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

Aymara M. M. Albury, Michael P. Jennings *

Department of Chemistry, The University of Alabama, 250 Hackberry Lane, Tuscaloosa, AL 35487-0336, United States

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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

* Corresponding author. Tel.: +1 (205) 348 0351; fax: +1 (205) 348 9104.
E-mail address: jenningm@bama.ua.edu (M.P. Jennings).

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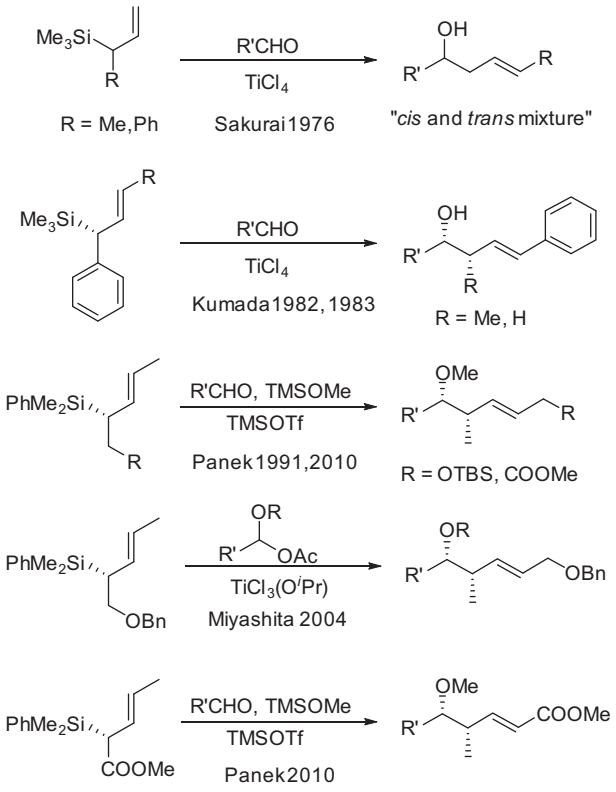
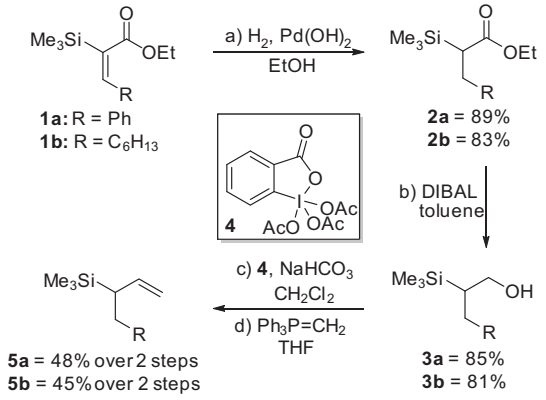


Scheme 1.

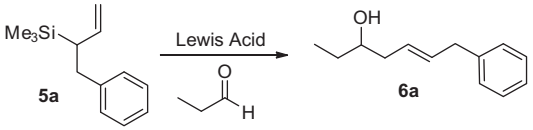


Scheme 2.

(generated from Ph_3P^+-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 $Ph_3P{=}O$ was preferential to that of a Peterson type olefination with a loss of TMSOH.[13]

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

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_2Cl_2	66	11/1
2	$BF3{\cdot}OEt_2$	CH_2Cl_2	7	5/1
3	TMSOTf	CH_2Cl_2	23	10/1
4	$SnCl_4$	CH_2Cl_2	—	—
5	$In(OTf)_3$[c]	CH_2Cl_2	—	—
6	$Sc(OTf)_3$[c]	CH_2Cl_2	—	—
7	$Er(OTf)_3$[c]	CH_2Cl_2	—	—
8	$TiCl_4$	Toluene	39	10/1
9	$TiCl_4$	$Cl(CH_2)_2Cl$	17	11/1
10	$TiCl_4$	Hexane	7	9/1

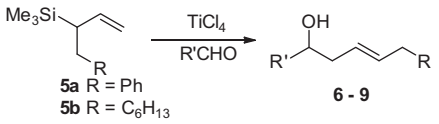
[a] Reaction ran with 1 equiv of **5a**, 1.3 equiv of Lewis acid, and 1.3 equiv of propanal for 3 h at −78 °C.
[b] *E/Z* ratio determined by ^1H NMR (500 MHz) from the purified reaction mixture.
[c] Lewis acid was dissolved in THF before being added to the reaction.

