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$TiCl_4$ mediated preparation of (*E*)-non-conjugated homoallylic alcohols with α-substituted allylsilanes

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ABSTRACT

The allylation of various aldehydes with α-substituted allylsilanes in the presence of $TiCl_4$ has been investigated. It has been shown that these reagents readily allow for good yields and high to excellent diastereoselectivities (up to >20:1) for a series of aldehydes, thereby providing a means of preparing non-conjugated (*E*)-homoallylic alcohols in a single step.

The Lewis acid mediated reaction of allylsilanes with carbonyl compounds has provided the synthetic chemist with a remarkable tool for the regio- and stereospecific preparation of homoallylic alcohols.[1] In 1976, Sakurai and co-workers reported that two α-substituted allylsilanes reacted with an aliphatic aldehyde under Lewis acidic conditions to afford the γ-substituted linear homoallylic alcohols as a non-defined *cis*- and *trans*-mixture of olefin geometry.[2] Later, Kumada investigated the addition of the chiral phenyl α-substituted allylsilane to a variety of aliphatic aldehydes and observed solely the *E* stereochemistry of the conjugated olefin product.[3,4] Subsequently, Panek and Miyashita have shown that substituted chiral crotylsilanes react with acetals to provide high levels of dr and er for the newly formed stereocenters coupled with selective (*E*)-olefin geometry formation of the α-substituted homoallylic ether products.[5,6]

While the synthesis of (*E*)-conjugated α-substituted homoallylic alcohols (or ethers) has been disclosed by means of substituted allylsilanes, surprisingly the synthesis of non-conjugated (*E*)-homoallylic alcohols derived from α-substituted allylsilane reagents has yet to be fully investigated as described in Scheme 1.[7] In order to obtain such said products prior to this investigation utilizing allylsilanes, further functionalization of the given terminal alkene resident in an unsubstituted homoallylic alcohol would have to be conducted.[8] A couple of options for this additional functionalization include a cross metathesis with another type I olefin or olefination of the resultant aldehyde (by means of oxidative cleavage of the terminal alkene) via a Julia–Kocieński protocol. Unfortunately, both of these mentioned processes have significant disadvantages.

For example, the terminal olefin moiety of a homoallylic alcohol typically undergoes a non-chemo and diastereoselective cross-metathesis reaction with another type I alkene to afford a low yield of product with modest *E*/*Z* selectivities.[9] Likewise, the Julia–Kocieński olefination would require a minimum of four reaction processes commencing with protection of the alcohol moiety, oxidative cleavage of the terminal alkene, olefination and a final deprotection to unmask the alcohol functional group.[10] Herein, we wish to report on a systematic study leading to the successful direct preparation of non-conjugated (*E*)-homoallylic alcohols in one step from the parent aldehyde via a Lewis acid mediated addition of α-substituted allylsilanes.

As shown in Scheme 2, preparation of the substituted allylsilanes **5a** and **5b** utilized vinyl silanes **1a** and **1b**, which were synthesized based on our previous report.[11] Thus, treatment of **1a** and **1b** with Pearlman's catalyst [$Pd(OH_2)$] under an atmosphere of H_2 in EtOH readily provided the saturated α-silyl esters **2a** and **2b** in 89% and 83% yields, respectively.[12] Initially, we had hoped to partially reduce the ester moieties of **2a** and **2b** with DIBAL to the corresponding aldehydes. However, we consistently observed over reduction of the carbonyls and after reaction optimization obtained alcohols **3a** and **3b** in yields of >80%. An ensuing oxidation of **3a** and **3b** with Dess–Martin Periodinane (**4**) furnished the desired, yet chromatography unstable α-silyl aldehydes which were used directly for the subsequent Wittig olefination. Accordingly, the crude aldehydes were added to the preformed methylene ylide

