# Ultrasound-promoted palladium-catalyzed carbonyl allylation by allylic alcohols with tin(II) chloride in non-polar solvents

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## Abstract

Heterogeneous ultrasound-promoted palladium-catalyzed carbonyl allylation by $\gamma$-substituted allylic alcohols with tin(II) chloride in non-polar solvents such as diethyl ether, diisopropyl ether and toluene was carried out stepwise (first, the formation of allylic tin intermediates by ultrasonication, followed by the allylation of aldehydes by the intermediates) to produce 1,4-disubstituted 3-buten-1-ols regioselectively in moderate yields. The regioselectivity ($\alpha$-selection) in the ultrasound-promoted reaction is the inverse of that ($\gamma$-selection) in the homogeneous palladium-catalyzed carbonyl allylation in polar solvents such as 1,3-dimethyl-2-imidazolidinone, DMF, DMSO and ethylene glycol. The more bulky the $\gamma$-substituent, the higher is the $\alpha$-regioselectivity.

*Key words:* Catalysis; Allylation; Ultrasound; Palladium complexes; Tin complexes; Regioselection

## Introduction

The allylation of aldehydes (carbonyl allylation) with $\gamma$-substituted allylmetal reagents, derived from $\gamma$-substituted allylic halides with metals or metal halides such as Mg, Ti, Cr, Mn, Zn, Si, Sn, Sb, Bi or Sm, usually occurs at $\gamma$-position of the allylmetal reagents with a diastereoselectivity [1]. $\gamma$-Substituted allylic halides have been recently found to add selectively at $\alpha$-position to aldehydes with metals such as Mg/$AlCl_3$ and Ba [2]. We have reported palladium-catalyzed carbonyl allylation by allylic alcohols with tin(II) chloride, which is superior to the allylation by allylic halides in the ease of preparation and storage of starting allylic compounds [3]. The palladium-catalyzed carbonyl allylation by $\gamma$-substituted allylic alcohols in polar solvents, such as 1,3-dimethyl-2-imidazolidinone (DMI), DMF, DMSO and ethylene glycol (EG), has led to the same $\gamma$-regioselective addition as that of the usual carbonyl allylation by $\gamma$-substituted allylic halides [4]. The regioselectivities in the palladium-catalyzed carbonyl allylation have proved to correlate with the dielectric constants of solvents; the lower the polarity of the solvents, the higher is the $\alpha$-regioselectivity. The reaction in non-polar solvents such as diethyl ether, chloroform, dichloromethane and toluene is very slow, probably due to the low solubilities of tin(II) chloride in those solvents. Ultrasound has been used to activate metals such as lithium, magnesium, aluminium and zinc, accelerating their organometallic reactions [5]. We hoped to enhance the solubility of tin(II) chloride locally in non-polar solvents by means of ultrasound irradiation. We here report an ultrasound-promotion method of palladium-catalyzed carbonyl allylation accompanying $\alpha$-regioselection by allylic alcohols with tin(II) chloride in non-polar solvents, cf. ref. 6.

## Experimental

Unless otherwise noted, all common reagents were used as obtained from commercial suppliers without further purification. All solvents were dried over desiccant and were distilled before being used. Bis(benzonitrile)dichloropalladium(II) was prepared by the literature procedure [7]. (*E*)-3-Cyclohexyl-2-propen-1-ol was prepared by the reaction of cyclohexanecarbaldehyde and ethyl diethylphosphonoacetate with t-BuOK, followed by reduction with DIBAL [8]. Ultrasonication was carried out by internal irradiation using an ultrasonic disruptor Tomy UD-201. $^1H$ NMR spectra were recorded on a Jeol GX-270 (270 MHz) spectrometer in $CDCl_3$. IR spectra were recorded on a Jeol JIR-RFX 3001 FTIR spectrometer. Gas chromato-

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graphic analysis (GC) was performed on either an Ohkura model 103 or a Shimadzu GC-14BPFsc (PEG 20M capillary column, 0.25 mmX30 m). Purification of products was carried out by means of column chromatography (Merck Silica gel 60 Art. 7734), preparative TLC (Harrison centrifugal thin-layer chromatotron, Merck silica gel 60 PF$_{254}$ Art. 7749) or HPLC (Japan Analytical Industry Co. Ltd. LC-908).

