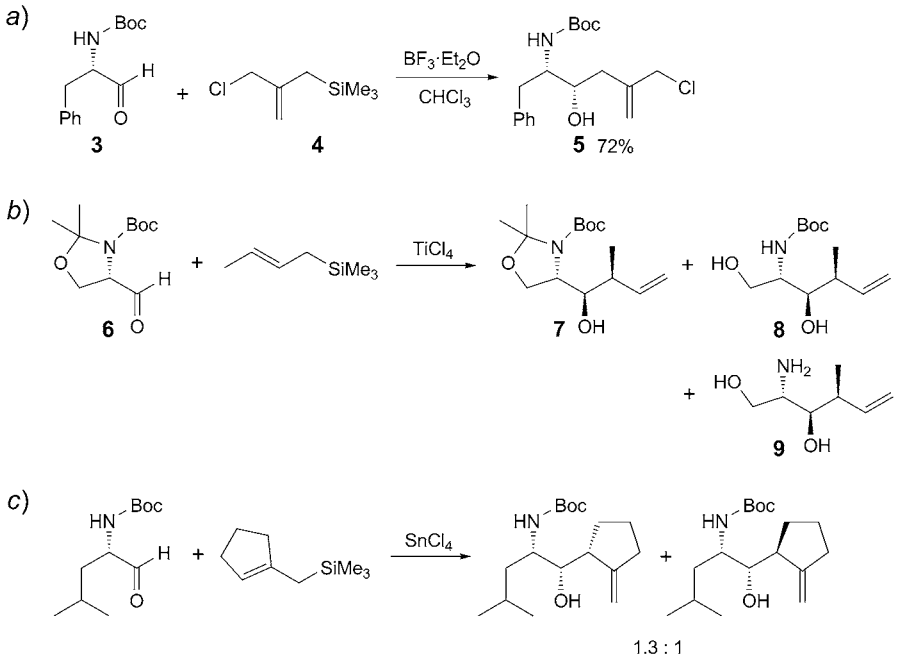


The second level of stereocontrol arises when both the γ-position of the allylsilane and the electrophile are appropriately substituted. Bimolecular processes often favor a *syn*-product irrespective of the geometry of the C=C bond (*Scheme 3*, *b*), although geometry of the C=C bond affects the degree of diastereoselectivity. The sizes of substituents and *Lewis* acid, and quantities of the acid used also alter the stereochemical outcome.

Several researchers have used allylsilanes to create compounds that at least are structurally related to amino acids, including from derivatives of α-amino aldehydes. For example, *Taddei* and co-workers reported that *N*-Boc amino aldehydes **3**, derived from naturally occurring α-amino acids, react with 2-(chloromethyl)-3-(trimethylsilyl)prop-1-ene (**4**) [16] in the presence of $BF_3 \cdot OEt_2$ to give amino alcohols **5**, resulting in key intermediates for the preparation of hydroxyethylene dipeptide isosteres: only

the *syn*-isomer was observed (*Scheme 4*,*a*). Analogous reactions between the crotylsilane and D-serine aldehydes **6** in the presence of $TiCl_4$ similarly gave *syn*-isomers at the new formed C–C bond in **7**, a process that was accompanied by ring-opening products **8** and **9** when higher levels of $TiCl_4$ were employed (*Scheme 4*,*b*) [17]. Cyclic (*E*)-crotylsilanes exhibited lower levels of stereoselectivity in analogous $SnCl_4$-catalyzed reactions (*Scheme 4*,*c*) [18].

