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Complete Regioselection in Palladium-Catalyzed Arylation and Alkenylation of Allylic Alcohols with Hypervalent Iodonium Salts

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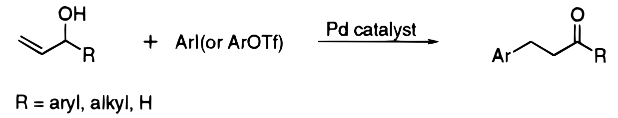
The formation of a carbon−carbon bond by palladium-catalyzed coupling of aryl or vinyl halides with olefins, known as the Heck reaction, has become a powerful tool in organic chemistry.[1] In the case of allylic alcohols, palladium-catalyzed reaction of organic halides usually affords β-substituted ketones or aldehydes rather than the β-substituted allylic alcohols (Scheme 1).[2]

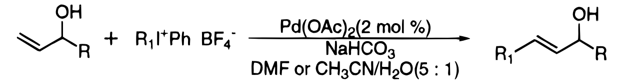
Jeffery[3] reported that in the presence of a stoichiometric amount of silver acetate or silver carbonate, a highly selective formation of the substituted allylic alcohols can be achieved. Cacchi[4] reported that Pd(0)-catalyzed reaction of allylic alcohols with triflates in the presence of Et_3N provided two isomeric substituted allylic alcohols. Tamaru[5] utilized *O*-substituted allylic alcohols to direct the Pd(0)-catalyzed coupling without elimination of proton adjacent to the oxygen-bearing carbon. Recently, we have found that the Pd-catalyzed coupling of allylic diols with iodobenzene in the presence of $Pd(OAc)_2$ and *n*-Bu_3P as catalysts using K_2CO_3 as base afforded phenyl-substituted allylic diols and using Et_3N as base under the same conditions afforded phenyl-substituted α-hydroxy ketones.[6] However, our efforts to get phenyl-substituted allylic alcohols with iodobenzenes and allylic alcohols in the presence of Pd-catalysts by adjusting the reaction conditions were fruitless as we obtained a mixture of substituted ketones and allylic alcohols.[6] Finally, we have found that the coupling reaction of hypervalent iodonium salts[7] with allylic alcohols in the presence of phosphine-free $Pd(OAc)_2$ catalyst afforded the substituted allylic alcohols as the sole products under mild conditions with high catalytic efficiency (Scheme 2).[8]

Scheme 1



R = aryl, alkyl, H

Scheme 2



R = H, nC_5H_{11}

R_1 = Ph, PhCH=CH-
(E)

This is in contrast to the result reported[9] that the reaction of allylic alcohols with diaryliodonium bromide in the presence of palladium catalyst and base yielded the corresponding arylpropanals.

The results of Pd-catalyzed coupling of allylic alcohols with hypervalent iodonium salts in dry DMF (nonaqueous conditions) and in CH_3CN/H_2O (5:1) (aqueous conditions) are summarized in Table 1. The allylic alcohol **1** (1 equiv) was reacted with diphenyliodonium tetrafluoroborate[10] (1 equiv) in the presence of $NaHCO_3$ using phosphine-free $Pd(OAc)_2$ (2 mol %) as catalyst in dry DMF (nonaqueous conditions) at room temperature for 1.5 h to afford the phenyl-substituted allylic alcohol **4** as the sole product in 87% yield (method A, entry 1, Table 1).[11−13] Under the same conditions using CH_3CN/H_2O (5:1) (aqueous conditions), the reaction proceeded faster. Stirring for 0.5 h afforded the cinnamyl alcohol **4** in 89% yield (method B, entry 1, Table 1).[13,14] When 1 mol % and 0.5 mol % of $Pd(OAc)_2$ were used, the yields were reduced to 83% and 81%, respectively.[15] When the reaction was conducted at 60 °C under the same conditions, only the phenyl-substituted allylic alcohol **4** was obtained in a rather low yield (40%) without any forma-

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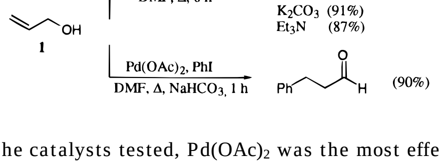
[10] Ochiai, M.; Sumi, K.; Takaoka, Y.; Shiro, M.; Fujita, E. *Tetrahedron* **1988**, *44*, 4095.