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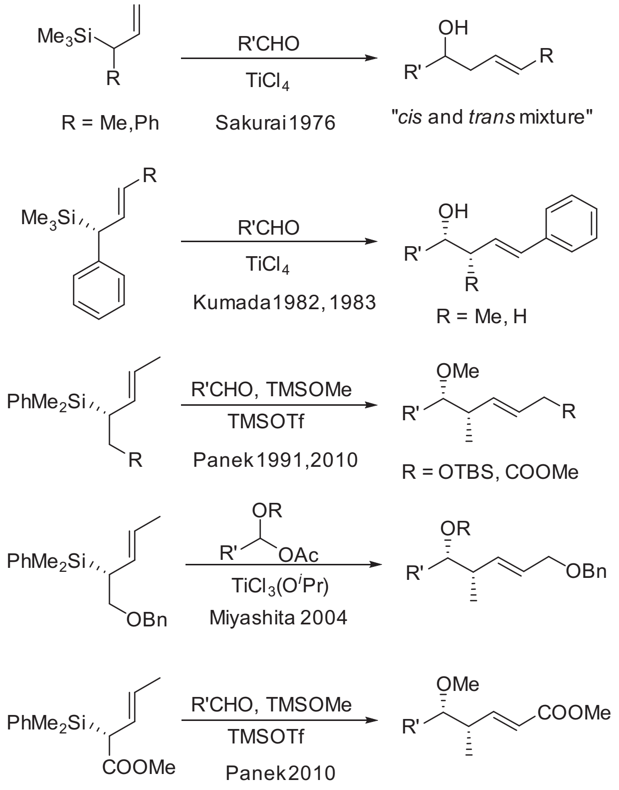
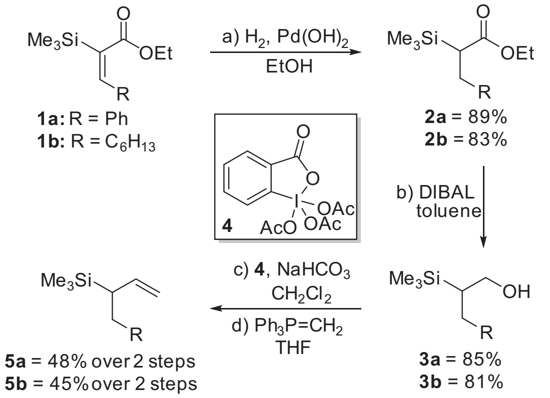


Scheme 1.

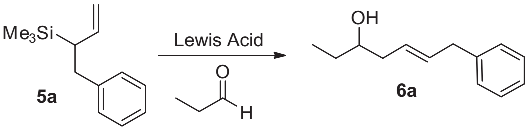


Scheme 2.

(generated from Ph$_3$P$^+$-CH$_3$ Br$^-$ and *n*BuLi) and afforded allylsilanes **5a** and **5b** in modest yields of 48% and 45% over two steps from **3a** and **3b**. It is worth noting that the elimination of Ph$_3$P=O was preferential to that of a Peterson type olefination with a loss of TMSOH.[13]

Table 1

Allylation of propanal with allylsilane **5a** in the presence of different lewis acids and solvents[a]



No.	Lewis acid	Solvent	Yield (%)	*E/Z*[b]
1	TiCl$_4$	CH$_2$Cl$_2$	66	11/1
2	BF3·OEt$_2$	CH$_2$Cl$_2$	7	5/1
3	TMSOTf	CH$_2$Cl$_2$	23	10/1
4	SnCl$_4$	CH$_2$Cl$_2$	—	—
5	In(OTf)$_3$[c]	CH$_2$Cl$_2$	—	—
6	Sc(OTf)$_3$[c]	CH$_2$Cl$_2$	—	—
7	Er(OTf)$_3$[c]	CH$_2$Cl$_2$	—	—
8	TiCl$_4$	Toluene	39	10/1
9	TiCl$_4$	Cl(CH$_2$)$_2$Cl	17	11/1
10	TiCl$_4$	Hexane	7	9/1

[a] Reaction ran with 1 equiv of **5a**, 1.3 equiv of Lewis acid, and 1.3 equiv of propanal for 3 h at −78 °C.