### *Ultrasound-promoted palladium-catalyzed allylation of benzaldehyde (2) by (E)-2-buten-1-ol (1) with tin(II) chloride*

*Method* A. To a solution of tin(II) chloride (0.95 g, 5 mmol), (*E*)-2-buten-1-ol (**1**, 0.22 g, 3 mmol) and benzaldehyde (2, 0.11 g, 1 mmol) in diethyl ether (5 ml) was added bis(benzonitrile)dichloropalladium (0.008 g, 0.02 mmol). Ultrasonic irradiation of the solution was carried out for 4 h at – 10 “C. The reaction mixture was diluted with ether (80 ml)-dichloromethane (40 ml) and was washed successively with aqueous 10% HCl solution (10 ml), water (10 ml) and brine (10 ml). The extracts were dried over anhydrous MgSO$_4$. Evaporation of solvent and purification by column chromatography on silica gel (hexane/ethyl acetate = 7/1) afforded 0.091 g (0.56 mmol, 56%) of a mixture of 1-phenyl-3-penten-1-ol and 2-methyl-1-phenyl-3-buten-1-01.

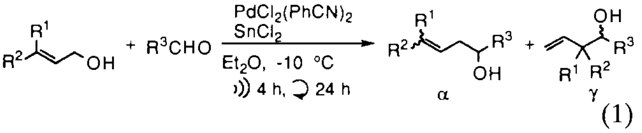
*Method B*. To a solution of tin(II) chloride (0.95 g, 5 mmol) and (*E*)-2-buten-1-ol (**1**, **0.22** g, 3 mmol) in diethyl ether (5 ml) was added bis(benzonitrile)dichloropalladium (0.008 g, 0.02 mmol). Ultrasonic irradiation of the solution was carried out for 4 h at – 10 °C, and then benzaldehyde (2, 0.11 g, 1 mmol) was added to the solution. After being stirred for 24 h, the reaction mixture was treated as in method A to give 0.12 g (0.76 mmol, 76%) of a mixture of 1-phenyl-3-penten-1-ol and 2-methyl-1-phenyl-3-buten-1-ol.

Ultrasound-promoted palladium-catalyzed carbonyl allylation by some allylic alcohols was carried out by method B. The structure of the products was determined by comparison of the $^1$H NMR and IR spectra with those from authentic samples prepared by palladium-catalyzed carbonyl allylation in THF without ultrasonication [4]. Regioisomer ratios, *E*,*Z*-isomer ratios, and diastereomer ratios were determined by $^1$H NMR and GC analysis (accuracy ± 1%).

## Results and discussion

### *Relation between regiochemistry and dielectric constant of solvents without ultrasonication*

The regioselectivity in palladium-catalyzed carbonyl allylation by allylic alcohols with tin(II) chloride correlates with the dielectric constant of the solvents; the lower the polarity of the solvents, the higher is the $\alpha$-regioselectivity [4]. Some representative results of the reaction of (*E*)-2-buten-1-ol (**1**) with benzaldehyde (2) at 25 °C are shown in Table 1 (eqn. (1)).



(1)

High y-regioselection with high yield in the carbonyl allylation was established by using polar solvents such as DMF and THF/H$_2$O (entries 2 and 5). The carbonyl allylation with $\alpha$-regioselectivity in a non-polar solvent such as diethyl ether is very slow, which is probably attributable to the low solubility of tin(II) chloride in diethyl ether (entry 6). The acceleration of the reaction with a-regioselectivity was thus carried out by the addition of a small amount of various polar solvents to the ethereal solution. Alcohols such as methanol, ethanol and butanol were effective cosolvents leading to a-regioselection in moderate yields after long stirring (entries 7-9). The a-regioselection in non-polar solvents may be induced via a coordination of unconfirmed tin oxide prepared *in situ* or excess tin(II) chloride to tin of (E)-2-butenyltrichlorotin intermediate [4], as illustrated in Scheme 1 [2a].