[11] Water only can be used as solvent, but the yield was lower (77%) with some side products after stirring at room temperature for 45 min. The reactions proceeded in the absence of base in CH_3CN/H_2O(5:1) at room temperature for 30 min with some side products in 73% yield. In our hands, with diphenyliodonium tetrafluoroborate (1 equiv) and $Pd(OAc)_2$ (2 mol %) in H_2O without using base cinnamyl alcohol (**4**) was obtained in 71% yield, although the reaction was not clean.

[12] In the literature, the coupling of alkenyl(phenyl)iodonium salts with olefins, 3 equiv of olefins were used. See ref 8a. In the palladium-catalyzed cross-coupling of alkenyl(phenyl)iodonium salts with organotin compounds, for the iodonium salts excess organotin compounds were used. See ref 8b.

[13] Diphenyliodonium and alkenyl(phenyl)iodonium triflates can be used. In our hands, with tetrafluoroborate the reactions were more clean.

[14] The reaction of allylic alcohol **1** with PhOTf in the presence of phosphine-free $Pd(OAc)_2$ catalyst and $NaHCO_3$ in DMF at room temperature did not give the coupled product and only the starting material was recovered. However, in the presence of $Pd(PPh_3)_4$ catalyst and K_2CO_3 or Et_3N as base, β-substituted aldehyde was obtained in 91 and 87% yields, respectively. In the case of iodobenzene with $Pd(OAc)_2$ at catalyst, the β-substituted aldehyde was afforded.



[15] Of the catalysts tested, $Pd(OAc)_2$ was the most effective. The reaction could be carried out without base. However, we could not get a higher yield in the absence of the base.

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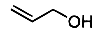
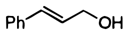
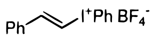
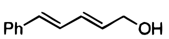
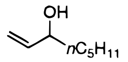
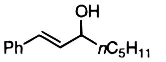
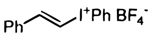
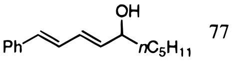
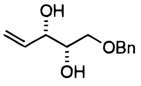
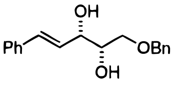
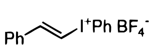
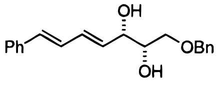
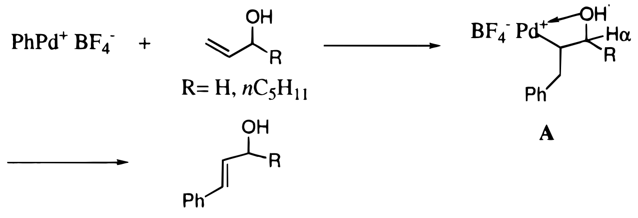
Table 1. Palladium-Catalyzed Arylation and Alkenylation of Allylic Alcohols with Hypervalent Iodonium Salts under Nonaqueous Conditions and Aqueous Conditions

Entry	Substrate	Iodonium Salts[a]	Reaction Conditions[b]	Product[c]	Yield(%)[d]
1	 **1**	$Ph_2I^+ BF_4^-$	A B	 **4**	87 89
2	**1**		A B	 **5**	81 83
3	 **2**	$Ph_2I^+ BF_4^-$	A B	 **6**	83 84
4	**2**		A B	 **7**	77 79
5	 **3**	$Ph_2I^+ BF_4^-$	A B	 **8**	76 78
6	**3**		A B	 **9**	71 72

[a] The iodonium salts were prepared by Ochiai's procedure. See ref 10. [b] All the reactions were run with the allylic alcohol (1 equiv) and iodonium salt (1 equiv) in the presence of $Pd(OAc)_2$ (2 mol %) and $NaHCO_3$ (2 equiv) at room temperature. Method A: dry DMF, 1.5 h (nonaqueous conditions). Method B: CH_3CN/H_2O (5:1) 0.5 h (aqueous conditions). [c] All products were characterized by ^1H NMR, IR, and MS or C, H combustion analysis. [d] The yields are isolated yields.

