Solvent-Mediated Allylation of Carbonyl Compounds with Allylic Stannanes

Teresa M. Cokley,† Peta J. Harvey,† Raymond L. Marshall,† Adam McCluskey,‡ and David J. Young*,†

Faculty of Science and Technology, Griffith University, Nathan 4111, Brisbane, Australia and Department of Chemistry, University of Newcastle, Callaghan NSW 2308, Australia

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Methanol promotes the addition of allyltrimethylstannane (**1a**) to isobutyraldehyde (**2a**, 30 °C) yielding the corresponding homoallylic alcohol (**3a**), without the necessity for added catalyst. The corresponding reaction of aldehydes **2a**−**e** or activated ketone **2f** with tetraallyltin (**1b**, 0.25 equiv) is substantially faster and proceeds in high yield (81−98%) and with easy separation of the product from tin residues. Aliphatic ketones **2g** and **2h** also react, but require more forcing conditions. Competitive experiments involving equimolar mixtures of selected aldehydes and ketones with **1b** indicates very high aldehyde chemoselectivity. The reaction of **1b** with aldehydes proceeds slowly at first, followed by a rapid acceleration which may be attributable to a build up of partially soluble tin(IV) methoxide. The increased rate of carbonyl allylation by **1a** and **1b** in methanol, relative to dimethyl sulfoxide, suggests that the primary activating influence of the solvent is via hydrogen bonding to the carbonyl oxygen. There is no NMR spectroscopic evidence for a significant change in the ground state structure of these allylic stannanes in methanol, relative to other solvents.

Introduction

The addition of allylic metal compounds to aldehydes and ketones to yield homoallylic alcohols is a useful transformation in organic synthesis and consequently has received considerable attention in recent years.[1] The reaction is synthetically analogous to the aldol condensation but allows for the subsequent introduction of a variety of alternative functional groups by manipulation of the alkene moiety.[2] Like the aldol reaction, addition can be achieved with high levels of regio- and stereoselectively by judicious choice of substrates and reaction conditions.[3] Allylic stannanes offer an attractive combination of configurational stability with relatively high reactivity and have been extensively employed for the allylation of aldehydes, in particular.[4] Other than for particularly reactive aldehydes (e.g. chloral), some form of promotion is usually required such as heat,[5] high pressure[6] or, more commonly, activation of the aldehyde with a Lewis acid.[7] Brønsted acids have also been employed for this purpose, and of particular relevance to this paper is a report of the allylation of carbonyl compounds with tetraallyltin in acidic aqueous media.[8] This procedure involved the use of 1 equiv of HCl (relative to tetraallyltin) in aqueous THF and resulted in the transfer of all four allyl groups with high chemoselectivity toward aldehydes relative to ketones, esters, and acyl chlorides and discrimination between different types of ketone.

Table 1. Allylation of Aldehyde 2a with Allyltrimethylstannane 1a in Different Solvents[a]

entry	carbonyl compound	solvent	product	conversion[b] (%)
1	**2a**	CD_2Cl_2	**3a**	3
2	**2a**	CD_3OD	**3a**	73
3	**2a**	$(CD_3)_2SO$	**3a**	5

[a] Reactions conducted at a concentration of 1.0 M in each reagent at 30 °C for 8 days. [b] Determined by ^{1}H NMR spectroscopy.

Also pertinent to the present discussion is that allylic,[9] propargylic,[10] and indenyl[11] stannanes are configurationally unstable in methanol and other polar solvents, undergoing a facile allylic isomerization at ambient temperatures. Speculation concerning the mechanism of this process has invoked a solvent stabilized ion-pair intermediate. It occurred to us that such an intermediate might be trapped with an electrophile, and we have recently communicated[12] that aldehydes react with tetraallyltin in methanol and other polar solvents at ambient temperatures to provide the corresponding homoallylic alcohols in high isolated yield. This reaction is comparable to the corresponding aqueous HCl-promoted process in that all four allyl groups are transferred quantitatively but require no added activating agent. We now report on aspects of the mechanism and chemoselectivity of this unusual effect of solvent on the addition of allylic stannanes to carbonyl compounds.