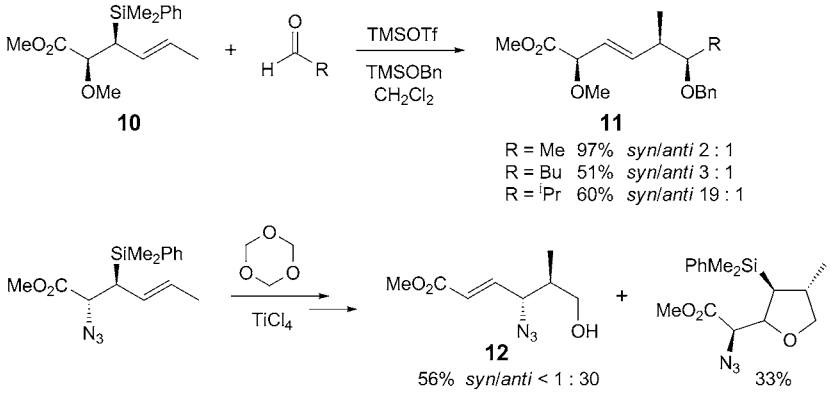
Scheme 4. *Reactions of Allylsilanes with Various α-Amino Aldehydes*



Far less is known about the behavior of systems in which the amino acid or its surrogate is found tethered to the silyl nucleophile. *Panek et al.* have made seminal contributions in this area. The diastereoselective addition of optically active *β*-MeO-substituted crotylsilane **10** derivatives to aldehydes [19], catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf), efficiently led to *syn*-product **11** (*Scheme 5*) [20]. The diastereofacial selectivity increases as a function of the size of the alkyl R group [21]. Analogous reactions between allylsilanes bearing an N_3 substituent α to the silyl and C=O groups, and trioxane – as formaldehyde surrogate – led cleanly to S_E2' addition; a subsequent suprafacial 1,3-N_3 rearrangement gave compound **12** (*Scheme 5*) [22].

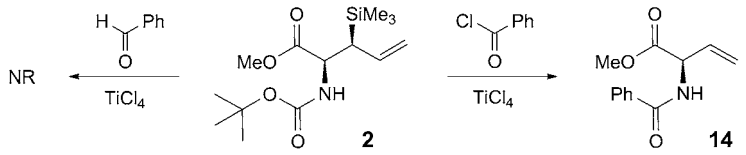
An interest in unnatural amino acids was engendered during my time in *Seebach*'s group. It was, therefore, a natural extension of our earlier work to examine the ability of allylsilane diastereoisomers **2** and **13** to add to carbonyl electrophiles. As described below, the level of diastereocontrol hinged on the electrophilicity of the C=O reaction partner, and the quantity and type of *Lewis* acid present.

Scheme 5. *Diastereoselective* S_E2' *Reactions of α-Functional Allylsilanes* (TMSOTf, Trimethylsilyl trifluoromethanesulfonate; Bn, benzyl)



Results. – The reactivity of **2** was tested against a series of electrophiles. Initially, **2** was reacted with PhCHO under a variety of reaction conditions including the use of a series of *Lewis* acids (*Scheme 6*). While formation of homoallylic alcohols with some level of diastereoselectivity was the expected outcome, the reaction was not successful: only starting material was recovered after 6 h at low temperature. Attempts to force the reaction by use of excess *Lewis* acid ($BF_3 \cdot OEt_2$, $TiCl_4$, or $SnCl_4$) and more elevated temperatures (0° – r.t.) led to the formation of complex mixtures of products.

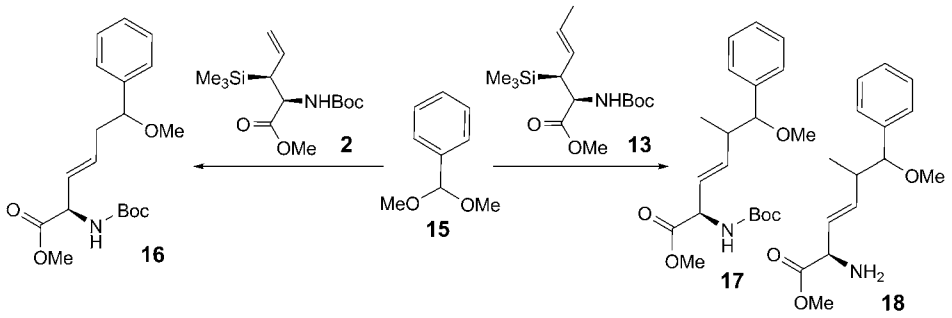
Scheme 6. Lewis *Acid-Mediated Addition of* **2** *to Two Normally Reactive Electrophiles* (NR, No reaction)



The use of a more reactive electrophile was also discouraging. Treatment of a mixture of allylsilane **2** and BzCl with 2 equiv. $TiCl_4$ led to no reaction at −78° over 3 h, and even after raising the temperature to 0° for several hours only an impractically low yield of uninteresting product **14** was observed (*Scheme 6*), which did not involve the desired C–C bond formation. This compound arose first from deprotection of the amine, then addition of the amine to BzCl, and was accompanied by protodesilylation, presumably during the reaction workup.