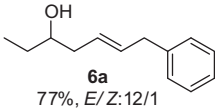
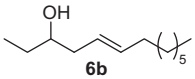
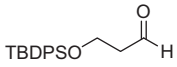
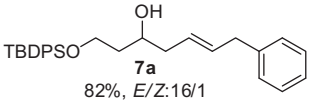
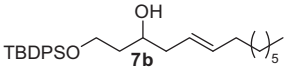
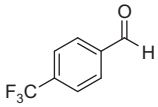
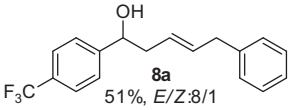
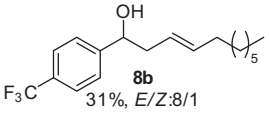
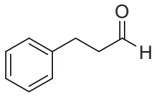
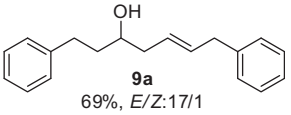
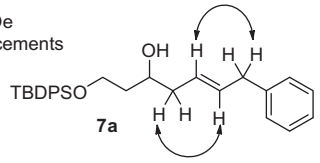
solution of **5a** and propanal (1.3 equiv) in CH_2Cl_2 at −78 °C for 3 h provided homoallylic alcohol **6a** in 66% yield with an *E/Z* ratio of 11/1. Exchanging the Lewis acid $TiCl_4$ for $BF_3{\cdot}OEt_2$ dramatically reduced both the yield of **6a** to 7% and diastereoselectivity (5/1) of the newly 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 $BF_3{\cdot}OEt_2$ 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_2Cl_2 for a variety of other non-polar solvents (toluene, hexane, and $ClCH_2CH_2Cl$) 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 $ClCH_2CH_2Cl$ afforded such a low yield of 17% compared to that of CH_2Cl_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 ^1H 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

Table 2
Allylation of various aldehydes with allylsilane **5a** and **5b**[a,b,c]



Aldehyde	Product yield (*E*/*Z*)
	 **6a** 77%, *E*/*Z*:12/1
	 **6b** 84%, *E*/*Z*:11/1
	 **7a** 82%, *E*/*Z*:16/1
	 **7b** 85%, *E*/*Z*:16/1
	 **8a** 51%, *E*/*Z*:8/1
	 **8b** 31%, *E*/*Z*:8/1
	 **9a** 69%, *E*/*Z*:17/1
Key nOe Enhancements	 **7a**

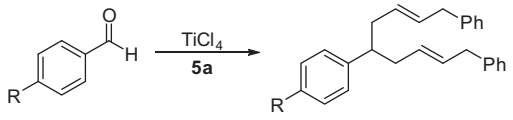
[a] Reaction ran with 2 equiv of **5a**/**5b**, 1.5 equiv of $TiCl_4$, and 1.0 equiv of aldehyde for 3 h at −78 °C.
[b] *E*/*Z* ratio determined by ^1H NMR (500 MHz) from the purified reaction mixture.
[c] Yields are of the isolated, pure compounds.

84% yield coupled with an 11/1:*E*/*Z* ratio. Likewise, allylation of the TBDPS protected aldehyde with **5b** provided alcohol **7b** with a very high diastereoselectivity of 16/1 favoring the *E* isomer in 85% yield. Similar to that of both of the other aliphatic aldehydes, allylation of 3-phenyl-1-propanal with **5a** readily proceeded to furnish the corresponding homoallylic alcohol **9a** in 69% yield and an *E*/*Z* ratio of 17/1. Interestingly, attempted allylation of electron neutral and rich aromatic aldehydes with both **5a** and **5b** failed to provide the desired homoallylic alcohols, vide infra. However, the electron deficient *p*-CF_3-benzaldehyde underwent allylation with both **5a** and **5b** to provide the corresponding homoallylic alcohols **8a** and **8b** in 51% and 35% yields, respectively. However, the *E*/*Z* ratios for both **8a** and **8b** (8/1 favoring the *E* isomer) were diminished to that of their aliphatic counterparts. As delineated in Table 2, the olefin geometry of **7a** was determined by means of ^1H NMR. The strong 1D NOE for both the methylene allylic and vinylic protons provided convincing evidence for the assigned *E*-olefin geometry. Based on the NOE experimental results for **7a**, the stereochemistry of the remaining homoallylic adducts was assigned by analogy.