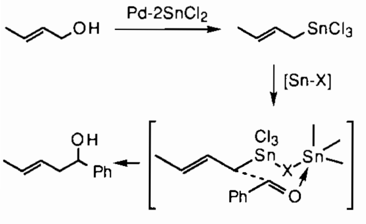
### *Ultrasound promotion retaining $\alpha$-regioselectivity in non-polar solvents*

Ultrasound promotion of the palladium-catalyzed carbonyl allylation with $\alpha$-regioselectivity in non-polar solvents was investigated by using (*E*)-2-buten-1-ol (**1**) as an allylic alcohol and benzaldehyde (2) as an aldehyde. The results are summarized in Table 2. The ultrasound-promoted allylation was carried out by two methods: (i) ultrasonic irradiation at – 10 °C for 4 h to the solution of **1**, 2, SnCl$_2$ and PdCl$_2$(PhCN)$_2$ (method A); (ii) ultrasonic irradiation at – 10 °C for 2-8 h to the solution of **1**, SnCl$_2$ and PdCl$_2$(PhCN)$_2$ followed by addition of 2 at 25 °C and then stirring of the mixture at 25 °C for 24 h (method B). The allylation in method A did not occur in hydrocarbons such as hexane and toluene, but did occur in ethers such as dibutyl ether, diisopropyl ether and diethyl ether (entries 1, 2, 3, 5 and 9). Method A in ethers led to $\alpha$-regioselection, but the yields were not so high. Method B was more efficient than method A in any ether used (entries 4, 6 and 10). The yield of 3 proved to be dependent upon the ultrasonication time in both methods (entries 7-12). Prolonged ultrasonication (for more than 4 h) lowered the yield in both of them. The lowering of the yield could be attributed to the decomposition of 3 in method A and the decomposition of **1** and/or 2-butenyltin intermediate in method B by prolonged ultrasonication. The structure of the decomposition by-products was

TABLE 1. Dependence of regioselection on solvent in the allylation of **2** by **1**[a]

| Entry | Solvent (ml) | Dielectric constant | Time (h) | Yield[b] of **3** (%) | $\alpha$:$\gamma$[c] |
|---|---|---|---|---|---|
| 1 | DMSO(3)[d] | 46.6 | 136 | 34 | 0:100 |
| 2 | DMF(3)[d] | 36.7 | 63 | 89 | 0:100 |
| 3 | n-BuOH(3)[d] | 17.1 | 64 | 72 | 6:94 |
| 4 | THF(3)[d] | 7.6 | 25 | 72 | 53:47 |
| 5 | THF(3)/$H_2O$(0.5) | | 6 | 74 | 0:100 |
| 6 | $Et_2O$(3)[d] | 4.2 | 72 | 8 | 94:6 |
| 7 | $Et_2O$(3)/MeOH(0.3) | | 168 | 41 | 85:15 |
| 8 | $Et_2O$(3)/EtOH(0.3) | | 168 | 76 | 72:28 |
| 9 | $Et_2O$(3)/BuOH(0.7) | | 168 | 46 | 85:15 |

[a]The allylation of benzaldehyde (**2**, 1 mmol) by (*E*)-2-buten-1-ol (**1**, 1.5 mmol) was carried out with bis(benzonitrile)dichloropalladium (0.02 mmol) and tin(II) chloride (3 mmol) at 25 °C. [b]Isolated yields of the mixture of regioisomers based on benzaldehyde. [c]The ratio was determined by $^1H$ NMR (GX-270) and GC (capillary column: PEG 20M, 0.25 mm×3 m, 155 °C). [d]See ref. 4.



