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NEW APPLICATIONS OF PALLADIUM IN ORGANIC SYNTHESES

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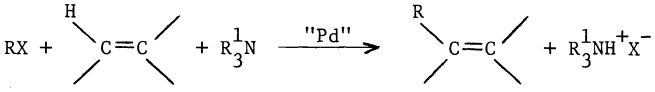
Abstract - The palladium catalyzed vinylic substitution reaction with organic halides is a new and useful method for producing carbon-carbon bonds.



The reaction is useful with aryl, heterocyclic, benzylic, and vinylic bromides and iodides. The most useful reactions are with bromides in which cases a triarylphosphine is required with the palladium catalyst. The best phosphine to employ for a specific synthesis can now be predicted based upon knowledge of how the phosphines influence vinylic substitution rates and side reactions forming phosphonium salts and palladium metal. Essentially all common functional groups can be tolerated by the reaction under the same conditions with the exception of α,β-unsaturated ketones and aldehydes. These react normally in the form of their acetals or ketals, however. Reactions proceed well with conjugated or isolated double bonds with mono-, di- and often tri-substituted olefins, generally in a stereospecific manner. A syn addition of the organopalladium compound to the olefin followed by a syn elimination of the palladium hydride is observed. The direction of addition of the organopalladium complex to the olefin depends upon the substituents present. Both steric and electronic influences have been observed. The direction of addition is dominated by steric effects; the organic group always adds, at least mainly, to the least substituted carbon of the double bond. Electron withdrawing substituents on the double bond generally cause exclusive addition of the organic group to the olefinic carbon not having the substituent. With electron donating groups, some addition to the carbon carrying the substituent is usually observed.

For about ten years we have been investigating the chemistry of organopalladium compounds. We have been mainly concerned with mono-organopalladium(II) species, $RPdL_2X$, where L is a ligand and X is a halide or acetate ion. Initially these complexes were prepared by exchange reactions of main group organometallics, principally mercurials, with palladium(II) salts (chloride or acetate). While this method works well, it suffers from the major disadvantage

$$RHgCl + PdCl_2 + 2L \longrightarrow RPdL_2Cl + HgCl_2$$

that many desirable main group organometallics are not easily accessible and even when they are they must be used in stoichiometric amounts in the synthesis of organic compounds. We, therefore, have turned to another method of preparation, the reaction of organic halides with either finely divided palladium metal or more frequently palladium(0) phosphine complexes.

$$RX + Pd(PR^1_3)_n \longrightarrow RPd(PR^1_3)_2X + (n-2)PR^1_3$$

The chemistry of the mono-organopalladium compounds has turned out to be extremely varied, unique in many respects, and of great potential use in the area of organic syntheses. In our own work, for example, we have found eight new reactions of synthetic value, all of which (with the possible exception of the last one which has not yet been studied in much detail) can be carried out catalytically with a wide variety of aryl, vinylic, heterocyclic, and benzylic bromides and iodides in good to excellent yields. These reactions are:

(1) Carboalkoxylation

$$RX + CO + R^1OH + R^3_3N \xrightarrow{\text{"Pd"}} RCO_2R^1 + R^3_3NH^+X^-$$

(2) Amidation

$$RX + CO + R^1R^2NH + R^3_3N \xrightarrow{\text{"Pd"}} RCONR^1R^2 + R^3_3NH^+X^-$$

(3) Formylation

$$RX + CO + H_2 + R^3_3N \xrightarrow{\text{"Pd"}} RCHO + R^3_3NH^+X^-$$

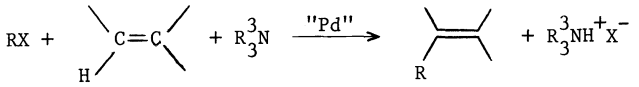
(4) Ethynylic Substitution

$$RX + HC{\equiv}CR^1 + R^3_3N \xrightarrow{\text{"Pd"}} RC{\equiv}CR^1 + R^3_3NH^+X^-$$

