

Highly Regioselective and Stereoselective Allylation of Aldehydes via Palladium-Catalyzed in Situ Hydrostannylation of Allenes

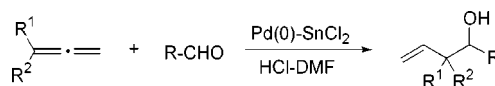
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ABSTRACT



Highly regio- and stereoselective allylation of aldehydes by allenes proceeds smoothly in aqueous/organic media in the presence of PdCl₂(PPh₃)₂, HCl, and SnCl₂. The reaction likely occurs via hydrostannylation of allenes and allylation of aldehydes by the in situ generated allyltrichlorotins to afford the final products.

Palladium-mediated substitution of allylic substrates is a powerful organometallic process for carbon–carbon and carbon–heteroatom bond formation.¹ The catalytic reactions generally proceed via the addition of a nucleophile to the electrophilic π -allylpalladium intermediate.² Recent studies on the transformation of a π -allylpalladium electrophilic species to a nucleophilic allyl group that is then used for the carbonyl allylation of aldehydes³ and ketones⁴ further widened the synthetic application of the π -allylpalladium chemistry. The charge reversal is achieved by reacting the π -allylpalladium intermediate with a low-valent metal compound to generate the corresponding allylic organometallic reagent.⁵ Examples of the low-valent metal (compounds) used included SnCl₂,³ Et₂Zn,⁴ SmI₂,⁶ Zn,⁷ In,⁸ and InI,⁹ etc.

Our interest in the development of new palladium-

mediated allene chemistry leads us to explore the possibility of employing allenes as the source for generating π -allylpalladium species¹⁰ and the application of the charge reversal method in the carbonyl allylation of aldehydes. Herein, we report a highly regio- and stereoselective carbonyl allylation of aldehydes mediated by the PdCl₂(PPh₃)₂–HCl–SnCl₂ system (Scheme 1). This new reaction proceeds smoothly in an aqueous/organic solvent system via an

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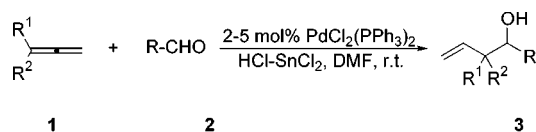
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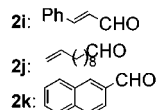
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Scheme 1



- 1a: R¹ = R² = CH₃
 1b: R¹ = Ph, R² = H
 1c: R¹ = *cyclo*-C₆H₉, R² = H
 1d: R¹ = *cyclo*-C₆H₁₁, R² = H
 1e: R¹ = *n*-C₄H₉, R² = H
 1f: R¹ = *m*-CH₃C₆H₄, R² = H
- 2a: R = Phenyl
 2b: R = 4-CN-C₆H₄
 2c: R = 4-Cl-C₆H₄
 2d: R = 2-F-C₆H₄
 2e: R = 3-Br-C₆H₄
 2f: R = 2,4-dichloro-C₆H₃
 2g: R = 4-MeC₆H₄
 2h: R = 2-OH-C₆H₄



unusual hydrostannylation of allenes and the allylation of aldehydes by the in situ generated allyltin species.

Treatment of 1,1-dimethylallene (**1a**) and SnCl₂ with benzaldehyde (**2a**), in a mixture of aqueous hydrochloric acid and DMF at ambient temperature in the presence of PdCl₂(PPh₃)₂ (2 mol %), leads to the formation of carbonyl allylation product **3a** in 95% isolated yield (Scheme 1). The reaction is completely regioselective, giving **3a** as the sole product. Control experiments show that no **3a** is formed in the absence of either SnCl₂ or hydrochloric acid (Table 1).

Table 1. Effect of Reaction Conditions on the Allylation of Benzaldehyde by 1,1-Dimethylallene (**1a**)^a

entry	catalyst	acid ^b	Sn ^x X ₂ (mmol)	yield (%)
1	no Pd catalyst	HCl	SnCl ₂	11
2	PdCl ₂ (PPh ₃) ₂	HCl		
3	PdCl ₂ (PPh ₃) ₂	HCl	SnCl ₂ (1)	18
4	PdCl ₂ (PPh ₃) ₂	HCl	SnCl ₂ (1.5)	28
5	PdCl ₂ (PPh ₃) ₂	HCl	SnCl ₂ (3)	>99
6	PdCl ₂ (PPh ₃) ₂	HCl ^d	SnCl ₂ (3)	95
7	PdCl ₂ (PPh ₂) ₂	PhCOOH ^e	SnCl ₂ (3)	22
8	PdCl ₂ (PPh ₃) ₂	CH ₃ COOH ^e	SnCl ₂ (3)	20
9	PdCl ₂ (pPh ₃) ₂	TsOH ^{e,f}	SnCl ₂ (3)	94
10	PdCl ₂ (CH ₃ CN) ₂	HCl	SnCl ₂ (3)	67
11	PdCl ₂ (PhCN) ₂	HCl	SnCl ₂ (3)	71
12	Pd(dba) ₂	HCl	SnCl ₂ (3)	58
13	PdCl ₂ (dppe)	HCl	SnCl ₂ (3)	16
14	PdCl ₂ (PPh ₃) ₂ /1PPh ₂	HCl	SnCl ₂ (3)	70
15	PdCl ₂ (PPh ₃) ₂ /2PPh ₃	HCl	SnCl ₂ (3)	54
16	PdCl ₂ (PPh ₃) ₂ /3PPh ₃	HCl	SnCl ₂ (3)	17
17 ^g	PdCl ₂ (PPh ₃) ₂	HCl	SnCl ₂ (3)	37
18	PdCl ₂ (PPh ₃) ₂	HCl	Sn(OAc) ₂ (3)	>99
19	PdCl ₂ (PPh ₃) ₂	HCl	SnSO ₄ (3)	77
20	PdCl ₂ (PPh ₃) ₂	HCl	SnO (3)	96

