Organometallic Reactions in Aqueous Media. The Nature of the Organotin Intermediate in the Tin-Mediated Allylation of Carbonyl Compounds

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Allyl bromide and tin reacted in aqueous media to give first allyltin(II) bromide (**5**) and then diallyltin dibromide (**4**). Either organotin intermediate can react with carbonyl compounds to give the corresponding homoallylic alcohols. Competitive experiment showed that **5** was more reactive than **4**.

Introduction

The classical Barbier reaction in which an organic halide couples with a carbonyl compound mediated by a metal to give the corresponding alcohol (Scheme 1), though discovered a century ago, has not been used extensively in organic synthesis despite its simplicity.[1] Its application in synthesis has been supplanted largely by the Grignard reaction and other similar organometallic reactions. This is because a host of side reactions, such as reduction and/or pinacol coupling of the carbonyl compound and reduction and/or Wurtz coupling of the halide, can also be mediated by the metal under the same conditions. The Grignard reaction, even with an extra step in the preparation of the Grignard reagent, largely avoids such complications. Recently, we and others have developed Barbier type reactions in *aqueous media*.[2] The use of aqueous medium has a number of advantages.[3] The use of inflammable and anhydrous solvents can be avoided. Many reactive functional groups, such as hydroxy and carboxylic functions, do not require the protection−deprotection protocol in such reactions. Many water-soluble compounds, such as carbohydrates, do not need to be converted into their derivatives and can be reacted directly.[4] Finally, it may also offer the advantage that the reaction conditions may be environmentally benign by reducing the burden of solvent disposal.[5] The metals that have been used in the aqueous Barbier type reactions include zinc,[6] indium,[7] bismuth,[8] and tin.[9] Of these metals, tin offers the greatest potential for industrial

Scheme 1

Scheme 2
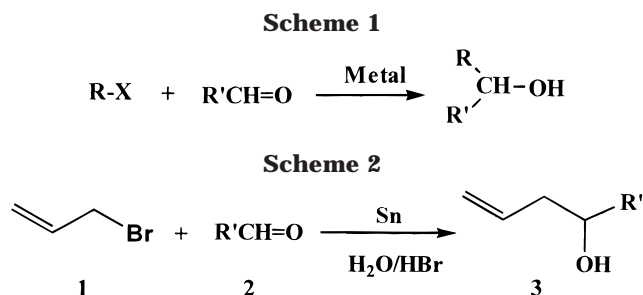
application because of its relative low cost, ready availability, and relatively low toxicity.[10] However, the side reactions of reduction and coupling, encountered in the classical Barbier reactions in organic solvents, are present in the aqueous media of tin-mediated allylation of carbonyl compounds. We are therefore interested in learning about the nature of the possible intermediates in the tin-mediated reactions with the expectation that a stepwise process can be developed for the aqueous organometallic reactions similar to the classical Grignard reaction.

In 1983, Nokami et al. first reported on the successful coupling of allyl bromide (**1**) with carbonyl compound (**2**) mediated by tin to give the homoallylic alcohol (**3**) in water (Scheme 2).[9a] However, the reaction requires a catalytic amount of hydrobromic acid. Later on, the addition of metallic aluminum powder or foil was found to improve the yield of the product dramatically.[9b] On the other hand, Wu and co-workers found that higher temperature can be used to replace aluminum.[9d] Alternatively, Luche found that the reaction can be performed in the absence of aluminum or hydrobromic acid by the use of ultrasonic irradiation together with saturated aqueous NH_4Cl/THF solution.[9e] Various mechanisms

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(10) See: (a) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987. (b) Smith, P. J. *Toxicological Data on Organotin Compounds*; International Tin Research Inst.: London, 1978.