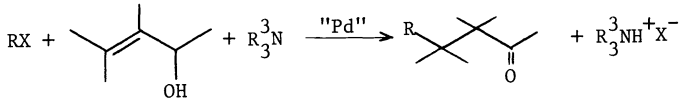
(5) Reduction

$$RX + HCO_2^-R^3_3NH^+ \xrightarrow{\text{"Pd"}} RH + CO_2 + H_2O + R^3_3NH^+X^-$$

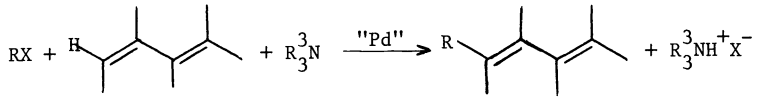
(6) Vinylic Substitution



(7) A Beta Substituted Ketone or Aldehyde Synthesis

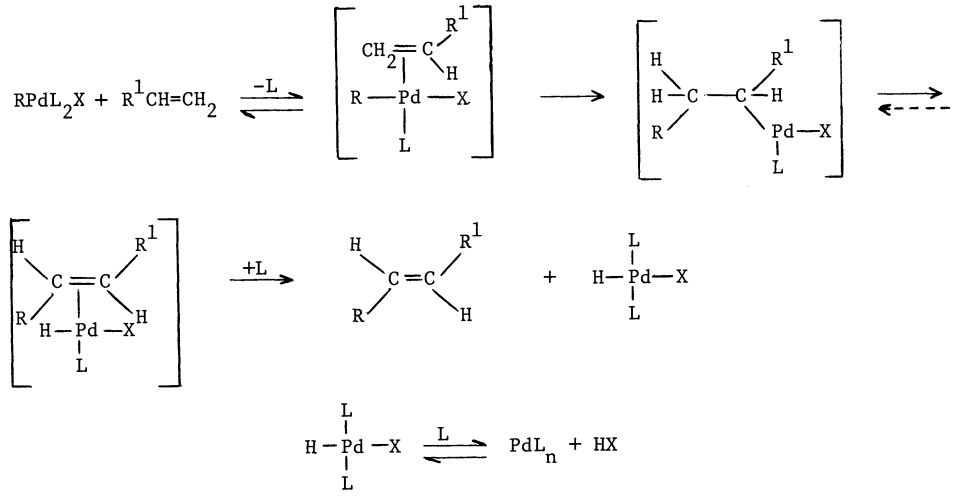


(8) Dienylation



There are, of course, many other known reactions discovered in other laboratories which also involve $RPdL_2X$ complexes. Of the eight reactions we have been concerned with, the most generally useful one appears to be the vinylic substitution, (6). Reactions (7) and (8) are really just variations of this one. This reaction has received most of our attention in the past few years and is the subject I will concentrate on in this lecture.

The mechanism of the vinylic substitution is not known in detail. We have been working on this problem for some time, however, various chemical complications have made progress very slow. In any case, we have good evidence to suggest that the mechanism, at least, is close to the following:



This reaction becomes catalytic in palladium if RX is added along with a base to remove HX from the final equilibrium. The base must be present or the reaction ceases after one or two cycles of the catalyst. We have generally empolyed triethyl- or tri-n-butylamine as the base although secondary amines may also be used in cases where they do not cause side reactions. Triarylphosphines are preferred over trialkylphosphines, triphenyl phosphite, or bisdiphenylphosphinoethane when a phosphine is used. We have now carried out a large number of these reactions and can make the following generalizations.