Acetals have previously been shown to be convenient alternatives to aldehydes in *Lewis* acid-catalyzed additions [23]. The initial reaction of **2** with benzaldehyde dimethyl acetal (**15**) was more promising than other electrophiles, leading to **16** in good yield (*Table 1*). Therefore, this reaction was used to optimize conditions. Early trials indicated that controlled reactions required adding and mixing the reagents at low temperature, and then allowing them to warm, typically to room temperature. Several *Lewis* acids at stoichiometries in the range of 0.5–4 equiv. were examined, including

Table 1. *Reaction of Allylsilane* **2** *or* **13** *with Benzaldehyde Dimethyl Acetal* (**15**)



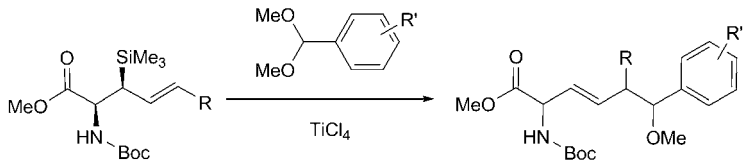
Entry	Allylsilane	*Lewis* acid (equiv.)	Time [h]	*T* [°]	Yield [%]	dr
1	**2**	$ZnCl_2$ (1)	10	– 78	0	
2	**2**	$BF_3 \cdot OEt_2$ (0.5)	15	– 78 → r.t.	0	
3	**2**	$BF_3 \cdot OEt_2$ (1)	10	– 78 → r.t.	20	
4	**2**	$BF_3 \cdot OEt_2$ (1.5)	7	– 78	40	
5	**2**	$BF_3 \cdot OEt_2$ (2)	10	– 78	66	
6	**2**	$TiCl_4$ (0.5)	24	– 78 → r.t.	0	
7	**2**	$TiCl_4$ (1.2)	24	– 78 → r.t.	51	
8	**2**	$TiCl_4$ (1.2)	7	– 78	70	
9	**2**	$TiCl_4$ (1.2)	15	– 78	78	
10	**2**	$TiCl_4$ (1)	24	– 78 → r.t.	48	
11	**2**	$TiCl_4$ (2)	0.16	– 78 → r.t.	25	
12	**2**	$TiCl_4$ (4)	24	– 78 → r.t.	30	
13	**13**	$BF_3 \cdot OEt_2$ (0.5)	12	– 78	0	
14	**13**	$BF_3 \cdot OEt_2$ (2.0)	10	– 78	70	5.8 : 1
15	**13**	$TiCl_4$ (0.2)			0	
16	**13**	$TiCl_4$ (0.5)	10	– 78	35	6.2 : 1
17	**13**	$TiCl_4$ (1.0)	6	– 78	60	6.2 : 1
18	**13**	$TiCl_4$ (1.2)	5	– 78 → r.t.	68	6.2 : 1
19	**13**	$TiCl_4$ (1.2)	24	– 78	80	6.2 : 1

$ZnCl_2$, $BF_3 \cdot OEt_2$ and $TiCl_4$: the efficacy of *Lewis* acid-catalyzed additions of silylated nucleophile often requires stoichiometric [24] or higher [25] concentrations of the 'catalyst'. Only the latter two, which are very commonly used [26], were effective: the highest yields required *ca.* 2 equiv. of the monodentate *Lewis* acid $BF_3 \cdot OEt_2$ or 1 equiv. of bidentate $TiCl_4$. Similar outcomes were observed with crotylsilanes **13** (→**17**), although marginally higher diastereoselectivities were observed, when $TiCl_4$ rather than $BF_3 \cdot OEt_2$ was used. As a consequence, the former *Lewis* acid was used to explore the addition of crotylsilanes ((but-2-en-1-yl)silanes) to other electrophiles.