Table 1. Allylation Reaction of Carbonyl Compounds by Diallyltin Dibromide in Water

Entry	Carbonyl Compounds(2)	Products(3)	Yield(%)
1	PhCHO	**6**	95
2		**7**	99
3	NO₂—CHO	**8**	97
4		**9**	95
5	OHCCHO	**10**	95
6	Ph—CHO	**11**	99[a]
7	Cl—CHO	**12**	99
8	Ph(Me)C=O	**13**	77
9	Et(Me)C=O	**14**	97
10	(n-Bu)₂C=O	**15**	99
11		**16**	95[b]
12	BrCH₂COCOOEt	**17**	95
13	D-Mannose	**18**	71[c]
14	L-Arabinose	**19**	84[d]

[a] No 1,4-addition product was observed. [b] *anti:syn* = 10:1 was determined from NMR, and relative configurations were determined from NOE. [c] Diastereomeration = 80/20. Relative configurations were not assigned. [d] Diastereomeration = 76/24. Relative configurations were not assigned.

have been proposed for the aqueous Barbier reactions, including the intermediacy of a radical,[10] radical anion,[11] and an allylmetal species.[12] In the latter case, it has been presumed that diallyltin dibromide (**4**) is the organometallic intermediate in the tin-mediated allylation reactions; however, no experimental proof has been offered.[13,14]

Results and Discussion

(a) Diallyltin Dibromide. We found that diallyltin dibromide[15] is an efficient allylation reagent of carbonyl compounds in aqueous media to give the corresponding homoallylic alcohols (Table 1). Either aldehydes or ke-

tones can be used, and the allylation products were usually obtained cleanly with high yields. With α,β-unsaturated aldehydes such as cinnamaldehyde, only the 1,2-addition product **11** was obtained (entry 6). The following typical experimental procedures were used: to a mixture of carbonyl compound (1 mmol) in 3–5 mL of water was added diallyltin dibromide (1 mmol) at room temperature. The mixture was stirred overnight and quenched with 1 N HCl solution (1 mL). The mixture was extracted with ether (3 × 10 mL), and the combined organic layer was washed with saturated aqueous NaHCO₃ solution and dried. The organic solvent was evaporated, and the crude product was purified by flash chromatography on silica gel. Less diallyltin dibromide (to 0.5 mmol) can be used. However, the reaction required longer time and gave lower yield after reacting overnight.

To prove that diallyltin dibromide is the putative reactive intermediate, we performed the following experiments. First, diallyltin dibromide (**4**) was found to be stable in water at room-temperature overnight. The ¹H NMR of **4** in D₂O remained unchanged[16] throughout this period, and the compound can be recovered by extraction with chloroform. This suggests that it is **4**, not its hydrolyzed derivatives, which reacts with the carbonyl compounds in water. Second, the reaction does not require acid catalyst, which may have been present in catalytic amount due to the partial hydrolysis of **4** in water. This is demonstrated by the fact that the reaction proceeded readily and gave the same yield when the reaction was carried out in a buffered aqueous solution at pH 9.

(b) NMR Investigations. While these results establish that **4** can react with carbonyl compounds in water to give the homoallylic alcohols, they do not by themselves establish that the aqueous Barbier reaction with tin has **4** as the necessary intermediate. Indeed, when allyl bromide and tin were stirred in D₂O at room temperature, and the reaction mixture was followed by ¹H NMR, no diallyltin dibromide was detected (Figure 1A). However, when the mixture was warmed to 60 °C, a new compound was formed as indicated by the appearance of a signal at 2.2 ppm (doublet) in the ¹H NMR, which was however not due to compound **4** (Figure 1B). At higher temperature (60–80 °C), compound **4** began to be formed and its characteristic allylic proton signal at 2.5 ppm was readily observed in the NMR (Figure 1C,D).[16] We assigned the signal at 2.2 ppm to allyltin(II) bromide (**5**) by comparison with an authentic sample prepared independently[17] (Figure 2D). The formation of **5** and then **4** from tin and allyl bromide in water at room temperature can be accelerated by the addition of a catalytic amount of HBr, again as observed by NMR[18] (Figure 1E,F). At the end of 8 h, all allyl bromide was consumed and only **4** and **5** were observed in the solution.

(c) Interconversion between Allyltin(II) Bromide (4) and Diallyltin Dibromide (5). The above experiments support strongly that the aqueous Barbier reaction with tin proceeds through allyltin(II) bromide (**5**) and diallyltin dibromide (**4**) as the organometallic intermedi-

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(14) In ref 9a, Nokami et al. showed that diallyltin dibromide (**4**) reacted with benzaldehyde in ether–water mixed solvent, but the intermediacy of **4** in the aqueous Barbier reaction was assumed but not demonstrated.