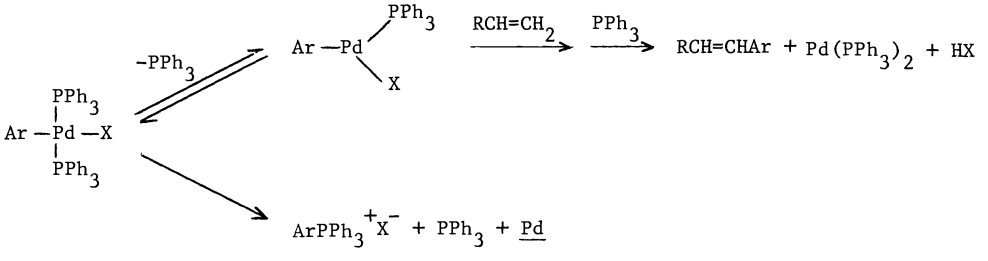
1. The organic group of the RX always adds exclusively or predominantly to the least substituted carbon of the double bond. If a functional group is attached directly to the double bond, the R group generally adds to the other carbon if steric factors are similar.

2. The reaction is stereospecific with 1,2-disubstituted alkenes, proceeding by a cis addition-cis elimination sequence. If there is a choice of hydrogens for elimination, the most stable products are preferred and the most hydridic hydrogen tends to be lost.

3. Generally, organic bromides do not undergo the reaction well unless the catalyst is a triarylphosphine or secondary amine complex. Organic iodides do not require the phosphine or secondary amine. Organic chlorides usually do not undergo the reaction under the usual conditions (<150°).

When the vinylic substitution is carried out with a triarylphosphine containing catalyst and an organic bromide, decomposition of the soluble catalyst species is sometimes observed. This is accompanied by precipitation of palladium metal and cessation of the reaction. The formation of small amounts of palladium during the course of a reaction is often observed and has little effect upon the reaction. In these cases, this is probably due to the oxidation or minor impurities in the reaction mixture by the palladium(II) catalyst. In the more serious cases, palladium precipitation appears to be due either to the conversion of the phosphine ligands into phosphonium salts or to a sterically induced ligand dissociation which results in aglomeration of the coordinately unsaturated palladium(0) intermediate with formation of the metal.

Several metals are known to catalyze the reaction of aryl halides with organophosphines to form phosphonium salts. Palladium, however, apparently had not been tried. We have found that palladium does catalyze the reaction and in some instances this reaction competes successfully with the vinylic substitution. We believe the phosphonium salt formation occurs by a reductive elimination of an aryl group and a triarylphosphine ligand from a four or possibly five coordinate Pd(II) complex and that this process competes with the desired phosphine dissociation, olefin complexation and insertion.



Some relative rates of palladium-catalyzed phosphonium salt formation based on half lives employing various organic halides and phosphines are shown in Table I. Table I shows that phosphonium salt formation is accelerated by electron donating substituents in the aryl halide and in the triarylphosphine although the effects are not very large. 3-Bromopyridine is unreactive with triphenylphosphine as were reactions with tri-o-tolylphosphine. The ortho-methyl substituents in the last case apparently sterically inhibit the reductive elimination. The ortho-methyl groups do not significantly decrease the ability of the phosphine to coordinate with the palladium, however, since this phosphine is effective in promoting the vinylic substitution with aryl bromides. In fact, it is a better phosphine to use than triphenylphosphine in almost every instance. It not only doesn't quaternize, but it appears to accelerate the reactions compared with triphenylphosphine, probably because the larger tri-o-tolylphosphine ligands dissociate more readily and promote coordination of the olefin and the vinylic substitution. The remarkable effect of using this phosphine in the reaction of 4-bromophenol with methyl acrylate, a case where quaternization with triphenylphosphine was very serious, is shown in Table II. These reactions and most of the others to be mentioned have been carried out with one mole percent

Table I.