Scheme 3



tion of the β-phenyl-substituted aldehyde. This fact suggests that reversible β-hydride elimination and reinsertion, i.e., the isomerization of the kinetic product (the substituted alcohol) to aldehyde can be ruled out. Consequently, preferential selectivity can be explained by assuming the formation of chelated organopalladium tetrafluoroborate **A**, which prevents the hydrogen atom-(H_α) on the hydroxy-bearing carbon of **A** from the *syn*-relationship with palladium for the palladium hydride elimination (Scheme 3).

As a control experiment for the important role of tetrafluoroborate as counterion in the reaction of diphenyliodonium tetrafluoroborate, when the allylic alcohol was reacted under the same conditions as the reported procedure[$Pd_2(dba)_3 \cdot CHCl_3$, Bu_3N, acetone, 50 °C, 3 h],[9] the phenyl-substituted allylic alcohol, cinnamyl alcohol (**4**), was afforded as a major product (53%) along with the β-phenyl-substituted aldehyde (21%). Using alkenyl(phenyl)iodonium tetrafluoroborate[10] under nonaqueous or aqueous conditions, alkenyl-substituted allylic alcohol **5**[16] was obtained (methods A and B, entry 2, Table 1). For the substituted allylic alcohol **2**, treatment with diphenyliodonium tetrafluoroborate under nonaqueous and aqueous conditions afforded phenyl-substituted allylic alcohol **6** in 83 and 84% yields, respectively (methods A and B, entry 3, Table 1).[17] With alkenyl(phenyl)iodonium tetrafluoroborate, alkenyl-substituted allylic alcohol **7** was afforded (entry 4, Table 1). The allylic diol **3** was reacted with diphenyliodonium tetrafluoroborate to afford phenyl-substituted diol **8** (methods A and B, entry 5, Table 1). Treatment of the allylic diol **3** with alkenyl(phenyl)iodonium tetrafluoroborate provided alkenyl-substituted allylic diol **9** (entry 6, Table 1).

It is presumed that facile oxidative addition of hypervalent iodonium salts to Pd(0) and the formation of the chelated organopalladium tetrafluoroborate would allow for the coupling under mild conditions with excellent regioselectivity.

The typical procedure is as follows. To a stirred solution of allylic alcohol **1** (56 mg, 0.92 mmol) in DMF (5 mL) at room temperature under nitrogen atmosphere was added diphenyliodonium tetrafluoroborate (344 mg, 0.92 mmol) and $Pd(OAc)_2$ (4.1 mg, 2 mol %), followed by $NaHCO_3$ (155 mg, 1.84 mmol). The reaction mixture was stirred at room temperature for 1.5 h and quenched with saturated NH_4Cl solution. The reaction mixture was extracted with ether (2 × 20 mL), and the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was separated by SiO_2 column chromatography (EtOAc/hexanes = 1:3, $R_f = 0.30$) to afford the coupled product **4** (107 mg, 87%). When the same conditions were applied except CH_3CN/H_2O (5:1) (5 mL), the yield was 89% after stirring for 0.5 h.

In summary, the selected formation of the substituted allylic alcohols without formation of β-substituted carbonyl compounds was achieved by reacting allylic alcohols with iodonium tetrafluoroborates in the presence of $Pd(OAc)_2$ as catalyst.

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Supporting Information Available: Experimental procedures and spectral and analytical data for the new compounds (7 pages).

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[16] Drew, J.; Letellier, M.; Morand, P.; Szabo, A. G. *J. Org. Chem.* **1987**, *52*, 4047.

[17] The reaction fo **2** with PhOTf in the presence of phosphine-free $Pd(OAc)_2$ catalyst and $NaHCO_3$ in DMF at room temperature did not afford the coupled product. In the presence of $Pd(PPh_3)_4$ as catalyst and K_2CO_3 or Et_3N as base, only β-phenyl-substituted ketone was obtained as the only product. With iodobenzene, a mixture of phenyl-substituted allylic alcohol and ketone was obtained.[6]