

Titanium Tetrafluoride/*L*-Prolinol Catalyzed Enantioselective Allylation of Aromatic Aldehydes with Allyltrimethylsilane

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Abstract: Aldehydes undergo smooth conversion to give homoallylic alcohols with allyltrimethylsilane employing 10 mol% of titanium tetrafluoride as a Lewis acid in the presence of 10 mol% of *L*-prolinol in CH₃CN/CH₂Cl₂ (8:2) for 2 h at room temperature. The presence of functionalities such as chloro, nitro and bromo is well tolerated in the presence of catalyst. The reaction proved to be of general nature with yields varying from moderate to excellent depending on the structure of aldehydes used to give enantiomerically enriched homoallylic alcohols. The reaction proceeds under mild condition with simple experimental procedures.

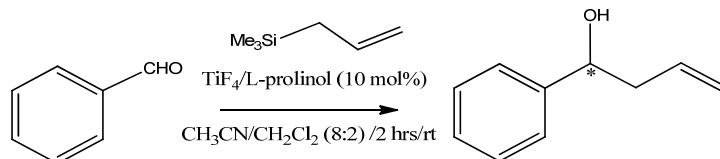
Keywords: Aldehydes, Allylation, Titanium tetrafluoride, *L*-Prolinol, Allyltrimethylsilane

Introduction

The allylation of carbonyl compounds is among the most important methods for the formation of homoallylic alcohol¹. Homoallylic alcohols so obtained are important building blocks for the synthesis of various natural products². Many of these transformations typically employ Lewis acid and have attracted tremendous interest throughout scientific communities witnessing unprecedented advances in the last decade. A large arsenal of Lewis acids catalyst thus have been documented so far^{1a,3} leading to development of a large and diverse array of chiral Lewis acid catalysts. Most of them consist of chiral ligands attached to metals such as Zn, Ti, B, Cr and Rh. Among the chiral modifiers to accomplish this are ligands such as bisoxazolines, bipyridines and terpyridine. Among the allyl transfer reagents allylic silanes and allylic stannanes have been extensively employed. A limitations to some of these protocols is the toxicity, moisture uptake, air tolerance and few of them employing expensive rare earths as Lewis acid catalyzed addition of the allyl transfer reagents to carbonyl functionality. Thus the development of new synthetic methods of a benign nature is of great interest today.

Of particular interest in this context is the use of metal fluorides like TiF₄, CsF and AgF as activators that promotes allylation of aldehydes and has long been of interest to synthetic chemist⁴. A common strategy is to use titanium diol coordination chemistry by employing

titanium tetrafluoride with complexes of the readily available bidentate chiral ligands such as 1,1'-binaphthalene-2,2'-diol (BINOL) complexes as the catalysts. The high reactivity of the catalyst is attributed to factors such as the strong Lewis acidity of TiF_4 derived complexes and the greater strength of the Ti-F bond compared to the Si-F bond which assists in catalyst turnover. In addition, a ternary transition structure has been proposed in which the electrophilic titanium center activates the aldehyde and the nucleophilic fluoride bridge to silicon increases the reactivity of allylsilane. Fluoride assisted conversions often proceeds with high degree of stereoselectivity⁵. Prolinol is used in broad variety of chemical reactions as chiral ligand, chiral catalyst or chiral auxiliary reagent in the Hajos-Parrish-Eder-Sauer-Wiechert reaction, the Baylis-Hillman reaction, Noyori type reaction and the Michael reaction⁶. Recently a combination of small dual molecules *L*-proline and *L*-prolinol has been reported to catalyze allylation of aldehydes by (triallyl)butylstannane⁷. With these precedence we herein report the nucleophilic addition of allyltrimethylsilane with titanium tetrafluoride in the presence of *L*-prolinol as chiral bidentate modifiers. It is noteworthy that *L*-proline and *L*-prolinol has have been shown to act as enantioselective catalysts for aldol reactions. In the present protocol reaction was performed between aldehyde substrate and allyltrimethylsilane using an optimum combination of titanium tetrafluoride and *L*-prolinol in $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$. The reaction proved to be of general nature, yields varying from moderate to excellent, proceeds under mild condition with reasonably low catalyst loading at room temperature to give enantiomerically enriched homoallylic alcohols. The reaction is easy to perform with simple experimental and isolation procedures.



Scheme 1. TiF_4 fluoride catalyzed allylation of benzaldehyde using allyltrimethylsilane in the presence of *L*-prolinol

Experimental

General reagents and solvents were purchased from commercial sources and used without further purification. Starting materials (glycerophosphocholine and acid chloride) reagents were purchased from Aldrich and used as received. Titanium tetraisopropoxide and triethyl amine were obtained from Merk India limited. NMR spectra were obtained using a Varian Mercury 400 instrument spectrometer. EI mass spectra were obtained in FAB+ ion mode with Bruker mass spectrometer. Reactions were carried out using syringe-septum technique. Column chromatography was performed using silica gel 100-200 mesh. Thin layer chromatography was done using manually coated plates, with visualization of spots in iodine chamber.