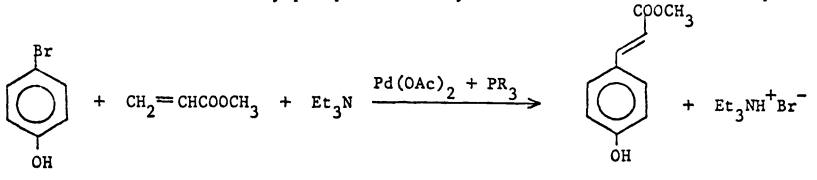
Relative Rates of Phosphonium Salt Formation at 100°

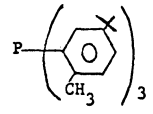
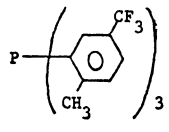
($Pd(OAc)_2$ Catalyst in CH_3CN or DMAA Solvent)

RX	PR'_3	Relative Rates Based on $T_{\frac{1}{2}}$
$4\text{-}HOC_6H_4Br$	Ph_3P	3.2
$4\text{-}H_2NC_6H_4Br$	Ph_3P	3.2
$4\text{-}CH_3C_6H_4Br$	Ph_3P	2.0
C_6H_5Br	Ph_3P	1.0
$3\text{-}CF_3C_6H_4Br$	Ph_3P	0.2
$3\text{-}C_5NH_4Br$	Ph_3P	< 0.1
$(CH_3)_2C{=}CHBr$	Ph_3P	0.5
C_6H_5Br	$(4\text{-}(CH_3)_2NC_6H_4)_3P$	6.4
C_6H_5Br	$(2\text{-}CH_3C_6H_4)_3P$	< 0.1
$4\text{-}HOC_6H_4Br$	$(2\text{-}CH_3C_6H_4)_3P$	< 0.1

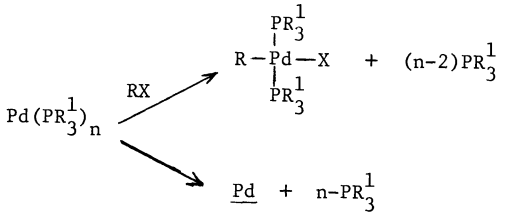
palladium acetate as the catalyst although considerably smaller amounts are sufficient under some conditions (see below).

Table II. The Effect of the Triarylphosphine on Vinylic Substitution with 4-Bromophenol



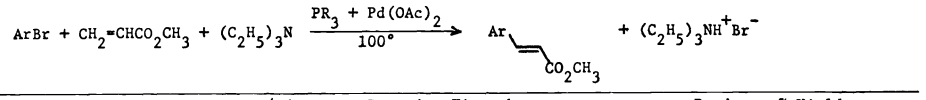
PR_3	P:Pd	Reaction Time	Temp.	% Yield (glc)
PPh_3	2:1	48 hr.	75°	3%
	6:1	100 hr.	75°	5%
$P(2\text{-}CH_3C_6H_4)_3$	2:1	38 hr.	75°	>95%
	6:1	48 hr.	75°	>95%
$P(2\text{-}C_2H_5C_6H_4)_3$	2:1	51 hr.	75°	58%
	6:1	50 hr.	75°	>95%
$P(2,5\text{-}i\text{-}Pr_2C_6H_3)_3$	2:1	53 hr.	75°	26%
	6:1	50 hr.	75°	68%
	2:1	51 hr.	75°	87%
	6:1	48 hr.	75°	>95%
	2:1	34 hr.	75°	29%
	6:1	48 hr.	75°	>95%

The "normal" 2:1 triphenylphosphine to palladium acetate catalyst gave only a 3% yield of product at 75° while the tri-o-tolylphosphine in a shorter time gave an essentially quantitative yield. Longer reaction times did not improve the yield in the triphenylphosphine reaction. The use of larger amounts of phosphine relative to the palladium had little effect in these cases although this sometimes increases yields significantly. Other entries in Table II show that larger ortho groups than methyl in the phosphine are detrimental to the vinylic substitution and electron donating or withdrawing groups in tri-o-tolylphosphine do not improve it. The larger ortho groups apparently promote dissociation of the $Pd(0)-PR_3$ intermediate complex to such an extent that aglomeration of the palladium atoms into metal occurs competitively with the vinylic substitution.



With the use of the proper triarylphosphine, then, it becomes possible to bring about vinylic substitutions with aryl halides and olefins containing almost any desired, unprotected, functional group. One exception is α,β-unsaturated ketones and aldehydes which are polymerized under the reaction conditions. Using methyl acrylate as a standard olefin since it always produces only E-cinnamic acid derivatives, we have substituted it with the various substituted aryl halides shown in Table III.