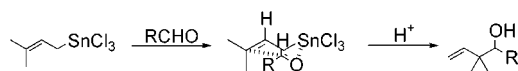
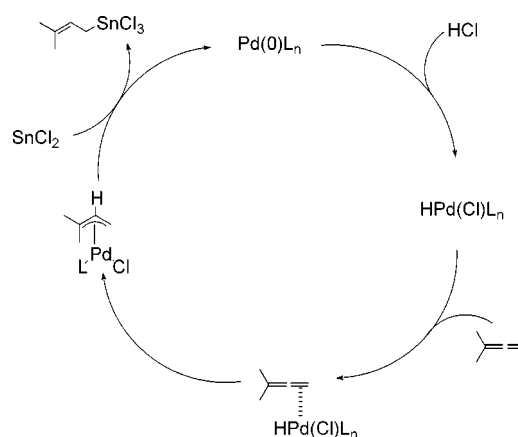
^a Reaction conditions: benzaldehyde (1.00 mmol), 1,1-dimethylallene (2.00 mmol), and Pd catalyst (0.020 mmol) in DMF (1.50 mL) at ambient temperature for 24 h. ^b Using 1.0 mL of HCl(aq). ^c The yields were determined by ¹H NMR analysis with an internal standard. ^d 0.50 mL. ^e 10.0 mmol. ^f *p*-Toluenesulfonic acid. ^g DMA was used as the solvent.

entry 2). A very low yield (11%) of **3a** is produced in the absence of palladium catalyst (Table 1, entry 1).

To further understand the nature of the present palladium-catalyzed reaction, the effect of acid, palladium catalyst, and the amount of PPh₃ and SnCl₂ on the product yield was examined. The results are listed in Table 1. In addition to hydrochloric acid, several other acids, *p*-toluenesulfonic acid, benzoic acid, and acetic acid, were tested for activity in the catalytic reaction. Only *p*-toluenesulfonic acid gave a high yield of product **3a** (entries 7–9). These observations clearly indicate that a strong acid is required in the reaction. Among the palladium complexes used, PdCl₂(PPh₃)₂, PdCl₂(CH₃CN)₂, PdCl₂(PhCN)₂, PdCl₂(dppe), and Pd(dba)₂, PdCl₂(PPh₃)₂ exhibits the highest catalytic activity for the carbonyl allylation (entries 5 and 10–13). Palladium complexes without PPh₃, PdCl₂(CH₃CN)₂, PdCl₂(PhCN)₂, and Pd(dba)₂ show lower catalytic activity. Presumably, this is due to the decomposition of these palladium complexes to the palladium metal as shown by the formation of a characteristic black precipitate (entries 10–12). However, addition of extra PPh₃ to the PdCl₂(PPh₃)₂ solution inhibits the catalytic activity (entries 14–16). The choice of solvent is crucial to the success of the catalytic reaction. DMF appears to be the best among the solvents employed. DMA is also effective, affording **3a** in 37% yield (entry 17). In other solvent systems, THF, toluene, CH₃CN, CH₂Cl₂, EtOH, DMSO, and DME, the reaction gives no desired allylation product. The amount of SnCl₂ used influences the yield of **3a** significantly, and 3 equiv of SnCl₂ is required to achieve high product yield (entries 3–5). Other tin(II) agents such as Sn(OAc)₂, SnSO₄, and SnO are also efficient and can be used as a substitute for SnCl₂ (entries 18–20).

On the basis of the above observations and the known palladium chemistry, we propose that this reaction proceeds in two stages (Scheme 2). The first stage is a palladium-catalyzed hydrostannylation of allene **1a**. Reduction of the palladium(II) complex to a palladium(0) species by tin(II)