† Griffith University. email: D.Young@sct.gu.edu.au.
‡ University of Newcastle.
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Table 2. Allylation of Aldehydes 2 (R^2 = H) with Tetraallytin 1b in Different Solvents[a]

entry	carbonyl compound	R^1	solvent	product	3 Yield (%)[b]
1	**2a**	i C_3H_7	CH_3OH	**3a**	84
2	**2a**	i C_3H_7	CH_2Cl_2	**3a**	(5)
3	**2b**	c C_6H_{11}	CH_3OH	**3b**	84
4	**2c**	Ph	CH_3OH	**3c**	81
5	**2c**	Ph	$HCONH_2$	**3c**	84
6	**2d**	$PhCH_2$	CH_3OH	**3d**	98
7	**2d**	$PhCH_2$	Me_2SO	**3d**	70[c]
8	**2e**[f]		CH_3OH	**3e**	95
9	**2e**[f]		CH_2Cl_2	**3e**	98

[a]Reactions conducted at 30 °C for *ca* 20 h unless otherwise stated. [b] Isolated yields, the value in parenthesis is a percentage yield determined by ^{1}H NMR spectroscopy. [c]After 63 h at 30 °C. [f] Rapid and exothermic reaction, required cooling in ice.

Table 3. Allylation of Ketones 2 with Tetraallyltin (1b) in Methanol[a]

entry	carbonyl compound	R^1	R^2	product	3 yield (%)[b]
1	**2f**	CH_3	CO_2Et	**3f**[c]	95
2	**2g**	CH_3	C_2H_5	**3g**	74
3	**2h**	$-(CH_2)_5-$		**3h**	76
4	**2i**	$-CH=CH(CH_2)_3-$		**3i**	<1
5	**2j**	CH_3	Ph	**3j**	(*ca* 20)

[a] Reactions conducted at reflux for 24 h unless otherwise stated. [b] Isolated yields, the value in parentheses is a percentage yield determined by ^{1}H NMR spectroscopy. [c] Conducted at 30 °C for 16 h. The product was hydrolyzed and isolated as the carboxylic acid.

Table 4. Competitive Allylation of Carbonyl Compounds (2) with Tetraallyltin (1b) in Methanol[a]

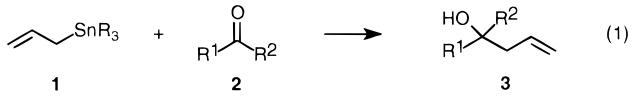
entry	aldehyde	ketone	ratio[b]
1	**2a**	**2g**	>98:<2
2	**2c**	**2h**	95:5
3	**2c**	**2j**	96:4

[a] Conducted with aldehyde (1.0 M), ketone (1.0 M), and **1b** (0.25 M) at 30 °C for 16 h. [b] Determined by ^{1}H and ^{13}C NMR spectroscopy.

Results

We first examined the reaction of allyltrimethylstannane (**1a**) with isobutyraldehyde (**2a**, 1 equiv, 30 °C) in different solvents (Table 1). The reactions were monitored by ^{1}H NMR spectroscopy for 8 days and while little conversion was observed in dichloromethane or dimethyl sulfoxide over this period, a significant amount of homoallylic alcohol **3a** was formed in methanol with trimethyltin methoxide as the only other product.

More useful from a synthetic perspective were the reactions of tetraallyltin (**1b**, 0.25 equiv) with aldehydes **2** in polar solvents, and particularly in methanol. These reactions proceeded at ambient temperature (30 °C) and provided the corresponding homoallyl alcohols **3** in good yield (Table 2). Reactions required approximately 2−20 h to reach completion, depending upon the aldehyde and also the purity of **1b**. Reactions involving **1b** which had developed a faint cloudiness on standing, proceeded faster than reactions in which **1b** had been distilled immediately prior to use, although all reactions were complete within 20 h and typically under 4 h. The product could be isolated either by aqueous workup or by evaporation of the solvent and washing the resulting slurry of **3** and tin salts with dichloromethane followed by kugelrohr distillation or filtration through silica gel. This simple workup is in marked contrast to the tedious separation of product from organotin residues often associated with the use of allyltrialkylstannanes.