Table III.



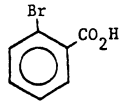
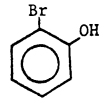
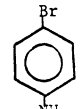
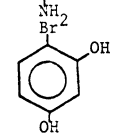
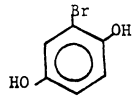
ArBr	PR_3	PR_3/Pd	Reaction Time, hrs.	Product, % Yield	
C_6H_5Br	o-Tol_3P	2	2 (125°)	E-$C_6H_5CH{=}CHCO_2CH_3$	95
4-ClC_6H_4Br	o-Tol_3P	2	18	E-4-$ClC_6H_4CH{=}CHCO_2CH_3$	93
4-NCC_6H_4Br	Ph_3P	2	2	E-4-$NCC_6H_4CH{=}CHCO_2CH_3$	80
4-$CH_3OCOC_6H_4Br$	Ph_3P	2	7	E-4-$CH_3O_2CC_6H_4CH{=}CHCO_2CH_3$	81
3-$HOCOC_6H_4Br$	o-Tol_3P	4	6	E-3-$HO_2CC_6H_4CH{=}CHCO_2CH_3$	67
4-$OCHC_6H_4Br$	o-Tol_3P	4	18	E-4-$OCHC_6H_4CH{=}CHCO_2CH_3$	72
4-$O_2NC_6H_4Br$	Ph_3P	2	7	E-4-$NO_2C_6H_4CH{=}CHCO_2CH_3$	73
4-$(CH_3)_2NC_6H_4Br$	o-Tol_3P	8	24	E-$(CH_3)_2NC_6H_4CH{=}CHCO_2CH_3$	80
4-HOC_6H_4Br	o-Tol_3P	2	22 (75°)	E-4-$HOC_6H_4CH{=}CHCO_2CH_3$	95
4-$H_2NC_6H_4Br$	o-Tol_3P	8	3	E-$NH_2C_6H_4CH{=}CHCO_2CH_3$	73
4-$CH_3SC_6H_4Br$	o-Tol_3P	4	72 (125°)	E-4-$CH_3SC_6H_4CH{=}CHCO_2CH_3$	77
4-$CH_3CONHC_6H_4Br$	o-Tol_3P	4	3	E-4-$CH_3CONHC_6H_4CH{=}CHCO_2CH_3$	83
2,5-i-$Pr_2C_6H_3Br$	Ph_3P	4	20 (125°)	E-2,5-i-$Pr_2C_6H_3CH{=}CHCO_2CH_3$	79
2-$CH_3OCOC_6H_4Br$	o-Tol_3P	4	3	E-2-$CH_3O_2CC_6H_4CH{=}CHCO_2CH_3$	69
2-$CH_3CO_2C_6H_4Br$	o-Tol_3P	8	18	E-2-$CH_3CO_2C_6H_4CH{=}CHCO_2CH_3$	66
9-$C_{14}H_9Br$	o-Tol_3P	4	4	E-9-$C_{14}H_9CH{=}CHCO_2CH_3$	72

Table III shows that the vinylic substitution reaction is tolerant of chloro, cyano, carbomethoxy, carboxy, aldehyde, nitro, dimethylamino, phenolic, amino,methylthio, acetamido, acetoxy, and polynuclear aromatic groups (9-phenanthryl). These groups may be ortho, meta, or para to the reacting bromo substituent. It is noteworthy that the highly hindered 1-bromo-2,5-diisopropylbenzene reacted in 79% yield in 20 hrs. at 125°. As is the case with almost every reaction, there are instances where it does not work or, at least, does not work well. Even in these instances, however, it is often possible to vary reactants and/or conditions to produce the desired product. For example, Table IV shows some examples

which have not given acceptable yields and some ways that yields have been improved.

Table IV.