A common by-product, when higher amounts of *Lewis* acid were involved, was deprotected amine **18** (*Table 1*): higher temperatures were also associated with enhanced deprotection. It was also discovered that Boc groups were somewhat more sensitive to deprotection than Cbz or Bz groups. Therefore, the reactions described below were quenched at – 78°, in which case amine deprotection did not arise.

The efficiency and diastereoselectivity of the reaction between **13** and acetals was affected by electronic demand provided by the aryl ring on the electrophile. For example, the *p*-anisaldehyde dimethyl acetal could not be induced to react with 1 (or more) equiv. of $TiCl_4$ (*Table 2*). By contrast, acetals of Br- and NO_2-substituted benzaldehyde reacted to give both higher yields and levels of diastereoselectivity than the parent compound **15**. At most, two diastereoisomers were formed, as shown by ^{1}H-NMR for **19**; HPLC was required for **20**–**22** that, in the latter case, showed a single diastereoisomer.

Table 2. *Diastereoselective Addition of Allylsilane to Acetals*[a])

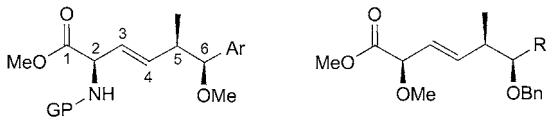


2/**13**

Allylsilane, R	Acetal, R′	Reaction time [h]	Product	Yield [%]	*syn*/*anti*
2, H	**15**, H	15	**16**	78	NA[b])
13, Me	4-MeO	24	–	0	
13, Me	**15**, H	24	**17**	58[c])	6 : 1
13, Me	4-NO_2	6	**20**	80	40 : 1
13, Me	4-Br	10	**21**	75	> 40 : 1
13, Me	2-Br	5	**22**	89	100 : 0

[a]) With 1 equiv. $TiCl_4$ at $-78°$. [b]) NA, Not available. [c]) In this case, higher yields were observed, when the amino group was protected with Bz instead of Boc (→ **19**; 77%); the *syn*/*anti* ratio of 6 : 1 was unchanged.

The conversion of crotylsilane **13** to products **19**–**22** involves the formation of a new C=C bond and two new stereogenic centers that form in a 1,2-relationship (C(5)–C(6), *Fig.*). Both the configuration of the newly formed C(3)=C(4) bond and the configuration of the emerging stereogenic centers should depend on the stereochemistry of the starting allylsilane **13**, which has an (*E*)-olefin moiety and a *syn*-relationship at C(2)–C(3). Regrettably, none of the products could be induced to form single crystals suitable for X-ray analysis. The following comments reflect our best ability to characterize the 3D structures of compounds **19**–**22**. In the ^{1}H-NMR, the C(3)=C(4) coupling constants exhibited were *ca.* 16.0 Hz, consistent with an (*E*)-C=C bond. Both diastereoisomers of product **19** could be characterized in the ^{1}H-NMR due to the stereogenic centers C(5) and C(6) (*Fig.*). Based on the data provided by *Panek* and *Yang* [21], who reported the ^{1}H-NMR spectra of a structurally analogous series of compounds including **23**, we assign the relative configuration of the major isomer at C(5)–C(6) to be *syn*. The similarity in ^{1}H-NMR spectra of **23** and **19**–**22** suggests that the relative configuration at these two centers is the same throughout the series. Similarly, but with less confidence, we tentatively assigned the relative configuration at the remote amine-bearing C-atom as shown in the *Figure*.