1 2 3 (1)

R = CH_3 (**1a**)
R = allyl (**1b**)

Again, allylation in dichloromethane (Table 2, entry 2) or dimethyl sulfoxide (entry 7) was substantially slower, although reaction in the latter solvent did proceed to completion (^{1}H NMR) and in 70% isolated yield over a longer period (63 h). Only reactive aldehyde **2e** underwent complete allylation in dichloromethane and yielded the expected Cram (*erythro*, de = 70%) addition product[13] predominantly in either dichloromethane (entry 9) or methanol (entry 8). Ketones other than the reactive ethyl pyruvate (**2f**) did not react at 30 °C, but alkyl ketones (**2g,h**) did proceed with complete conversion (^{1}H NMR) and in good isolated yield at reflux for 24 h while allylation of acetophenone (**2h**) did proceed to a limited extent under these conditions (Table 3). Competitive experiments involving equimolar mixtures of selected

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Table 5. The Effect of Solvent on Selected NMR Parameters for Organostannanes[a]

compound	NMR parameter	CD_2Cl_2	$(CD_3)_2SO$	CD_3OD	$HCONH_2$
1b	δ ^{119}Sn	−49.4	−47.1	−51.1	−48.6
1b	$^1J(^{119}Sn-^{13}CH_2)$	264	261	267	*b*
1a	$^1J(^{119}Sn-^{13}CH_3)$	331	326	329	*b*
$(CH_3)_4Sn$	$^1J(^{119}Sn-^{13}CH_3)$	336	332	339	*b*

[a] All spectra obtained at a concentration of 0.2 M. [b] Could not be accurately determined in this non-deuterated solvent.

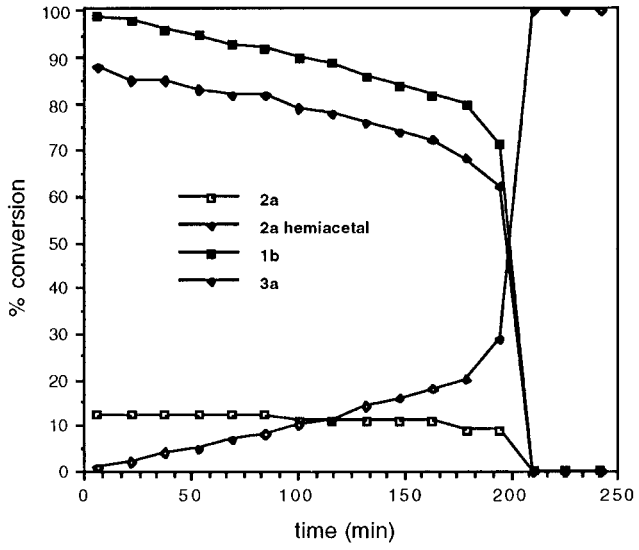

Figure 1. Allylation of aldehyde **2a** (1.0 M) with tetraallylstannane (**1b**, 0.25 M) in CD_3OD at 30 °C.

aldehydes and ketones with **1b** (0.25 equiv) at 30 °C in methanol (Table 4) indicated very high aldehyde selectivity.