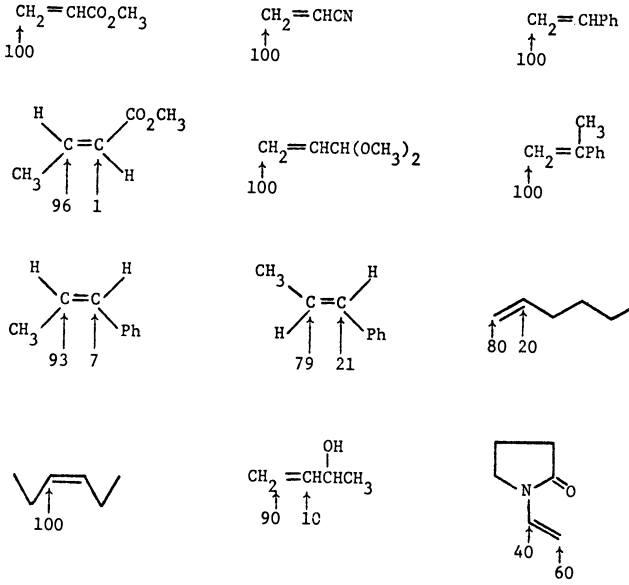
Aryl Halides which React Poorly with Methyl Acrylate

Aryl Halide	Product	Remarks
	None	Probably forms Pd chelate. Methyl ester gives 69%.
	24%	Acetate gives 69%. Iodide without PR_3 gives 95%.
	48% (Po-tol_3/Pd = 4)	N-Acetyl derivative gives 83%.
	None	Diacetate gives 26%.
	None	Diacetate gives 2%.

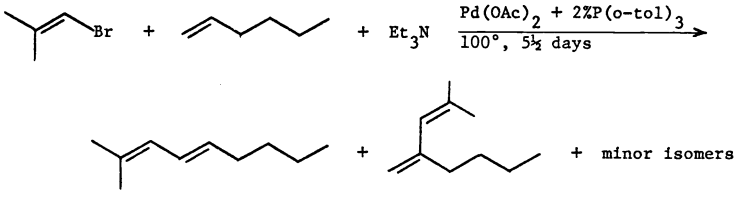
o-Bromobenzoic acid fails to react probably because it forms a very stable chelate with the palladium. The methyl ester which would not be expected to form such a stable chelate reacts normally. o-Bromophenol gives only a 24% yield of product perhaps because of competing quaternization of the phosphine. Deactivation by acetylation or use of o-iodophenol instead of the bromo compound in the absence of a phosphine however gives good results. Acetylation of p-bromoaniline also substantially improves the product yield over p-bromoaniline itself. Both bromoresorcinol and bromohydroquinone fail to react normally with methyl acrylate. A serious side reaction of the bromoresorcinol is reduction to resorcinol under the reaction conditions. Diacetylation of these phenols helps the reaction but still yields are poor. Attempts to deactivate the bromoresorcinol by making the bismethanesulfonate or bistrifluoroacetate and then reacting with methyl acrylate also failed to improve the reaction. Other problems sometimes arise in the vinylic substitution when too many or very large substituents occur in the reactants near the halo group or the double bond.

The question of where the substitution occurs with unsymmetrical olefins is an important one to answer if the reaction is to be useful for organic syntheses. The positions of substitution of bromobenzene or iodobenzene in twelve representative olefins are as follows: The position of the substitution is not much affected by the triarylphosphine used (even those with large o-substituents) of if the iodide is used without a phosphine. Substituents in the bromobenzene likewise, even o-methyl, have relatively little influence on the direction of addition. The direction of elimination of the hydridopalladium species, however, is sometimes influenced by these changed judging from the few examples we have studied. The situation is somewhat more complex in vinylic substitutions with vinylic halides which produce dienes.