General procedure for the allylation of **1a**

A mixture of TiF_4 (0.1 mmol) and ligand (0.1 mmol) in $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ (8:2) was stirred for 15 minutes at room temperature. Aldehyde **1a** (1 mmol) and allyltrimethylsilane **2** (3 mmol) was then sequentially added at room temperature. The reaction mixture was allowed to stir for appropriate time. After the completion of the reaction (TLC monitored), solvent removed *in vacuo*, the reaction mixture was quenched with 2N HCl (10 mL) and extracted with diethylether several times. The combined organics was washed with water, sat. brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. Further purification of the desired product was done on silica gel column. Characterization of alcohol products via NMR and MS was done

with reference to literature values: 1-Phenyl-3-en-1-ol (**3a**)^{8a}, 1-(4-bromophenyl)but-en-1-ol (**3b**)^{8b}, 1-(4-nitrophenyl) but-3-en-1-ol (**3c**)^{8a}, 1-(4-methoxyphenyl)-3-buten-1-ol (**3d**)^{8c}, 1-Pyridin-3-yl)but-3-en-1-ol (**3e**)^{8d}, 1-(Furan-2-yl)but-3-en-1-ol (**3f**)^{8e}, 1-(4-Dimethylamino-phenyl)-but-3-en-1-ol (**3g**)^{8f}, Dec-1-en-4-ol (**3h**)^{8g}.

Results and Discussion

Benzaldehyde (**1a**) was examined as a model substrate and the reaction conditions was optimized by screening the solvents such as CH₃CN, CH₂Cl₂, Et₂O, dioxane and THF, changing the ratio of benzaldehyde (**1a**)/allyltrimethylsilane (**2**) and by varying of the catalyst loading (Table 1). Under the optimized condition the best results (82% yield) were obtained by stirring the reaction mixture using a substrate ratio of 1:3 (**1a/2**) and 10 mol% of titanium tetrafluoride in the presence of 10 mol% of *L*-prolinol in CH₃CN/CH₂Cl₂ (8:2) for 2 h at room temperature. Among the halogenated solvents CH₂Cl₂ gave the best observed yields and selectivity. The use of ethereal solvents such as THF, dioxane and ether proved beneficial in terms of selectivity but gave lower yields (Table 1. Entry 1, 2 and 4). However the use of protic solvent like MeOH considerably reduced the yield and also selectivity. Consistent with the previous studies the presence of acetonitrile as solvent was necessary for the reaction to proceed to a optimum extent (**1e**) and a study of variation in the catalyst composition revealed a ratio of 1:1 (metal/ligand) to be optimum. Increasing the amount of catalyst to 20% of TiF₄ and 20 mol% of ligand showed a decrease in the product yield from 82% to 68% (entry 6). However reducing the catalyst loading to less than 5 mol% of (TiF₄) and 5 mol% of ligand, the yield of **3a** was significantly reduced to 45% (entry 8). With the use of 10 mol% of catalyst longer reaction times increased the yields but furnished lower selectivity. The catalytic action of TiF₄ was evident as no reaction product was observed under the optimized condition when a solution of **1a** in CH₃CN/CH₂Cl₂ (8:2) was charged directly with allyltrimethylsilane **2** in the presence of the catalyst even after prolonged time.

Table 1. Effect of reaction condition on the TiF₄ catalyzed allylation of aldehyde (**1a**) using allyltrimethylsilane (**2**) in the presence of *L*-prolinol

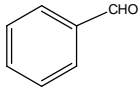
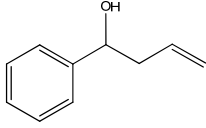
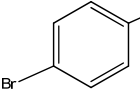
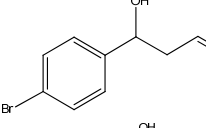
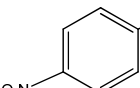
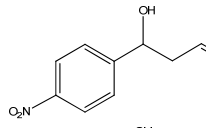
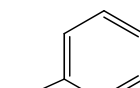
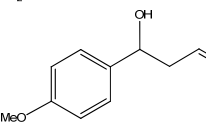
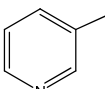
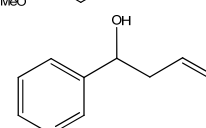
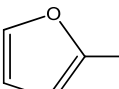
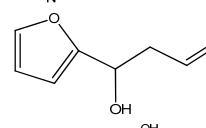
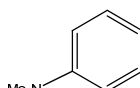
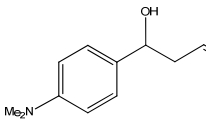
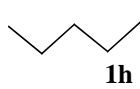
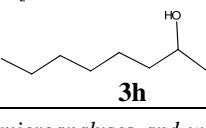
Entry	Solvent ratio (8:2)	Time, h	Catalyst, mol%	Yield, %	er [*]
1	CH ₃ CN/Et ₂ O	2	10	56	91/9
2	CH ₃ CN/THF	2	10	30	83/17
3	CH ₃ CN/MeOH	2	10	25	65/35
4	CH ₃ CN/Dioxane	2	10	45	74/26
5	CH ₃ CN/CHCl ₃	2	10	72	75/25
6	CH ₃ CN/CH ₂ Cl ₂	2	10	82	80/20
7	CH ₃ CN/CH ₂ Cl ₂	2	20	68	86/14
8	CH ₃ CN/CH ₂ Cl ₂	2	5	45	70/30
9	CH ₃ CN/CH ₂ Cl ₂	5	10	82	65/35