The allylation of carbonyl compounds **2a**−**f** with **1b** were performed in CD_3OD at 30 °C and monitored by ^1H NMR spectroscopy. The allylation of **2a** was also monitored by ^{119}Sn NMR spectroscopy which revealed a decrease in the signal for **1b** (δ −51.15) and the concomitant appearance of a series of signals (some broad) beween approximately −600 and −640 ppm which is consistent with the formation of polymeric tin(IV) methoxide species.[14] No intermediate allyl tin species $(allyl)_{4-n}Sn(OR)_n$ ($n = 1-3$) were observed in any of these spectroscopic studies, indicating that transfer of the first allyl group is slower than subsequent transfers. Each reaction proceeded slowly before undergoing a rapid acceleration (Figure 1). This kinetic profile was quite reproducible, only varying in the length of the lag period which was dependent on both the aldehyde and the purity of **1b**. The aliphatic aldehydes **2a** and **2b** exist primarily (*ca.* 85−90%) as the hemiacetals in CD_3OD under these conditions (1.0 M, 30 °C).

In an attempt to elucidate the enhanced reactivity of allylic stannanes toward carbonyl compounds in polar solvents, and in methanol in particular, we carefully examined the ground state structure of **1a** and **1b** in different solvents by NMR spectroscopy. Parameters such as ^{119}Sn chemical shift and $^{119}Sn-^{13}C$ coupling constants are very sensitive to the substituents and symmetry about the tin atom and are, therefore, a convenient probe for small structural changes including weak donor−acceptor interactions in solution.[14] Selected NMR parameters for these substrates and for the reference compound tetramethyltin in different solvents are included in Table 5. These exhibited surprisingly little variation with solvent.

Discussion

While it is interesting to note that methanol promotes the addition of allyltrimethylstannane (**1a**) to aldehydes, this reaction is too slow to be of practical use. The allylation of aldehydes with **1b**, however, occurs at a convenient rate, proceeds with clean and quantitative transfer of all four allyl groups, and is very simple to conduct and to monitor by NMR spectroscopy. Also important from a synthetic perspective is that the resulting homoallylic alcohols can be easily separated from the relatively insoluble and involatile polymeric tin salts. Such mild reaction conditions should be compatable with a wide variety of other functional groups, although it was noted that substrate **2f** did undergo some transesterification to yield a small amount of the corresponding methyl ester over the period of the reaction and consequently the product **3f** was hydrolyzed and isolated as the carboxylic acid.

This allylation procedure is also highly chemoselective as indicated by the varying reaction times and temperatures required for different types of carbonyl compounds (Tables 2 and 3) and the high level of discrimination between aldehydes and ketones (Table 4). This degree of chemoselectivity is not possible with other more commonly used allylating reagents such as allylmagnesium bromide, allyllithium, or allyltributyltin/$BF_3{\cdot}OEt_2$.[8] The diastereoselectivity observed on reaction with chiral aldehyde **2e** is better than that obtained with some achiral allylmagnesium, titanium, and -chromium reagents,[15] but less than that obtained with chiral allylstannane[16] and -boron[13] reagents. The diastereomers of **3e** are, however, easily separated by derivatization and chromatography[17] and, in our experience, the high chemical yield and convenience of the present procedure compensates for the minimal effort of the subsequent separation.

Our NMR spectroscopic study of the ground state structure of **1a** and **1b** in different solvents provided no evidence for the solvent-stabilized ion-pair species proposed as an intermediate in the isomerization of allylic stannanes.[9−11] If such a species is in equilibrium with the tetrahedral allylic stannanes in polar solvents, it can only be present as a minor component undergoing exchange at a rate faster than the NMR timescale. The observation that both reaction of **1a** and of **1b** are accelerated in methanol to a greater extent than in the more polar, aprotic dimethyl sulfoxide also suggests that the primary influence of the solvent is not to activate the

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(17) We have found that the diasteromers of **3e** can be easily separated as the corresponding SEM ethers by chromatography on silica (10% ethyl acetate in hexane). They can also be separated after benzylation using Mulzer's procedure (reference 15).