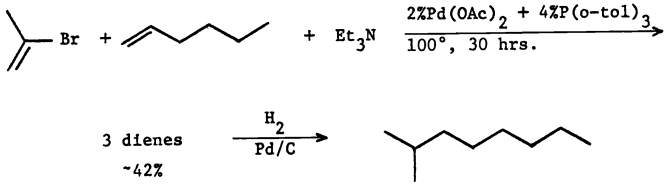
The reactions of various vinylic halides with methyl acrylate proceed with exclusive terminal substitution as in the aryl halide cases although subsequent Diels-Alder reactions or polymerizations are sometimes problems. The primary vinylic halide, 1-bromo-2-methyl-1-propene, and 1-hexene form a mixture of two major and four minor dienes. Hydrogenation reduced the dienes to two products which were obtained in a 1:1 ratio. One hydrocarbon product came from terminal addition and the other from addition of the vinylic group to the second carbon of the olefin. The initial, two major products were the two expected conjugated dienes. More information is needed to determine whether this product mixture results primarily from electronic or steric effects.



Direction of addition is not significantly influenced by the PR_3 used in these examples.



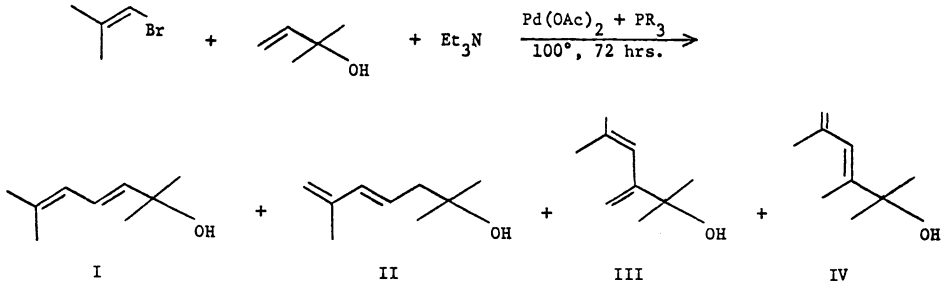
2-Bromopropene, as might be predicted on the basis of its size, gave only the products from terminal addition to 1-hexene (three major isomers).



In additions to more hindered olefins than 1-hexene, 1-bromo-2-methyl-1-propene shows a significant preference for terminal addition which can be enhanced by using triarylphosphines with large ortho substituents. The reaction of this bromide with 2-methyl-3-buten-2-ol affords four isomeric dienol products. The total yields of these and the percentages of each depend upon the phosphine used as shown in Table V. As the bulk of the phosphine increases, total yields improve to 81% with the large tris-2,5-diisopropylphenylphosphine, and, at the same time, the percentage of the terminal adduct, I, increases to 81% of the total. The increase in yield of the isomer arising by addition of the palladium-phosphine group to the more hindered carbon of the double bond, with increasing steric size of the phosphine is surprising. A possible explanation for this result is that the very large phosphine group prevents symmetrical pi-bonding of the unsaturated alcohol in the

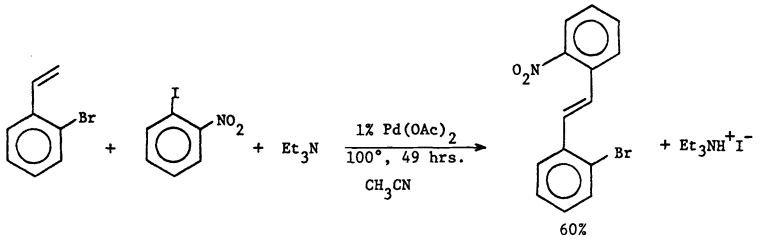
intermediate by pushing the dimethylcarbinol end away from the palladium. Then, when migration of the 2-methyl-1-propenyl group occurs it will occur more often to the end of the olefin closest to the palladium, the terminal carbon of the double bond.