^{*}The enantiomeric ratio was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane: *i*-propanol)

With the optimized condition in hand we then evaluated the scope of the reaction using a variety of structurally divergent aldehydes (Table 2). While with benzaldehyde 82% of allylated product was obtained under the optimized condition in 2 h, activated 3-nitrobenzaldehyde afforded the allylated product in 92% yield in the same 2 h conversion.

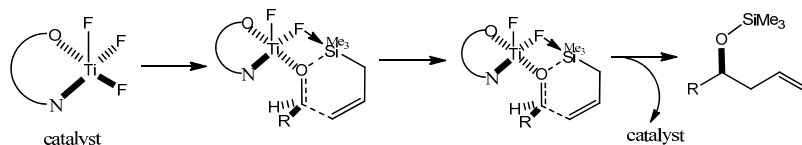
An electron withdrawing substituent on the ring facilitated a nucleophilic attack on the carbonyl while with the presence of an electron donating substituent (deactivated aryl aldehydes), the reaction was sluggish and a longer reaction time was registered for an acceptable yield. As anticipated the allylation of electron rich heteroaromatics (**1e** and **1f**) also took a longer reaction time to accomplish. These observed rates can be explained on the basis of simple arguments based on electronic effects of groups present on the ring. As shown in Table 2, all the aldehydes including enolizable aldehydes furnished the products in high enantioselectivities (74-84%) in good yields.

Table 2. Fluoride catalyzed allylation of aldehyde **1a** using allyltrimethylsilane in the presence of *L*-prolinol

Entry	Aldehyde	Time, h	Product	% Yield ^{a,b}	er
1	 1a	2	 3a	82	80/20
2	 1b	1.5	 3b	85	76/24
3	 1c	2	 3c	92	79/21
4	 1d	6	 3d	72	81/19
5	 1e	7	 3e	75	75/25
6	 1f	7	 3f	78	72/28
7	 1g	9	 3g	75	84/16
8	 1h	9	 3h	68	83/17

^aIsolated yields. ^bAll compounds gave satisfactory microanalyses and were characterized by ¹H NMR spectra by direct comparison with reported authentic samples⁸. Typical reaction condition: aldehyde:allyltrimethylsilane (1:3), 10 mol% catalyst combination: TiF₄ in CH₃CN:CH₂Cl₂ (8:2). The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiralcel OD column (Hexane: *i*-propanol)

The reaction proved to be of general nature and could be applied to a broad range of substrates. Both aromatic and aliphatic aldehydes gave good yields. The reaction proceeds under mild condition and even aliphatic enolizable aldehydes can be allylated (Table 2, entry 8). Under the optimized condition ketones were not allylated. A study of variation in the catalyst composition revealed that employing a 0.5 mol% TiF_4 with respect to the ligand (5 mol% of TiF_4 and 10 mol% of ligand) still enabled a satisfactory yield within a period of 3 h. Even with only 2.5 mol% of TiF_4 with respect to ligand, 75% of the allylated product was obtained in a 6 h conversion. These observations suggests that the relationship between TiF_4 and ligand is not a simple stoichiometric one. As can be judged from Table 1. the use of ethereal solvents provided greater variation in the product yields (Table 2, entry 1 and 2). Presumably, the coordination of solvent in the transition state influences the product formation in these transformations. By conducting the reaction over a range of decreasing catalyst loading (starting from 20 mol% of catalyst) and keeping the concentration of the substrate constant we found an inverse relationship between the catalyst loading and the chemical yield. Decreasing the amount of catalyst led to a steady increase of the product till an optimum value at 10 mol% of loadings. Since a catalytic amount of TiF_4 is required to accomplish the reaction following transition state may be proposed⁹ involving initial activation of allyltrimethylsilane to to the increased electrophilicity of carbonyl carbon coordinated to titanium (Scheme 2).



Scheme 2. Plausible mechanism for the TiF_4 fluoride catalyzed allylation of aldehyde using allyltrimethylsilane in the presence of *L*-prolinol

Conclusion

In conclusion a convenient and practical method for the synthesis of enantiomerically rich homoallylic alcohol in good yields in the presence of catalytic amount of *L*-prolinol and TiF_4 and in a one-pot reaction procedure has been accomplished under a mild reaction condition. We have demonstrated the scope and a novel use of *L*-prolinol as a ligand in the catalytic allylation reactions. The reaction smoothly proceeds without pretreatment of the reagents and uses no additives. The mild reaction condition and low cost of reagent should make the present methodology synthetically useful.

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