(15) Prepared from allyl bromide and tin powder in boiling toluene with mercuric chloride as catalyst. Sisido, K.; Takeda, Y. *J. Org. Chem.* **1961**, *26*, 2301.

(16) Compound **4** showed a characteristic methylene hydrogen doublet at 2.5 ppm in D₂O.

(17) Prepared by the reaction of allylmagnesium bromide with tin-(II) chloride in ether. Compound **5** was dissolved in D₂O, and the ¹H NMR spectra were compared. Compound **5** showed the characteristic methylene proton doublet at 2.2 ppm in D₂O.

(18) The formation of **5** and **4** can also be catalyzed by aluminum powder as observed by NMR.
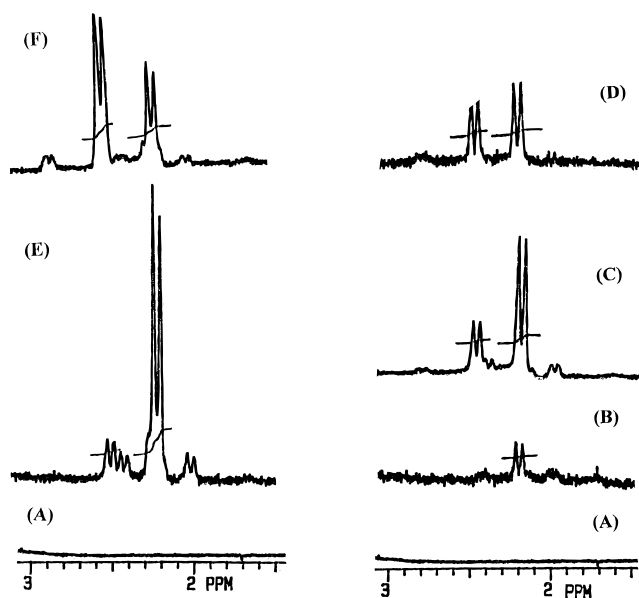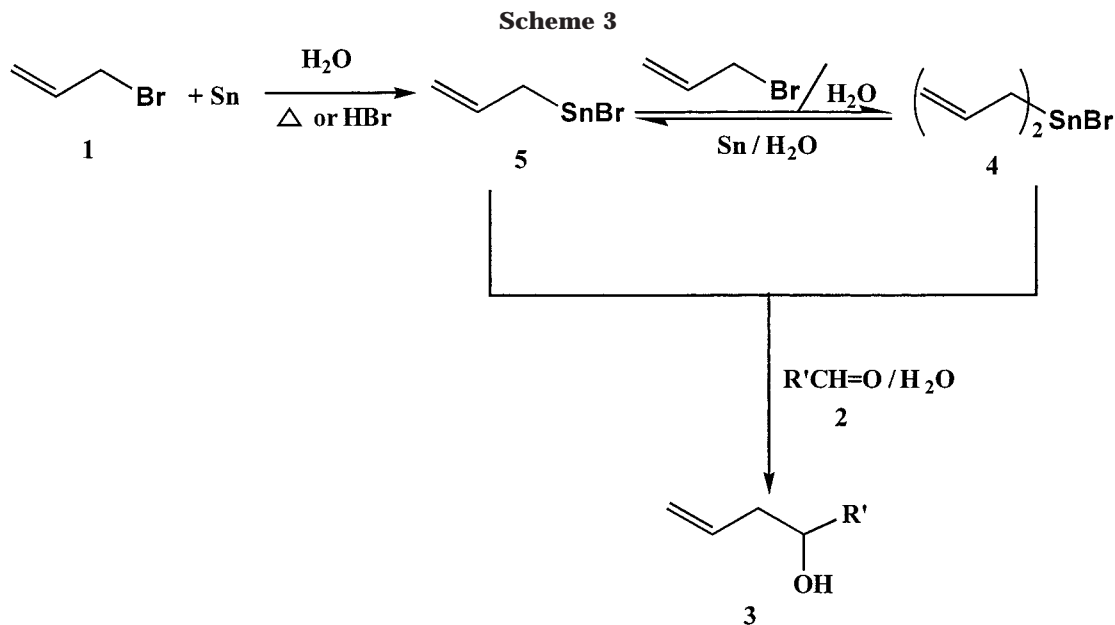
Scheme 3