[b] *E/Z* ratio determined by ^{1}H NMR (500 MHz) from the purified reaction mixture.

[c] Lewis acid was dissolved in THF before being added to the reaction.

With the desired allylsilanes in hand, we proceeded to investigate the Lewis acid-mediated addition of **5a** to propanal under a variety of reaction conditions as shown in Table 1. We initiated the inquiry with a couple of objectives in mind. First, we wanted a process that would provide solely the linear homoallylic alcohol and not the ether product (via the acetal or intramolecular cyclization to afford the substituted THF ring) as developed by Panek.[14] Secondly, the yield and *E/Z* selectivity must mirror or be greater than that of any multi-step approach. With these goals in mind, we initiated our examination by scanning a variety of Lewis Acids. As shown in Table 1, the slow addition of 1.3 equiv of TiCl$_4$ to a solution of **5a** and propanal (1.3 equiv) in CH$_2$Cl$_2$ at −78 °C for 3 h provided homoallylic alcohol **6a** in 66% yield with an *E/Z* ratio of 11/1. Exchanging the Lewis acid TiCl$_4$ for BF$_3$·OEt$_2$ dramatically reduced both the yield of **6a** to 7% and diastereoselectivity (5/1) of the newly formed olefin moiety. Similarly, the usage of TMSOTf provided a low 23% yield of **6a**, however the *E/Z* ratio was restored to ~10/1 favoring the *E*-alkene. It is worth noting that under both reaction conditions utilizing BF$_3$·OEt$_2$ and TMSOTF, the major product was the substituted THF ring as reported by Panek, Woerpel and Roush.[15] Surprisingly, when we examined SnCl$_4$ in place of TiCl$_4$ little to no homoallylic alcohol **6a** was isolated, but complete decomposition of allylsilane **5a** was observed. Correspondingly, the utilization of rare-Earth triflate salts [In(OTf)$_3$, Sc(OTf)$_3$ and Er(OTf)$_3$] as Lewis acids led to limited product formation (<5%) and quantitative re-isolation of starting material **5a**.

Armed with the knowledge that TiCl$_4$ was the optimal Lewis acid and provided **6a** with the greatest yield (66%) and *E/Z* selectivity (11/1), we sought to further define the reaction scope by examining a potential solvent effect. We exchanged CH$_2$Cl$_2$ for a variety of other non-polar solvents (toluene, hexane, and ClCH$_2$CH$_2$Cl) and observed significantly reduced yields (7–39%) while maintaining the olefin diastereoselectivity of ⩾9/1 for the *E*-alkene. It was a little unexpected that ClCH$_2$CH$_2$Cl afforded such a low yield of 17% compared to that of CH$_2$Cl$_2$ (66%). With the reaction conditions (1.3 equiv of TiCl$_4$) in hand as described in Table 1, we desired to further investigate the scope and limitations of both **5a** and **5b** as allylating reagents with an assortment of aldehydes.

Initial treatment of the TBDPS protected aldehyde[16] (derived from 1,3-propanediol) with **5a** in the presence of 1.3 equiv of TiCl$_4$ provided alcohol **7a** in ~50% yield with an *E/Z* ratio of 13/1 as determined by ^{1}H NMR while a significant amount of aldehyde remained unreacted (~35–40%). Thus, addition of another 0.2 equiv of TiCl$_4$ and a second equiv of silane **5a** readily promoted the complete consumption of the aldehyde and afforded **7a** in 82% yield with an *E/Z* ratio of 16/1 as described in Table 2. Based on this improvement in yield and diastereoselectivity of the newly formed alkene, we carried out the remaining allylations with both **5a** and **5b** (2 equiv) utilizing 1.5 equiv of TiCl$_4$. Hence, treatment of propanal and **5a** with 1.5 equiv of TiCl$_4$ furnished **6a** in a greater yield of 77% with an increased *E/Z* ratio of 12/1. Under identical reaction conditions, the addition of **5b** to propanal afforded homoallylic alcohol **6b** with