Scheme 2

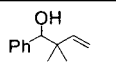
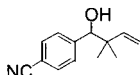
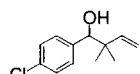
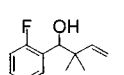
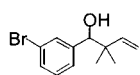
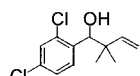
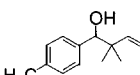
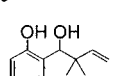
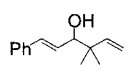
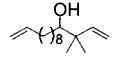
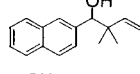
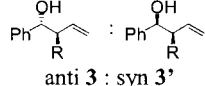


likely initiates the catalytic reaction. Protonation of the palladium(0) species and coordination of **1a** to the resulted Pd(II)-H species followed by insertion of **1a** to the Pd-H bond leads to the formation of a π -allylpalladium intermediate. Nucleophilic attack of SnCl₂ (or SnCl₃⁻) at the π -allyl group gives the hydrostannylation product, Me₂C=CHCH₂-SnCl₃, and regenerates the palladium(0) species. In the second stage, allylation of benzaldehyde (**2a**) by the in situ generated allyltin species Me₂C=CHCH₂SnCl₃ via a chair form six-membered ring transition state gives the final homoallylic alcohol **3a** and completes the reaction. The use of SnCl₂ as a nucleophile attacking the π -allylpalladium species is known.¹¹ A six-membered ring transition state has been proposed for the allylation of carbonyl groups by organometallic allylic reagents to account for the observed γ -addition products.¹²

Under reaction conditions similar to those for the formation of compound **3a**, reductive allylation of aromatic and aliphatic aldehydes (**2b-k**) by 1,1-dimethylallene (**1a**) proceeds smoothly to give the corresponding 1-substituted 2,2-dimethyl-3-buten-1-ols (**3b-k**) in 45–86% yields. The results are summarized in Table 2. Aromatic aldehydes bearing either an electron-withdrawing or an electron-donating group readily undergo the allylation. It is noteworthy that aromatic aldehydes with fluoro, chloro, or bromo substituents were allylated by **1a** without difficulty, indicating that oxidative addition of the aromatic-halogen bond to Pd(0) is slow relative to the allylation process (entries 3–6). Salicylaldehyde is also successfully allylated by **1a** (entry 8), but aliphatic aldehydes are less reactive toward **1a**, giving lower yields of the allylation products (entry 10).

Monosubstituted allenes RCHCCH₂ (R = Ph, **1b**; cyclopentyl, **1c**; cyclohexyl, **1d**; *n*-Bu, **1e**; *m*-CH₃C₆H₄, **1f**) also undergo hydrostannylation and then allylation with benzaldehyde (**2a**) to give the corresponding carbonyl allylation products (**3** and **3'**) with high regio- and stereoselectivity. Allylation occurs at the substituted terminal carbon of the allyl group exclusively, and the anti stereoisomer was observed as the major product for each reaction. For phenyl- and *m*-tolylallene, the anti/syn ratio is greater than 99/1 (entries 12 and 16). The ratio drops to 95/5 for cyclohexylallene, 63/37 for *n*-butylallene, and 64/36 for cyclopentylallene (entries 13–15). It appears that allenes bearing a bulky group strongly favor anti selectivity. The stereochemistry of these products was determined on the basis of comparison of the spectral data, particularly the ¹H NMR results, with those reported previously.¹³ On the basis of the proposed mechanism for the allylation of aldehyde, the formation of an anti stereoisomer is probably via the chair form six-

Table 2. Results of Allylation of Aldehydes by Allenes^a

entry	Allene	Aldehyde	Product	Yield (%) ^b (3 : 3')
1	1a	2a		3a 95
2	1a	2b		3b 68
3	1a	2c		3c 52
4	1a	2d		3d 86
5	1a	2e		3e 78
6	1a	2f		3f 68
7	1a	2g		3g 83
8	1a	2h		3h 66
9	1a	2i		3i 75
10	1a	2j		3j 54
11	1a	2k		3k 45
				
12	1b	2a	3l : 3l' (R: Ph)	72 (>99:1)
13	1c	2a	3m : 3m' (R: C ₅ H ₉)	78 (64:36)
14	1d	2a	3n : 3n' (R: C ₆ H ₁₁)	79 (95:5)
15	1e	2a	3o : 3o' (R: ^t Bu)	95 (67:33)
16	1f	2a	3p : 3p' (R: <i>m</i> -MeC ₆ H ₄)	88 (>99:1)

^a The allylation of various aldehydes (1.00 mmol) by allenes (2.0–3.0 mmol) with PdCl₂(PPh₃)₂ (0.020–0.050 mmol), HCl (0.50–1.0 ml) and SnCl₂ (2.50–3.0 mmol) was carried out at 25 °C for 24 h in DMF (1.0–1.50 mL). ^b Isolated yields.

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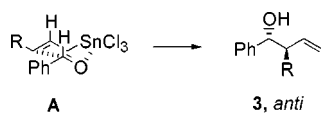
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membered cyclic transition state **A** with the phenyl group from benzaldehyde and the substituent R from allene occupying the equatorial positions of the cyclic transition state (Scheme 3).

We have demonstrated that carbonyl allylation of aldehydes by allenes proceeds smoothly in aqueous/organic medium in the presence of PdCl₂(PPh₃)₂, HCl, and SnCl₂.

Scheme 3



The reaction likely proceeds in two stages. The allenes first undergo hydrostannylation to give allyltrimethylstannanes which then allylate aldehydes to afford the corresponding homoal-

lylic alcohols. In these reactions, allenes function as synthons of allylic carbanions. High chemo-, regio-, and stereoselectivity can be achieved by a proper choice of the reaction conditions.

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