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Niobium(V) chloride-mediated allylation of aldehydes. Scope and stereoselectivity

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Abstract—Niobium chloride promoted the addition of allylstannanes to aromatic and aliphatic aldehydes. Excellent *syn* diastereoselectivity was obtained in the addition of *E*-cinnamylstannane to benzaldehyde (49:1). In the addition of allylstannane to racemic 2-phenylpropionaldehyde, *syn* diastereoselection (Cram–*anti*-Cram=3:1) was observed. The same level of diastereoselection was achieved in the reaction between crotylstannane and benzaldehyde. © 2001 Elsevier Science Ltd. All rights reserved.

The Lewis acid-mediated addition of allylstannanes to carbonylic compounds has been extensively studied.¹ A variety of Lewis acids have been employed successfully in these reactions, including TiCl₄, BF₃·OEt₂, SnCl₄, AlCl₃, InCl₃, among others.

The homoallylic alcohols so obtained, are important and versatile intermediates in the synthesis of more complex products since the double bond can be further functionalized (Scheme 1).

Motivated by some recent work which demonstrated the Lewis acidity of niobium² and tantalum^{2c,d,f} compounds in organic reactions, we decided to investigate the use of NbCl₅ on the allylation of aldehydes. NbCl₅ has a great oxophylicity and is readily available in our country since Brazil accounts for about 60% of total niobium production.³



Scheme 1.

In order to investigate the feasibility of the reaction, various aldehydes were reacted with allyltri-*n*-butyl-stannane, in the presence of NbCl₅. In our search for the best experimental conditions the following parameters were evaluated: solvent, temperature, stoichiometric relationship and the order in which the reagents were added. The results are summarized in Table 1.

The best results were obtained when 2 equiv. of the allylstannane were used, at -15° C, in diethyl ether as the solvent (entries 6, 10 12, 14 and 16).⁴ NbCl₅ promoted the ring-opening of the THF, leading to polymeric products (entry 7). When the more coordinating solvents DME and CH₃CN were used the yields lowered (entries 9 and 13) or the reaction failed completely (entries 8, 11 and 15). When isobutyraldehyde was used yields were low (ca. 20–30%), probably due to the volatility of the product. In contrast, a much better yield was obtained when 2-phenylpropionaldehyde was employed (Table 2).

In a similar reaction, Suzuki et al.^{2b} reported the double addition and exclusive formation of a cyclopropane derivative when allylsilanes reacted with aldehydes, in the presence of NbCl₅ (Scheme 2). Such a compound was never observed in the reaction with allylstannane. These interesting results show the versatility of NbCl₅ as a Lewis acid.

After establishing the best experimental conditions, we turned our attention to the stereoselectivity of these reactions. The Cram–*anti*-Cram selectivity was addressed in the reaction between (\pm) -2-phenylpropionaldehyde and allylstannane in the presence of NbCl₅ (Table 2). The diastereofacial selectivity was low (3:1),

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Table 1. Experimental conditions and yields of the reactions between aldehydes and allyltri-n-butylstannane^a



Entry	R	Solvent	Temp. (°C)	Time (h)	Yield ^c (%)
1	Ph ^b	CH ₂ Cl ₂	- 78	2.5	41
2	Ph	CH ₂ Cl ₂	-78	1.5	38
3	Ph	CH ₂ Cl ₂	-15	1	45
4	Ph^{b}	Et ₂ O	- 78	2	48
5	Ph^{b}	Et ₂ O	-15	2	47
6	Ph	Et ₂ O	-15	0.5	100
7	Ph^{b}	THF	- 78	2.5	_
8	Ph^{b}	CH ₃ CN	-43	2	_
9	Ph	DME	-15	2	70
10	<i>p</i> -OMePh	Et ₂ O	-15	1.5	50
11	<i>p</i> -OMePh	DME	-15	2	_
12	p-NO ₂ Ph	Et ₂ O	-15	1.5	70
13	$p-NO_2Ph$	DME	-15	2	50
14	p-ClPh	Et ₂ O	-15	0.5	71
15	<i>p</i> -ClPh	DME	-15	2	_
16	2-Furyl	Et ₂ O	-15	0.5	50

m-border > -15ca = "D" > > 0.5ca = "D" > > 50

^a Unless otherwise noted 2 equiv. of allylstannane were employed.

^b Reaction with 1 equiv. of allylstannane in relation to the aldehyde.

^c Isolated yields of the chromatographically pure products.

Table 2. Results of the reaction between allylstannane and (\pm) -2-phenylpropionaldehyde in Et₂O

Ph H	NbCl ₅ , Et ₂ O	Ph OH OH syn (Cram) +	Ph OH OH anti (anti-Cram)
Entry	Temp. (°C)	Syn:anti	Yield (%) ^a
1 2	78 15	3:1 1.6:1	63 75

^a Isolated yields of the chromatographically pure products (*syn/anti* mixture).