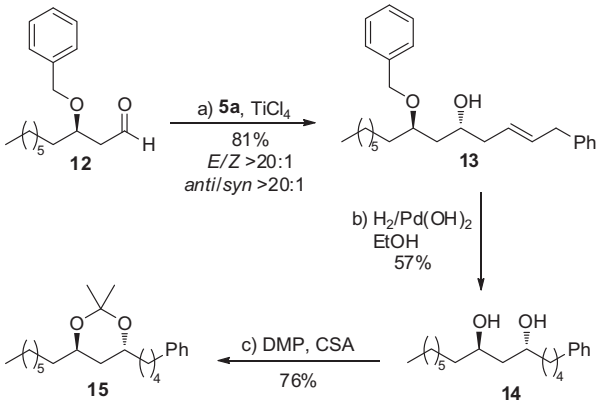
As noted above, attempted $TiCl_4$-mediated allylation of *p*-tolylaldehyde and *p*-anisaldehyde with **5a** under the standardized reaction conditions from Table 2 did not afford the desired homoallylic alcohols. As shown in Scheme 3, the addition of 2 equiv of **5a** to *p*-tolylaldehyde (with 1.5 equiv of $TiCl_4$) afforded the diallylated compound **10a** in 46% yield with an *E*/*Z* ratio of 9/1.[17] Likewise, treatment of *p*-anisaldehyde under identical conditions as noted furnished the diallylated compound **11a** in 61% yield and a slightly decreased *E*/*Z* ratio of 8/1.

As reported by Reetz and Keck, allylsilanes and stannanes typically react via a chelation controlled addition to a β-ether carbonyl to furnish the 1,3-*anti* diol product.[18,19] With this in mind, we elected to investigate the allylation of the benzyl protected β-hydroxy aldehyde **12** under the previously described reaction conditions with silane **5a**. As described in Scheme 4, treatment of **12**[20] with 1.5 equiv of $TiCl_4$ presumably formed the six-membered chelated intermediate coupled with the addition of the allylsilane reagent **5a** led to the formation of the 1,3-homoallylic alcohol **13** with a diastereomeric ratio of >20:1 with the presumed *anti*-stereochemistry (based on literature precedent) in 81% yield. In addition, the *E*/*Z* ratio of the newly formed alkene was determined to be >20/1 by ^1H NMR. In order to unequivocally determine the diol stereochemistry resident in **13** we subsequently performed a concomitant hydrogenation/hydrogenolysis of both the olefin and benzyl ether with 1 atm of H_2 and 10% $Pd(OH)_2$ in EtOH to afford diol **14** in 57% yield. Final acetonide formation of **14** under the standard reaction conditions of 2,2-dimethoxypropane and CSA provided acetal **15** in 76% yield.

With **15** in hand, we initially hoped to determine the *anti*-stereochemistry via 1D NOE spectroscopy. Unfortunately, non-resolved ether methine signals at ~3.7 ppm in the ^1H NMR spectrum (500 MHz) did not permit for the preferred NOE experiment. However, close inspection of the ^{13}C NMR did provide the necessary information for the positive confirmation of the proposed *anti*-stereochemistry. As noted by Rychnovsky, the ^{13}C NMR chemical shifts of the two geminal methyl groups of an *anti*-acetonide moiety should exhibit pseudo-equivalent signals



Scheme 3.



Scheme 4.

due to the twist boat conformation at ~25 ppm.[21] In our specific case, the methyl signals for acetonide **15** overlap at 24.8 ppm (as determined by HSQC) in the ^{13}C NMR. Based on literature precedence, we felt confident that the stereochemistry of the 1,3-diol subunit was indeed *anti*.[21]

In conclusion, we have shown, by means of a systematic study, a 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. Future directions of investigation will include further developments of novel chiral allyl silane reagents derived from our previously reported vinyl silanes and their utilization in target driven synthesis. Results from these studies will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.047.

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