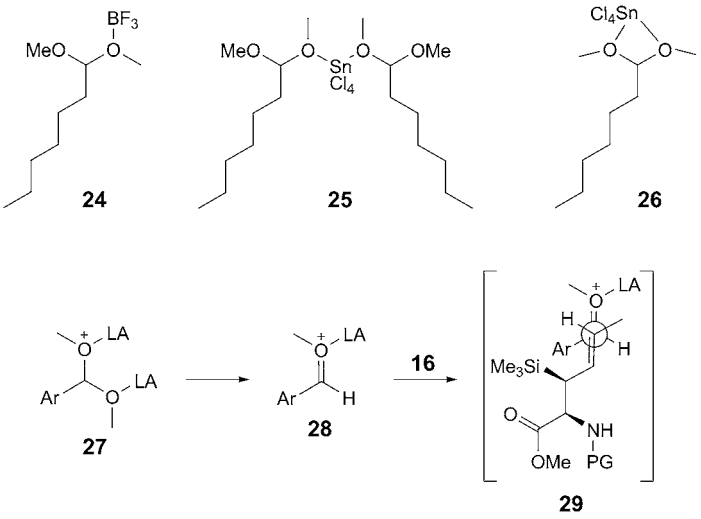


19 – 22 **23**

Figure. *Tentative assignment of the major products of* **19** – **22** *based on* **23** [21]

Discussion. – The optimal level of stereocontrol in the addition of **13** to acetals arose from the use of 2 equiv. of monodentate, or one of a bidentate *Lewis* acid, which must inform consideration of the mechanism of the process. There are a variety of internal *Lewis* bases that can compete for *Lewis* acids both on the acetal electrophile and the amino acid fragments adjacent to the allylsilane. However, the key interaction appears to be between the *Lewis* acid and the acetal O-atoms. Low-temperature ^{13}C-NMR studies by *Denmark* and *Willson* [23e] have established the formation of 1 : 1 *Lewis* acid–acetal complexes **24** using $BF_3 \cdot OEt_2$ as the *Lewis* acid, where only one MeO group complexes with $BF_3 \cdot OEt_2$. In the case of $SnCl_4$, two different complexes were reported depending on the amount of $SnCl_4$ used. One-half equiv. of $SnCl_4$ induced the formation of the 2 : 1 complex **25**, in which a single MeO group of each acetal is complexed to the Sn-atom. However, upon addition of 1 equiv. of $SnCl_4$, complex **26** was formed in which both MeO groups of the acetal are complexed (*Scheme 7*).

Scheme 7. Lewis *Acid Complexes to Acetals, Including* **13**

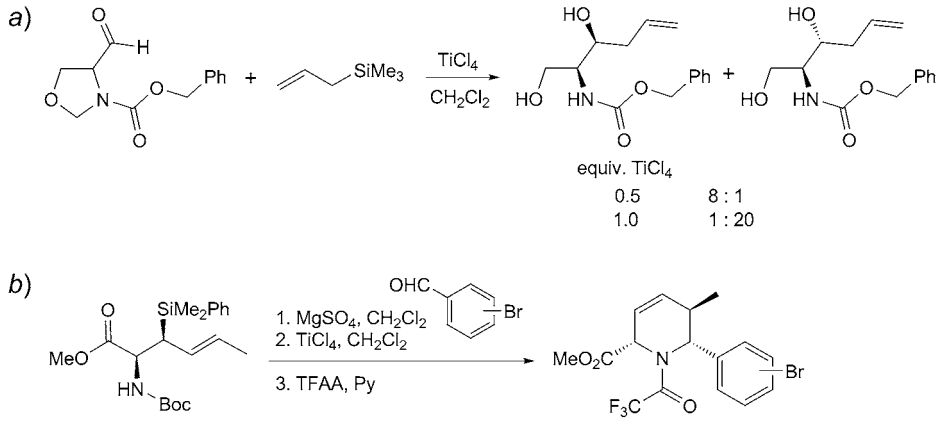


The requirement for 2 equiv. of a *Lewis* acid for optimal reaction in the case here is consistent with a process in which both acetal O-atoms of **27** are initially complexed by a *Lewis* acid leading to a carboxonium ion intermediate **28** after loss of one MeO group from the acetal (*Scheme 7*). This proposal matches that of *Hosomi et al.* who reported that allylsilanes underwent reactions with various acetals in the presence of $TiCl_4$ to

afford the corresponding homoallylic ethers [27]. The only exception to this rule was anisaldehyde that, with 1 or 2 equiv. of $TiCl_4$, did not react at all. Although complexation of the 4-methoxyaryl group with a *Lewis* acid could account for this change in reactivity, it may similarly be attributed to a reduction in electrophilicity of the acetal as a consequence of electronic donations from the methoxyaryl group. Support for the latter hypothesis comes from the observation that enhanced reactivity and diastereoselectivity accompanied the use of electron-deficient Br- and NO_2-substituted aryl acetals. It seems likely that a tighter transition state **29** resulting from a more electrophilic aryl group can account for the observed, enhanced diastereoselectivity.