Scheme 1.

not confirmed. The addition of other non-polar solvents, particularly toluene, to the ethereal solution did not give such good yields, but did enhance $\alpha$-regioselectivity (entries 15 and 16). Yield and $\alpha$-regioselectivity were inversely affected by changes in the ratio of **1** to **2** in diethyl ether (method A, ultrasonication time 4 h); in the smaller ratio, $\alpha$-regioselectivity was high but yield was low, and in the larger ratio, yield was high but $\alpha$-regioselectivity was low, as shown in Table 3. The lowering of $\alpha$-regioselectivity in entry 4 was presumably caused by an increase of solvent polarity which accompanied the addition of excess starting alcohol **1**.

### *Application of the ultrasound promotion to various palladium-catalyzed carbonyl allylations*

Ultrasound-promoted palladium-catalyzed allylation of some aldehydes with some allylic alcohols was carried out under the same conditions as those of entry 10 in Table 2 (eqn. (2)). The results are summarized in

TABLE 2. Ultrasonic promotion in the allylation of **2** by **1** in various non-polar solvents

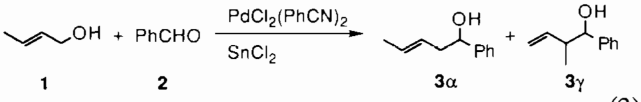
| Entry | Solvent | Dielectric constant | Method[a] | Time[b] (h) | Yield[c] of **3** (%) | $\alpha$:$\gamma$[d] |
|---|---|---|---|---|---|---|
| 1 | hexane | 1.89 | A | 4 | 0 | |
| 2 | toluene | 2.24 | A | 4 | 0 | |
| 3 | $Bu_2O$ | 3.06 | A | 4 | 24 | 68:32 |
| 4 | $Bu_2O$ | 3.06 | B | 4 | 30 | 65:35 |
| 5 | i-$Pr_2O$ | 4.99 | A | 4 | 10 | 72:28 |
| 6 | i-$Pr_2O$ | 4.99 | B | 4 | 56 | 67:33 |
| 7 | $Et_2O$ | 4.20 | A | 2 | 17 | 82:18 |
| 8 | $Et_2O$ | 4.20 | B | 2 | 38 | 83:17 |
| 9 | $Et_2O$ | 4.20 | A | 4 | 56 | 78:22 |
| 10 | $Et_2O$ | 4.20 | B | 4 | 76 | 75:25 |
| 11 | $Et_2O$ | 4.20 | A | 8 | 46 | 80:20 |
| 12 | $Et_2O$ | 4.20 | B | 8 | 44 | 81:19 |
| 13 | $Et_2O$–hexane(1:1) | | A | 4 | 15 | 78:22 |
| 14 | $Et_2O$–dioxane(1:1) | | A | 4 | 20 | 82:18 |
| 15 | $Et_2O$–toluene(1:1) | | A | 4 | 21 | 89:11 |
| 16 | $Et_2O$–toluene(4:1) | | A | 4 | 34 | 92:8 |

[a]Method A: ultrasonic irradiation at −10 °C to the solution of **1** (3 mmol), **2** (1 mmol), $SnCl_2$ (5 mmol) and $PdCl_2(PhCN)_2$ (0.02 mmol). Method B: ultrasonic irradiation at −10 °C to the solution of **1** (3 mmol), $SnCl_2$ (5 mmol), and $PdCl_2(PhCN)_2$ (0.02 mmol) followed by the addition of **2** (1 mmol) at 25 °C. [b]Ultrasonication time. [c]Isolated yields of the mixture of regioisomers based on benzaldehyde. [d]The ratio was determined by $^1H$ NMR (GX-270) and GC (capillary column: PEG 20 M, 0.25 mm×3 m, 155 °C). $\alpha$: *E*/*Z* = 75/25–88/12. $\gamma$: *syn*/*anti* = 75/25–83/17.

