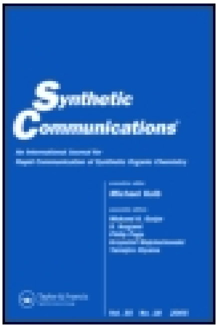

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Vinylation of Alkyl Halides Catalyzed by Palladium Catalyst

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VINYLATION OF ALKYL HALIDES CATALYZED BY PALLADIUM CATALYST

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ABSTRACT: *The palladium catalyzed vinylation of alkyl halides, especially benzyl chlorides, with a variety of olefins has been studied. A possible free radical mechanism was proposed.*

The palladium-catalyzed vinylation of organic halides provides a very convenient method for forming carbon-carbon bonds at unsubstituted vinylic positions[1]. The organic halides employed is limited to aryl, heterocyclic, or vinyl types, with bromides and iodides seen most often. Relatively little work has been done with alkyl halide. Only one case was reported, benzyl chloride could react with methyl acrylate at 100°C to give 67% of methyl 4-phenyl-3-butenoate and 9% of methyl 4-phenyl-2-butenoate[2]. From the synthetic point of view the important questions are: besides methyl acrylate and benzyl chloride, if other olefins or alkyl halides can undergo this kind of reaction, and what is the

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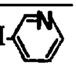
Table 1. The Effect of Catalysts on the Reaction of Benzyl Chloride **1a** with Styrene **2a**[a]

Catalyst	$PdCl_2(PPh_3)_2$[3]	$Pd(OAc)_2$	$Pd(OAc)_2$·bpy[4]
Yield %[b]	12	57	28
Catalyst	$Pd(PPh_3)_4$[5]	P-bpy·$Pd(OAc)_2$[6]	Si-CH_2-NH-
Yield %[b]	0	2	trace

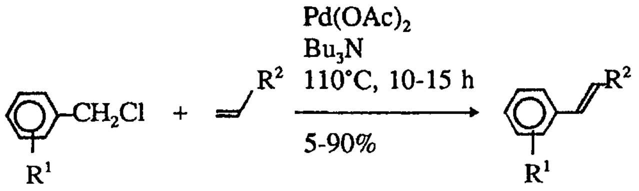
a A mixture of $PhCH_2Cl$(10 mmol), styrene (11 mmol), *n*-Bu_3N (11 mmol), catalyst (0.1 mmol) was stirred at 100°C for 15 h.
b Yield of isolated product **3a** based on **1a**.

possible reaction mechanism? Up to now, there is still no good approach for introducing an alkyl group to olefinic carbon. Hence the vinylation reaction with alkyl halides might be of considerable synthetic value. We therefore were intrigued with the vinylation reaction of alkyl halide. In this study, we wish to report the influences of catalyst, reagents, and reaction conditions on the reaction, as well as the possible reaction mechanism.

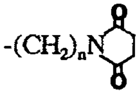
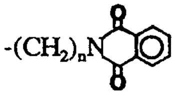
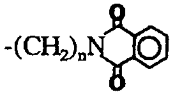
We first examined the effect of a variety of catalysts for the reaction of benzyl chloride with styrene in the presence of tri-*n*-butylamine. As can be seen in Table 1, palladium acetate was found to be the most effective catalyst for the reaction. It is notable that when a catalyst with ligand (such as triphenyl phosphine[3,5] or bipyridine[4]) was used, the yield of the reaction was dramatically decreased. In the case of tetrakis(triphenylphosphine)palladium(0), no product was observed. The polymer-supported catalysts[6-7], which are quite effective in the traditional vinylation reaction by using aryl halide as the arylation reagent, failed to catalyzed this reaction.

The base exerted a great influence on the reaction of benzyl chloride with styrene in the presence of palladium acetate. Tri-*n*-butylamine, which has most often been used in vinylation reaction, gave significant faster rates and good yields. It is well-known that a potential problem with benzyl halides in vinylation reaction is quaternization of tertial amine, and best results are obtained with more hindered amines. However, hindered amines, such as N,N-dicyclohexyl methyl amine, N,N-dicyclohexylethylamine, and N-cyclohexyl-cyclohexylamine gave no expected product in above reaction but some tar, which appeared the polymeric product of styrene, the starting material benzyl chloride remained unchange and could almost all be recovered. No improvement was achieved with less hindered tertial amines. For example, when triethylamine or tri-*n*-propylamine was used as the base, only a trace of product was obtained. Pyridine was not effective for the reaction too.