The other alternative, in which intramolecular chelation between reaction partners controls C–C bond formation, does not seem to be operating. For example, *Kiyooka et al.* noticed a dramatic change in diastereoselectivity depending upon the quantity of $TiCl_4$ used during the addition of allyl(trimethyl)silane to chiral α-[(benzyloxy)carbonyl]amino aldehydes (*Scheme 8,a*) [24]. Rather than the redirection of the diastereoselectivity in this case, we found that additional *Lewis* acid led to little change in stereoselectivity, but was accompanied by additional degradative pathways, particularly amine deprotection.

Scheme 8. *Effects of Internal Chelation of the* Lewis *Acid* (TFAA, Trifluoroacetic anhydride)



The stereochemical outcomes of the reaction of the (*E*)-crotylsilanes with acetals [27] are generally ethers with (*E*)-*syn*-configuration: (*Z*)-crotylsilanes are less selective [28]. Thus, the outcomes described above are common for *Lewis* acid-activated reactions of allylsilanes, as noted above (*Schemes 3* and *5*). Unless very large substituents are found on the electrophile or other geometric constraints are provided – for example, an intramolecular cyclization that constrains product olefin geometry to (*Z*) (*Scheme 8,b*) [29] – (*E*)-alkenes are favored. Similarly, *ul* addition processes (*Scheme 7*) are normally favored (for reviews, see [30]) in such reactions to give *syn*-products at the newly formed bond.

What is unusual, perhaps, in this reaction is the absence of an impact of the amino acid residue on the outcome of the *Lewis* acid-promoted reaction. In spite of the

abundance of *Lewis* basic atoms in the amino acid residue, *anti*-silicon S_E2' processes drive the reaction. This bodes well for the utilization of this reaction, and that with related *Lewis*-activated electrophiles, to diastereoselectively generate unnatural amino acids to permit an exploration of their potential utility as bioactive molecules [5][31].

Conclusions. – Aromatic acetals react cleanly with amino acid-modified allylsilanes in the presence of 2 equiv. of $BF_3 \cdot OEt_2$ or one of $TiCl_4$. The good yield and diastereoselectivity in the formation of new unnatural amino acids with *syn*-relative configuration at the new formed C–C bond is attributed to an *ul* approach of the allylsilane and acetal that is made more efficient by the presence of electron-withdrawing groups on the aryl group, which increase the electrophilicity of the carboxonium intermediate. Thus, the anisaldehyde methyl acetal was unreactive, while benzaldehyde dimethyl acetal (**15**) showed modest diastereofacial selectivity and yield. By contrast, yields in excess of 75% and *syn*/*anti* selectivities were observed with acetals of bromo- and nitrobenzaldehyde.

We gratefully acknowledge the financial support of the *Natural Sciences and Engineering Research Council of Canada* for financial support of this work.

Experimental Part

General. All the syntheses were performed with dry glassware under dry N_2. The following reagents were purchased from *Aldrich: benzaldehyde dimethyl acetal* (**15**). Allylsilanes **2** and **13** were prepared as described in [11]; $ZnCl_2$ was flame-heated/dried, $BF_3 \cdot OEt_2$ and TiO_4 were distilled prior to use. Silica gel was purchased from *Silicycle.* CH_2Cl_2 was distilled from phosphorus pentoxide before use. GC: *Hewlett-Packard 5890A* gas chromatography equipped with a conventional heated injector, a flame ionization detector, a *Hewlett-Packard 3393A* integrator, and a *DB-1* megabore cap. column (30 m × 0.54 mm, *Chromatographic Specialities, Inc.*). IR Spectra: *Biorad* spectrometer; in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker AV-200*, *-300*, or *-500* MHz spectrometers in $CDCl_3$; δ in ppm rel to $CDCl_3$, J in Hz. Electron impact (EI) and chemical ionization (CI, NH_3) MS: at 70 eV with a source temp. of 200° on a *VG Instrument analytical ZAB-R* mass spectrometer equipped with a *VG 11–250* data system; *m*/*z* (rel.).