Scheme 2.

even at -78° C. These results are similar to those obtained with other Lewis acids such as BF₃·OEt₂ and TiCl₄.⁵ The diastereomers were identified by the ¹H NMR chemical shifts of the methyl groups⁶ by comparison to those described in the literature⁷ and quantified by GC.

Next we examined the stereo- and regioselectivity of these NbCl₅-promoted allylation reactions. In this way, crotylstannane (3-methyl-allylstannane, 1:1 mixture of isomers) and benzaldehyde were reacted in the presence of NbCl₅ (Table 3). The reaction proved to be regiospe-

cific in that no linear product was formed under any conditions.

It is reported that the order of addition of the reagents in SnCl_{4^-} and TiCl_4 -mediated allylation reactions alters the diastereomeric ratio of the homoallylic alcohol as well as the regiochemistry of the reaction, due to transmetallation.⁸ The reactions performed with normal addition (addition of crotylstannane to a suspension of benzaldehyde and NbCl₅ in Et₂O) afforded a mixture of diastereomers⁹ in good yields (Table 3, entries 1 to 3). The best results were obtained at -15°C with shorter reaction periods. When the reactions were performed at lower temperatures (-78°C) or when 2 equiv. of NbCl₅ were used (entry 3), no significant improvements were achieved either in yield or in selectivity.

In the reactions with inverse addition (addition of benzaldehyde to a suspension of crotylstannane and NbCl₅ in Et₂O), the yields and diastereoselectivities were similar to those obtained with normal addition (entry 4). Furthermore, linear products were not detected under any conditions, as already mentioned. Although no spectroscopic studies were performed,¹⁰ these results suggest that the transmetallation process is not occurring.

In order to get a better insight on the stereochemistry of the NbCl₅-mediated additions to aldehydes, the reaction between *E*-cinnamylstannane¹¹ (3-phenyl-allylstannane) and benzaldehyde was studied.

The reaction proceeded smoothly, but in this case the *syn* diastereomer was obtained almost exclusively, in good yield (Scheme 3).¹² This result is in sharp contrast to those obtained with $ZnCl_2$ in DMF¹³ and SnCl₂ in

Table 3. Results of the reaction between crotylstannane^a and benzaldehyde in Et₂O

		Ph H $E/Z = 1:1$ NbCl ₅ , Et ₂ O	Ph +	Ph OH anti	
Entry	Temp. (°C)	Mode of addition	Syn:anti ⁹	Time (h)	Yield ^c (%)
1	-15	Normal	1.9:1	1.5	63
2	-15	Normal	2.6:1	0.3	91
3 ^b	-15	Normal	2.5:1	0.3	83
4	-15	Inverse	2.2:1	0.3	91

^a In all cases 2 equiv. of crotylstannane were used.

^b 2 equiv. of NbCl₅ were used.

^c Isolated yields of chromatographically pure products (syn/anti mixture).

CH₃CN,¹⁴ which gave predominantly the *anti* isomer.¹⁵ In both cases, a cyclic transition state was proposed to explain the *anti* stereoselectivity. Although it is reported that BF₃·OEt₂ is also *syn*-selective,¹³ the reaction is run at -78° C. The advantage here is that the reaction can be warmed up to 0°C without lowering the selectivity.

To confirm the stereochemical assignment of our major isomer, an enriched (5:1) mixture of the *anti* isomer was prepared following the procedure of Wilson et al.¹⁶ The spectroscopic data of the major isomer in the above 5:1 mixture matched those reported for our *anti* isomer¹⁷ whereas the data for the minor isomer in the mixture above fully agreed with those obtained for our major isomer in the NbCl₅-mediated reaction.¹⁸

The mechanism of these reactions is still a matter of much controversy. Either the *antiperiplanar* transition state (**ET2**) proposed by Yamamoto⁴ or the *syn-syn-clinal* transition state (**ET1**) proposed by Keck¹⁹ can be invoked to explain the selective formation of the *syn* isomer in this case (Fig. 1).²⁰ It also seems possible that the double bond geometry plays an important role in the reaction diastereoselectivity.

In conclusion, the scope and limitations of the NbCl₅mediated allylation of aldehydes have been studied. The methodology allows the obtention of homoallylic alcohols in good yields. NbCl₅ proved to be an effective Lewis acid and a promising tool in the control of diastereoselectivity in these reactions. The exceptional selectivity obtained with cinnamylstannane makes NbCl₅ an attractive choice when the *syn* isomer is required. Our results on the allylation of imines²¹ and





Figure 1. *Syn-synclinal* and *antiperiplanar* transition states for *E*-cinnamylstannane.

also in aldol reactions using $NbCl_5$ will soon be published.

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