Temperature also exerted great influence on the reaction. For the reaction of benzyl chloride with styrene, the reaction rate was very slow at lower temperature. For example, running the reaction at 80°C for 10 h, only a little product was obtained. As the temperature was elevated to 100 or 110°C, in 10 h the yield increased to 47% or 57%, respectively. However, over 110°C polymerization of olefin was frequently observed as a side reaction.



1a-o 2a-o 3a-o

1-3	R^1	R^2	1-3	R^1	R^2	
a	H	-Ph				
b	H	-CONH$_2$				
c	H	-COOMe	e	H		(2e:n=0, 3e:n=1)
d	H	-COOEt				
h	4-Me	-COONH$_2$	f	H		(2f:n=0, 3f:n=1)
i	2-Me	-COONH$_2$				
j	2-OMe	-COONH$_2$				
k	2,5-Me$_2$	-COONH$_2$	g	H		(2g:n=1, 3g:n=2)
l	4-Cl	-COONH$_2$				
m	2-Cl	-COONH$_2$				
n	3-Cl	-COONH$_2$				
o	3,4-di- oxymethylene	-COONH$_2$				

Scheme 1

Solvents may be used but often are not necessary. Sometimes, DMF was added in order to increase the solubility of the reactants.

A variety of olefins have been treated with benzyl chloride in the presence of tri-*n*-butylamine and palladium acetate (Scheme 1). As the results shown in

Table **2**, all the reactions gave the products that the olefinic bond conjugated with benzene ring. Generally, the olefins with electron-withdrawing substituent or conjugating group on a double-bond carbon displayed high reactivity in the reaction with benzyl chloride. The olefins lacking electron-withdrawing substituent or cyclic olefins, such as cyclohexylene and 1-heptene, gave no reaction at all.

In order to evaluate the activity of substituted benzyl chlorides, acrylamide was used as the substrate (Scheme **1**), the results are presented in Table **2**. Benzyl chloride showed almost the same reactivity as that of benzyl bromide, the yields were 50% and 57%, respectively. An important observation is that the reaction yield was very dependent on the substituents on the benzene ring. Benzyl chlorides with electron-donating substituent led to smooth catalytic reaction and afforded higher yields. By contrast, the presence of an electron-withdrawing substituent often suppressed the reaction. For example, *m*- and *p*-nitro, *o*- and *m*-chloro benzyl chloride reacted very poorly or not at all with acrylamide. *p*-Chloro benzyl chloride was an exception, the reason is not yet clear. With halides other than benzyl halides the reactions were quite different. Chloro diphenylmethane gave the coupling product 1,1,2,2-tetraphenylethane in 80% yield under the identical reaction. In case of 2-chloroacetophenone, acetophenone was found as the only product(50%). 2-Bromoacetic acid ester also did not undergo the reaction in normal manner.

Table 2. Physical data of the products of arylation of benzyl chlorides with olefins