Representative Experimental Procedure for the $TiCl_4$-Promoted Reaction of Methyl 2-(PG-amino)-3-(trimethylsilyl)pent-4-enoate (PG = protecting group) **2** *with Aromatic Acetals.* In a round-bottomed flask, a mixture of **15** (0.2 g, 1.3 mmol) and **2** (0.39 g, 1.3 mmol) in freshly distilled CH_2Cl_2 (2 ml) soln. was cooled at −78°. The mixture was allowed to stir for 10 min before a soln. of *Lewis* acid (0.5–4 equiv.; *Table 1*, *e.g.*, $TiCl_4$ (1.2 equiv., 1.6 mmol)) was introduced through a syringe and a needle over 20 min. The mixture was optionally allowed to warm to r.t. overnight. After the reaction was judged by ^1H-NMR or TLC to be complete, the mixture was diluted with a sat. soln. of $NaHCO_3$ (5 ml) and extracted with AcOEt (2 × 5 ml). The combined org. layers were dried with ($MgSO_4$), filtered, and solvent was removed *in vacuo*. The product was purified by CC (silica gel; 25% AcOEt/pentane).

*Methyl (3*E*)-2-[(*tert*-Butoxycarbonyl)amino]-6-methoxy-6-phenylhex-3-enoate* (**16**). Purification of the crude product by CC (25% AcOEt/pentane) afforded (0.34 g, 1.0 mmol, 77%). IR (neat): 3363, 2979, 1749, 1495. ^1H-NMR (500 MHz): 7.36–7.25 (*m*, 5 H); 5.76 (*m*, 1 H); 5.46 (*dd*, *J* = 5.3, 15.2, 1 H); 5.09 (br. *d*, 1 H); 4.78 (br. *s*, 1 H); 4.17–4.13 (*m*, 1 H); 3.73 (*s*, 3 H); 3.22 (*s*, 3 H); 2.42–2.39 (*m*, 2 H); 1.46 (*s*, 9 H). ^{13}C-NMR (50.32 MHz): 171.49; 154.80; 130.30; 128.27; 127.59; 126.90; 126.76; 83.31; 79.90; 56.56; 55.21; 52.27; 40.71; 28.25. CI-MS (NH_3): 367 ($[M + NH_4]^+$), 350 ($[M + H]^+$), 311, 279, 250, 218, 121, 91, 57.

*Methyl (3*E*)-2-(Benzoylamino)-6-methoxy-5-methyl-6-phenylhex-3-enoate* (**19**). IR (neat): 3435, 2940, 1742, 1661, 1282, 909, 734. ^1H-NMR (300 MHz): 8.0 (*m*, 2 H); 7.40 (*m*, 3 H); 7.32 (*m*, 5 H); 5.68 (*dd*, *J* = 7.0, 15.1, 1 H); 5.40 (*dd*, *J* = 5.8, 15.2, 1 H); 5.19 (br. *m*, 1 H); 4.69 (br. *s*, 1 H); 3.92 (br. *d*, *J* = 6.8,

1 H); 3.74 (*s*, 3 H); 3.21 (*s*, 3 H); 2.59–2.55 (*m*, 1 H); 1.09 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR (50.32 MHz): 171.58; 166.98; 140.08; 136.76; 133.91; 128.70; 128.13; 127.66; 127.26; 124.25; 87.74; 57.14; 54.33; 52.77; 43.15; 15.81. CI-MS (NH_3): 368 ($[M+H]^+$, 5), 336 (22), 121 (100), 77 (5).