Figure 1. Partial ^{1}H NMR spectra of allyl bromide and tin stirred in D$_2$O solution. (A) At room temperature, 5 min to overnight, no signal from 1.0 to 3.0 ppm; (B) 5 min at 60 °C; (C) 5 min at 70 °C; (D) 5 min at 80 °C; (E) 30 min at room temperature with HBr as catalyst; (F) 10 h at room temperature with HBr as catalyst.

ates according to Scheme 3. The first step leading to the formation of **5** is the slow step and requires heating (or ultrasonic irradiation) or the use of catalyst (HBr or Al). The conversion of **5** to **4** depends on the relative amount of allyl bromide and tin in the reaction system. We demonstrated that a solution of **4** in D$_2$O (Figure 2A) could be converted into a mixture of **5** and **4** by the addition of tin metal to the solution as observed by ^{1}H NMR (Figure 2B,C). Furthermore, compound **5** can also react with benzaldehyde in water to give the corresponding homoallylic alcohol. In a competitive experiment, an equal mixture of **4** and **5** in D$_2$O was quenched with 0.5 equiv of benzaldehyde. After 0.5 h, the reaction mixture was examined by ^{1}H NMR; all the benzaldehyde had been converted to the product **6** but with unreacted compound **4** still remaining. This suggests that between **4** and **5**,
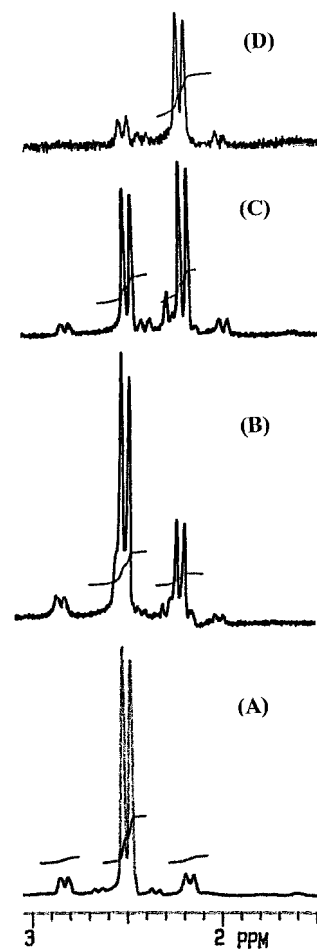
Figure 2. Partial ^{1}H NMR spectra of diallyltin dibromide and allyltin(II) bromide in D$_2$O solution. (A) Diallyltin dibromide alone in D$_2$O at room temperature overnight; (B) diallyltin dibromide with metallic tin powder in D$_2$O at room temperature for 5 min; (C) same as B but for 24 h; (D) allyltin(II) bromide prepared from allyl magnesium bromide and tin(II) chloride in ether, and extracted into D$_2$O for NMR.

compound **5** is the more reactive toward the carbonyl compounds.[19]

(d) Synthetic Implications. These results demonstrate quite convincingly that both allyltin(I) bromide (**5**) and diallyltin dibromide (**4**) are formed as organotin intermediates in the aqueous Barbier reaction of allyl bromide and tin. Either **4** or **5** can react with carbonyl compounds to give the corresponding homoallylic alcohols. These results however do not eliminate the possibility of a parallel process of metal surface mediated radical or radical anion reactions.[20] Nevertheless, the understanding that the reaction can proceed through an organotin intermediate has useful synthetic applications. For example, *p*-nitrobenzaldehyde is known to be reduced under the metallic tin conditions and cannot undergo the aqueous Barbier allylation reaction.[21] However, diallyltin dibromide (**4**) cleanly allylated *p*-nitrobenzaldehyde to the corresponding alcohol **8** (Table 1, entry 3) in nearly quantitative yield. Another example is that α-bromocarbonyl compounds are usually reduced by metallic tin.[22] However, compound **4** reacted cleanly with ethyl α-bromopyruvate to give the allylation product **17** in excellent yield (entry 12). Finally, in the aqueous Barbier reaction with carbohydrate compounds, because the aldehydic form of the carbohydrate is often present in low concentration in its equilibrium with the cyclic acetal form, the reaction may sometimes proceed in low yield.[23] The use of a higher concentration of preformed diallyltin dibromide can improve the yield of the allylation reaction as demonstrated in the formation of compounds **18** and **19** (entries 13 and 14). Finally, reactive α-dicarbonyl compounds such as glyoxal reacted under the aqueous Barbier conditions to give complex mixtures of products due to the ease of the carbonyl functions to undergo reduction and pinacol coupling mediated by metal. However, with diallyltin dibromide, the allylation reaction (entry 5) proceeded uneventfully to give the diol **10** with good diastereoselectivity in high yields.