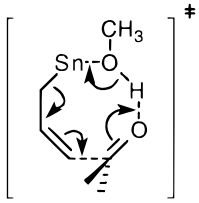


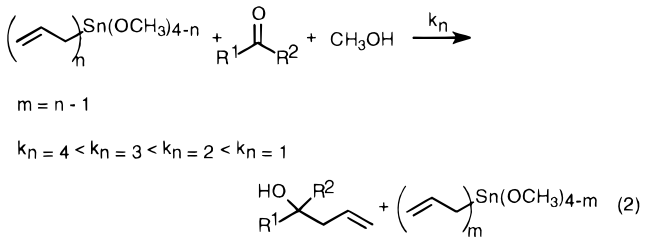
Figure 2. Possible transition state for the methanol-mediated addition of allylic stannanes to carbonyl compounds.

allylic stannane via formation of an ionized intermediate. Rather, we suggest that hydrogen bonding between the carbonyl compound and methanol is the predominant activating effect, and an eight-membered transition state involving methanol coordination to tin and hydrogen bonding to the carbonyl compound can be invoked (Figure 2). A similar mechanism can be used to account for the corresponding HCl-mediated reaction of **1b** with carbonyl compounds.

The kinetic scheme depicted in eq 2 is consistent with the results from our spectroscopic monitoring of the reactions in methanol (Figure 1) and from what is known of the reactivity of allylic stannanes bearing electron-withdrawing groups on tin. Each substitution of alkoxide for an allyl group would be expected to yield a more reactive allylating species.[18] The kinetic profile of this reaction, i.e. rapid rate acceleration after a lag period, is difficult to explain but may result from autocatalysis provided by build up in the concentration of partially soluble tin(IV) methoxide oligomers. This autocatalysis does not occur in the corresponding reaction of **1a** for which the trimethyltin methoxide produced is much less Lewis acidic. The presence of a minute amount of a Lewis acidic impurity would account for the decreased lag time in reactions of older, slightly cloudy samples of **1b**.

Experimental Section

Materials. Allyltrimethylstannane (**1a**) was prepared from allylmagnesium bromide and trimethyltin chloride as previously described.[19] Tetraallyltin **1b** was purchased from Aldrich and distilled immediately before use. Carbonyl compound **2e** was prepared by periodate oxidation of 1,2:5,6-diisopropylidene-D-mannitol as previously described.[20] All other carbonyl compounds were purchased from Aldrich and distilled immediately before use.



$m = n - 1$

$k_{n=4} < k_{n=3} < k_{n=2} < k_{n=1}$

(2)

General Procedure for Allylations with 1b. Carbonyl compounds (**2**, 10 mmol) and tetraallyltin (**1b**, 2.5 mmol) were dissolved in methanol (10 mL) and stirred at either 30 °C or at reflux for up to 24 h. The methanol solution was then poured into water (50 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo* or by fractional distillation for particularly volatile products (e.g. **3a**). The crude product **3** was purified by kugelrohr distillation or filtration through a short bed of silica gel (dichloromethane).

Competition Experiments. The competitive allylation experiments were conducted according to the standard procedure above with aldehyde (1.0 M), ketone (1.0 M), and **1b** (0.25 M) at 30 °C for 16 h. The proportion of each allylated product **3** in the mixture was determined by ^1H and ^{13}C NMR spectroscopy.

Allylation Products. Homoallylic alcohols **2** obtained by allylation of aldehydes and ketones were characterized by ^1H and ^{13}C NMR spectroscopy and comparison with literature values: 2-methyl-5-hexen-3-ol (**3a**),[21] 1-cyclohexyl-3-butenol (**3b**),[21] 1-phenyl-3-butenol (**3c**),[21] 2-phenyl-4-penten-2-ol (**3d**),[22] 1,2-*O* -isopropylidene-5-hexene-1,2,3-triol (**3e**),[13] ethyl 2-hydroxy-2-methyl-4-pentenoate (**3f**),[23] 3-methyl-5-hexen-3-ol (**3g**),[24] 1-allylcyclohexanol (**3h**),[21] 2-phenyl-4-penten-2-ol (**3j**).[25]

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