*Methyl (3*E*)-2-{[(*tert*-Butoxy)carbonyl]amino}-6-methoxy-5-methyl-6-(4-nitrophenyl)hex-3-enoate* (**20**). IR (KBr): 3383, 2935, 1715, 1524, 1348, 734. ^{1}H-NMR (300 MHz, major isomer): 8.15 (*d*, *J* = 8.7, 2 H); 7.35 (*d*, *J* = 8.7, 2 H); 5.61 (*ddd*, *J* = 1.1, 7.7, 15.5, 1 H); 5.41 (*dd*, *J* = 6.1, 15.5, 1 H); 5.07 (br. *d*, *J* = 16.2, 1 H); 4.69 (br. *d*, *J* = 6.2, 1 H); 4.04 (*d*, *J* = 6.3, 1 H); 3.64 (*s*, 3 H); 3.19 (*s*, 3 H); 2.55–2.45 (*m*, 1 H); 1.40 (*s*, 9 H); 0.99 (*d*, *J* = 6.78, 3 H). ^{13}C-NMR (50.32 MHz): 171.48; 154.82; 147.93; 147.49; 135.02; 128.32; 125.72; 123.31; 86.75; 80.17; 57.53; 55.25; 52.52; 43.13; 28.39; 15.57. HR-MS: 409.1975 ($C_{20}H_{28}N_2O_6^+$; calc. 409.1977). EI-MS: 409 (1), 353 (5), 293 (4), 249 (5), 166 (100), 57 (71), 41 (25).

*Methyl (3*E*)-6-(4-Bromophenyl)-2-[(*tert*-butoxycarbonyl)amino]-6-methoxy-5-methylhex-3-enoate* (**21**). IR (KBr): 3366, 2978, 1747. ^{1}H-NMR (300 MHz): 7.34 (*d*, *J* = 8.3, 2 H); 6.97 (*d*, *J* = 8.3, 2 H); 5.43 (*dd*, *J* = 15.5, 7.7, 1 H); 5.16 (*dd*, *J* = 15.4, 5.9, 1 H); 4.95 (br. *s*, 1 H); 4.60 (br. *s*, 1 H); 3.80 (*d*, *J* = 6.6, 1 H); 3.59 (*s*, 3 H); 3.09 (*s*, 3 H); 2.39 (*m*, 1 H); 1.40 (*s*, 9 H); 0.93 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR (75 MHz): 171.48; 154.79; 139.05; 135.63; 131.08; 129.17; 125.01; 121.24; 86.93; 79.95; 67.03; 57.00; 52.37; 42.95; 28.52; 15.56. HR-MS: 442.1229 ($C_{23}H_{29}BrNO_5^+$; calc 442.1234).

*Methyl (3*E*)-6-(2-Bromophenyl)-2-{[(*tert*-butoxy)carbonyl]amino}-6-methoxy-5-methylhex-3-enoate* (**22**). Purification of the crude product by CC (30% AcOEt/pentane) afforded (0.47 g, 1.1 mmol, 89%). IR (neat): 3367, 2979, 1718, 1501, 1166, 757, 733. ^{1}H-NMR (500 MHz): 7.40–7.12 (*m*, 4 H); 5.76 (*dd*, *J* = 7.8, 15.6, 1 H); 5.36 (*dd*, *J* = 5.7, 15.4, 1 H); 5.01 (br. *m*, 1 H); 4.72 (br. *m*, 1 H); 4.45 (*d*, *J* = 5.61, 1 H); 3.68 (*s*, 3 H); 3.17 (*s*, 3 H); 2.54–2.51 (*m*, 1 H); 1.42 (*s*, 9 H); 0.99 (*d*, *J* = 6.8, 3 H). ^{13}C-NMR (50.32 MHz): 171.79; 154.73; 139.68; 136.26; 132.72; 128.92; 128.63; 127.49; 124.73; 124.07; 85.29; 80.05; 57.45; 55.21; 52.53; 42.43; 28.43; 14.65. HR-MS: 382.1017 ($[M-CO_2Me]^+$, $C_{18}H_{25}BrNO_3^+$; calc. 382.1001). ESI-MS: 464 ($[M+Na]^+$), 482 ($[M+K]^+$).

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