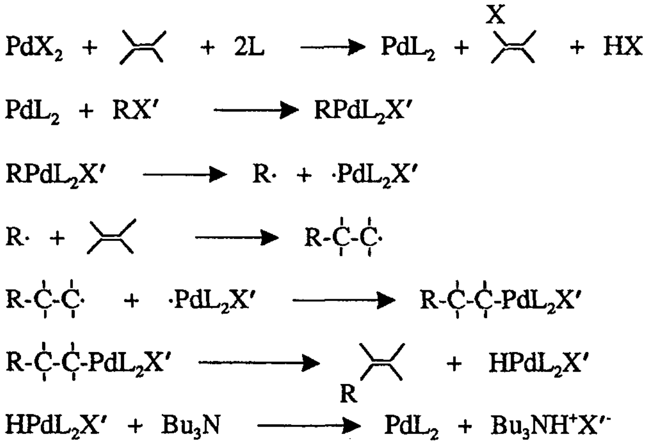
Product	Yield[a] (%)	mp(°C) or bp(°C/mbr) (Lit. data)	IR(KBr/Nujol ν(cm^{-1})	^{1}H NMR(acetone-d6/TMS), δ(ppm), J(Hz)
3a	57	144/3 (145-147/3[8])	3050, 3010, 1595, 1492, 960, 740	3.70(t, 2H, CH_2), 6.60(m, 2H, =CH), 7.40(m, 10H, ArH)
3b	50	133-134 (127-128.5[9])	3384, 3193, 3083, 3028, 1649, 965, 746	3.25(d, 2H, CH_2), 5.80(b, 2H, NH_2), 6.50(m, 2H, =CH), 7.30(m, 5H, ArH)
3c	65	110/3 (108-110/3[10])	3027, 2952, 1739, 1657, 1436, 967, 748	3.20(d, 2H, CH_2), 3.65(s, 3H, CH_3), 6.35(m, 2H, =CH), 7.30(m, 5H, ArH)
3d	70	120-125/2 (156/3.5[11])	3028, 2982, 1735, 1653, 967, 749	1.25(t, 3H, J=7, CH_3), 3.20(d, 2H, CH_2), 4.15(q, 2H, J=7, CH_2), 6.30(m, 2H, =CH), 7.30(m, 5H, ArH)
3e	63	143-145	3024, 2940, 1774, 1700, 968, 761	2.70(s, 4H, CH_2CH_2), 4.25(d, 2H, CH_2), 6.30(m, 2H, =CH), 7.30(m, 5H, ArH)
3f	65	153-155 (151-153[12])	3080, 3029, 2912, 1771, 1705, 1612, 970, 727,	4.45(d, 2H, CH_2), 6.59(m, 2H, =CH), 7.31(m, 5H, ArH), 7.82(m, 4H, ArH)
3g	60	145-146	3079, 3025, 2932, 1773, 1707, 970, 721	2.70(m, 2H, CH_2), 3.86(t, 2H, CH_2), 6.37(m, 2H, =CH), 7.31(m, 5H, ArH), 7.80(m, 4H, ArH)
3h	57	167-168	3380, 3189, 2988, 1649, 962, 788	2.55(s, 3H, CH_3), 3.36(d, 2H, CH_2), 6.00(b, 2H, NH_2), 6.66(m, 2H, =CH), 7.40(m, 4H, ArH)
3i	70	118-120	3390, 3195, 2967, 2894, 1654, 966	2.40(s, 3H, CH_3), 3.25(d, 2H, CH_2), 5.80(b, 2H, NH_2), 6.50(m, 2H, =CH), 7.20(m, 4H, ArH)
3j	82	147-148	3378, 3189, 2906, 1650, 973, 754	3.20(d, 2H, CH_2), 3.83(s, 3H, OMe), 5.80(b, 2H, NH_2), 6.40(m, 2H, =CH), 6.90-7.15(m, 4H, ArH)

3k	90	129-131	3398, 3203, 2976, 1656, 967	2.30(s, 6H, 2xCH_3), 3.20(d, 2H, CH_2), 5.80(b, 2H, NH_2), 6.50(m, 2H, =CH), 7.25(m, 3H, ArH)
3l	69	160-162	3379, 3187, 2904, 1650, 986	3.20(d, 2H, CH_2), 5.80(b, 2H, NH_2), 6.35(m, 2H, =CH), 7.25(m, 4H, ArH)
3m	5	124-125	3384, 3198 2906, 1653, 962	3.20(d, 2H, CH_2), 5.80(b, 2H, NH_2), 6.30(m, 2H, =CH), 7.20(m, 4H, ArH)
3n	22	155-156	3378, 3192, 2901, 2228, 1649, 970	3.23(d, 2H, CH_2), 5.58(b, 2H, NH_2), 6.49(m, 2H, =CH), 7.65(m, 4H, ArH)
3o	66	177-179	3385, 3201, 2904, 1649, 1446, 954	2.99(d, 2H, CH_2)[b], 6.03(s, 2H, OCH_2O), 6.33(m, 2H, =CH), 6.94(m, 3H, ArH)

a Yield of isolated product **3** based on **1**. Reaction time: 3a-g, 10 h; 3h-o, 15 h. Satisfactory microanalyses obtained: C±0.31, H±0.25, N±0.23.
b Using DMSO-d6 as the solvent.