TABLE 3. Influence of the ratio of **1** to **2** on yield and $\alpha$-regioselectivity

| Entry | **1** (mmol) | **2** (mmol) | Yield of **3** (%) | $\alpha$:$\gamma$[a] |
|---|---|---|---|---|
| 1 | 0.5 | 1 | 20[b] | 96:4 |
| 2 | 2 | 1 | 32[c] | 80:20 |
| 3 | 3 | 1 | 56[c] | 78:22 |
| 4 | 5 | 1 | 54[c] | 65:35 |

[a] The ratio was determined by $^1$H NMR (GX-270) and GC (capillary column: PEG 20 M, 0.25 mm×3 m, 155 °C). [b] Isolated yields of the mixture of regioisomers based on (*E*)-2-buten-1-ol. [c] Isolated yields of the mixture of regioisomers based on benzaldehyde.



(2)

Table 4. Aromatic aldehydes bearing an electron-withdrawing group caused the $\alpha$-regioselective allylation (entries 1–3), in contrast with aromatic aldehydes bearing electron-donating groups, such as salicylaldehyde, 4-methoxybenzaldehyde and piperonal. Aliphatic aldehydes such as cyclohexanecarbaldehyde and heptanal were also utilized for the ultrasound-promoted allylation; the $\alpha$-regioselectivities were quite high but the yields were low (entries 4 and 5). Allylic alcohols with a more bulky substituent than methyl at the $\gamma$-position exhibited high $\alpha$-regioselectivity (entries 6–8). The allylation of benzaldehyde with $\alpha$-substituted allylic alcohols, such as 3-buten-2-ol and linalool, produced the same products as those of the allylation with $\gamma$-substituted allylic alcohols, such as **1** and geraniol, in low yields (21%, $\alpha$:$\gamma$=90:10; 14%, $\alpha$:$\gamma$=99:1) respectively. In the case of linalool, non-polar by-products were detected by TLC but those structures were not determined. Secondary or tertiary alcohols such as 3-buten-2-ol and linalool may be more easily dehydrated than primary $\gamma$-substituted allylic alcohols by ultrasonication.

The ultrasound-promoted palladium-catalyzed carbonyl allylation by $\gamma$-substituted allylic alcohols in non-polar solvents thus exhibits $\alpha$-regioselectivity, the inverse of regioselectivity ($\gamma$) in the palladium-catalyzed carbonyl allylation in polar solvents.

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TABLE 4. Ultrasound-promoted palladium-catalyzed carbonyl allylation by method B[a]

| Entry | Alcohol | | Aldehyde $R^3$ | Yield[b] (%) | Ratio[c] | | |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | | | $\alpha$:$\gamma$ | *E*:*Z* | *syn*:*anti* |
| 1 | Me | H | $4\text{-}MeOOCC_6H_4$ | 83 | 84:16 | 86:14 | 48:52 |
| 2 | Me | H | $4\text{-}NCC_6H_4$ | 51 | 69:31 | 85:15 | 56:44 |
| 3 | Me | H | $4\text{-}ClC_6H_4$ | 49 | 66:34 | 93:7 | 57:43 |
| 4 | Me | H | $c\text{-}C_6H_{11}$ | 15 | 95:5 | 71:29 | 52:48 |
| 5 | Me | H | $C_6H_{13}$ | 23 | 91:9 | 56:44 | 84:16 |
| 6 | $CH_3(CH_2)_2$ | H | $C_6H_5$ | 57 | 98:2 | 67:33 | 70:30 |
| 7 | $Me_2C{=}CH(CH_2)_2$ | Me | $C_6H_5$ | 46 | 90:10 | [d] | [d] |
| 8 | $c\text{-}C_6H_{11}$ | H | $C_6H_5$ | 69 | 99:1 | 99:1 | [d] |

[a] Conditions: $PdCl_2(PhCN)_2$ 0.02 mmol, $SnCl_2$ 5 mmol, allylic alcohol 3 mmol, ultrasonication −10 °C, 4h; aldehyde 1 mmol, 25 °C, 24–48 h. [b] Isolated yields of the mixture of regioisomers based on aldehydes. [c] The ratio was determined by $^1$H NMR (GX-270) and/or GC (capillary column: PEG 20 M, 0.25 mm×3 m). [d] The ratio of stereoisomers (*E*:*Z* or *syn*:*anti*) was not confirmed.

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