Experimental Section

Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F$_{254}$ plastic-backed plates and was visualized by dipping into a solution of ammonium molybdate (2.5 g) and ceric sulfate (1 g) in concentrated H$_2$SO$_4$/H$_2$O (10 mL/90 mL) and heated with a heat gun.

Solvents were reagent grade unless otherwise specified. THF was dried and distilled from Na. Tin powder (150 mesh, 99.99%, 100 g packing) was freshly opened for use. Carbonyl compounds were checked for purity by ^{1}H NMR and were distillated or recrystallized if impure. Diallyltin dibromide was prepared following the method reported in the literature.[24]

General Method for Allylation of Carbonyl Compounds in Aqueous Media. To a mixture of carbonyl compound (1 mmol) in water (3−5 mL) was added diallytin dibromide (0.6−1 mmol) at room temperature. The mixture was stirred overnight and quenched with 1 N HCl (1 mL) solution. The mixture was extracted with ether (3 × 10 mL), and the combined organic layer was washed with saturated aqueous NaHCO$_3$ solution and dried. The organic solvent was evaporated, and the product homoallylic alcohol was usually obtained pure according to ^{1}H NMR and can be further purified by flash chromatography on silica gel if necessary. All the products except **17** obtained in this work are known compounds, so the structures were determined by comparison of their ^{1}H and ^{13}C NMR spectral data with those given in the literatures: α-2-propenylbenzenemethanol[25] (**6**), 1-decene-4-ol[26] (**7**), 4-chloro-α-2-propenylbenzenemethanol[27] (**12**), α-propenylcyclohexanemethanol[28] (**9**), 1,7-octadiene-4,5-diol[29] (**10**), 1-phenyl-1,5-hexadien-3-ol[21] (**11**), α-methyl-α-2-propenylbenzenemethanol[30] (**13**), 3-methyl-5-hexen-3-ol[30] (**14**), 5-(2-propenyl)-5-nonanol[31] (**15**), 2-methyl-1-(2-propenyl)cyclohexanol[32] (**16**), *p*-nitro-α-2-propenylbenzenemethanol[33] (**8**), 1,2,3-trideoxy-D-mann-non-1-enitol[34] (**18**), 1,2,3-trideoxy-L-arabino-oct-1-enitol[19] (**19**).

4-Pentenoic acid, 2-hydroxy-2-(bromo-)methylene, ethyl ester (17): ^{1}H NMR (200 MHz CDCl$_3$) δ 5.78(m, 1H), 5.12-(m, 2H), 4.25(q, *J* = 7.30 Hz, 2H), 3.45−3.60(m, 2H), 3.55(s, 1H), 2.52(m, 2H), 1.38(t, *J* = 7.30 Hz, 3H); ^{13}C NMR (50 MHz CDCl$_3$) δ 172.54, 131.56, 119.84, 77.60, 63.52, 43.23,40.28, 15.85; IR (KBr) ν(cm^{-1}) 3522, 2982, 1736, 1438,1292, 1230, 1182, 1095, 919, 648 MS(CI) *m/z* 237 (M + 1); HRMS(CI) calcd for C$_8$H$_{14}$O$_3$Br (M + H) 237.01263, found 237.01271.

(19) Tetraallytin also reacts with carbonyl compounds in aqueous media to give the homoallylic alcohols. However, the reaction requires Lewis acid catalyst. Hachiya, I.; Kobayashi, S. *J. Org. Chem.* **1993**, *58*, 6958.

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