Based on the above observations that (1) strong ligand existed on the catalyst would suppress or totally stop the reaction, (2) solvent did not exert great effect on the reaction, (3) only activated olefins with electron-withdrawing substituent could take the reaction, chloro diphenylmethane coupled instead of vinylation, (4) in the case of 2-chloroacetophenone only reduced product acetophenone was obtained, it appeared that the reaction might involve intermediate free radicals. Further, we found that radical scavenger could suppress the reaction of benzyl chloride with styrene. When 5 mole% of 1,4-dinitrobenzene was added to the reaction mixture, the reaction yield dropped from 57% to 20%. As the amount of 1,4-dinitrobenzene increased to 50 mole%, the reaction was totally stopped. This result further supported the possibility of an intermediate free radical process.

As literatures[13] reported, oxidative addition of alkyl halides to low valent group VIII transition metal complexes may involve intermediate free carbon radicals or occur by an SN2-type transition state depending upon the nature of the reactants. In order to elucidate the reaction mechanism, spin trapping experiments for the reaction of benzyl chloride with styrene were carried out using *tert*-nitrosobutane as a spin trap. The composition of reaction mixture was the same as that of the actual reaction, except the addition of *tert*-nitrosobutane. At room temperature, no free radical signal could be observed. However, when the reaction mixture was heated at 100°C for 10 minutes, the esr spectrum showed a clear signal of benzyl *tert*-butyl nitroxide radical (a^N=15.20, a^H=7.20), as well as a triplet for di-*tert*-butyl nitroxide radical (a^N=15.56). Under the identical experimental conditions and in the absence of catalyst palladium acetate, the spectrum of above reaction mixture showed only a signal for di-*tert*-butyl nitroxide due to the decomposition of *tert*-butyl nitroxide. However, without benzyl chloride, only the signal of styryl *tert*-butyl nitroxide was observed besides the signal of di-*tert*-butyl nitroxide. The spin trapping results suggest that the reaction may first involve an oxidative addition of benzyl chloride to palladium(0) species. The formation of benzyl *tert*-butyl nitroxide radical is most likely the consequence of a radical decomposition of the



Scheme 2

oxidative addition adduct. This possibility was demonstrated by the fact that benzyl *tert*-butyl nitroxide is indeed formed (as observed by its esr spectrum) on mixing benzyl chloride, tri-*n*-butylamine, palladium acetate, and *tert*-nitrosobutane at 100°C for 10 min. The proposed radical mechanism for the reaction might be outlined in Scheme 2. First, the reaction was believed to undergo an oxidative addition of halide to palladium(0) species, which generally is coordinated with a pair of ligands. The radical decomposition of the oxidative adduct $RPdL_2X'$ in turn occurred in the rate-determining step. In agreement with our observation, the reaction rate could be retarded by the strong ligand, which stabilized the adduct. The electron-withdrawing groups bearing on the benzene ring would be expected to stabilize the benzylic free radical by resonance, and therefore decreased the reaction rate or suppressed the reaction entirely. The fact that 2-chloroacetophenone and 2-bromoacetic acid ester could not undergo the vinylation reaction is most likely due to the same effect. Probably because of the steric hindrance, diphenyl-methylene radical dimerized instead of added to olefin. The other alkyl radical, such as methyl and neopentyl radical, underwent dimerization more rapidly than reaction with olefin due to their highly activity. In these cases polymeric product of olefin was generally formed. It should be emphasized that for very active halides, such as benzyl bromide and 2-chloroacetophenone, one-electron transfer might be operated:

$$\mathrm{RBr} + \mathrm{PdL_2} \longrightarrow \mathrm{R}\cdot + \mathrm{PdL_2Br} \rightleftharpoons \mathrm{RPdL_2Br}$$

As mentioned above the reaction of benzyl chloride with olefin could not occur by using high hindered tertial amines, it appeared that tert-*n*-butylamine was not only served as a base, but also played another important role in the reaction. We will report further on this in a subsequent paper.

EXPERIMENTAL

Vinylation; General procedure: A mixture of benzyl chloride (**1**, 10 mmol), olefin (2a-g, 11 mmol), *n*-Bu_3N(11 mmol), and $Pd(OAc)_2$ (0.1 mmol) was stirred at 110°C for the desired length of time (see Table 2). Water (100 ml) was added. The mixture was allowed to stand for 1-2 h, the precipitated product was isolated by suction and recrystallized from ethanol to give compound **3**.

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