Table V. The Effect of Phosphines on the Vinylic Substitution with 1-Bromo-2-Methyl-1-Propene

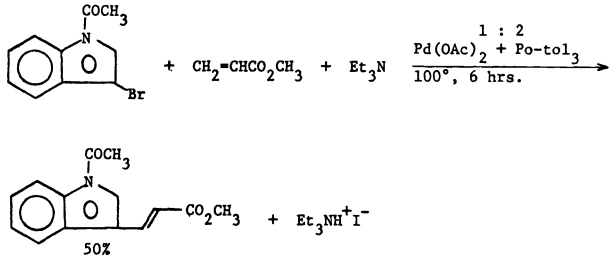


PR_3	P:Pd	Product Yields				
		Total %	%I	%II	%III	%IV
PPh_3	2:4	59	50	9	29	11
Po-tol_3	2:4	63	64	7	22	5
Po-tol_3	2:12	73	63	6	25	6
Po-EtPh	2:4	65	68	10	16	6
$P(2,5\text{-}i\text{-}Pr_2Ph)_3$	2:4	81	81	5	12	2

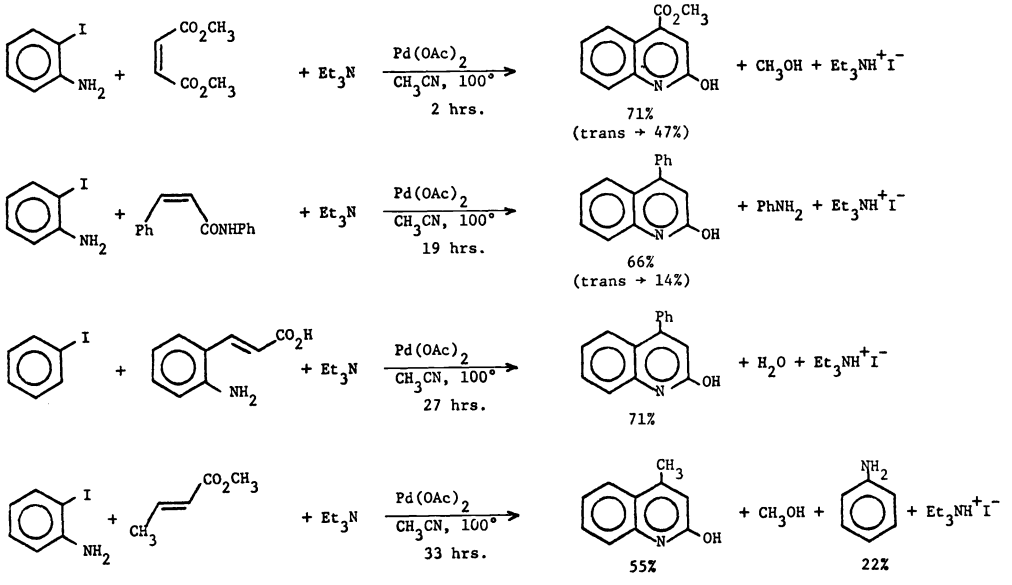
Aromatic dihalides may be reacted twice. For example, p-diiodobenzene and excess styrene produce E,E-p-distyrylbenzene in 67% yield. Bromoiodoaromatics are potentially more useful, however, if two different groups are to be added. In the absence of a phosphine or secondary amine, only the iodo group reacts while addition of a phosphine causes the bromo (and iodo) group to react. Thus, 4-bromoiodobenzene and methyl acrylate in the presence of palladium acetate form E-methyl p-bromocinnamate in 76% yield. This product on treatment with styrene and 1:2 palladium acetate-tri-o-tolylphosphine forms E,E-methyl 4-styrylcinnamate in 63% yield. Similarly, 2-bromoiodobenzene and acrylic acid (triethylamine salt, 2 equivalents of amine are required) with palladium acetate react in one hour at 100° to form E-2-bromocinnamate acid in 82% yield. The two halogen substituents may even be selectively reacted if they are on different molecules. Thus, 2-bromostyrene and 2-iodonitrobenzene react with a palladium acetate catalyst to form only E-2-bromo-2'-nitrostilbene in about 60% yield. Clearly, such reactions will provide extremely simple routes to numerous types of polynuclear compounds. Examples of such syntheses are now being investigated.



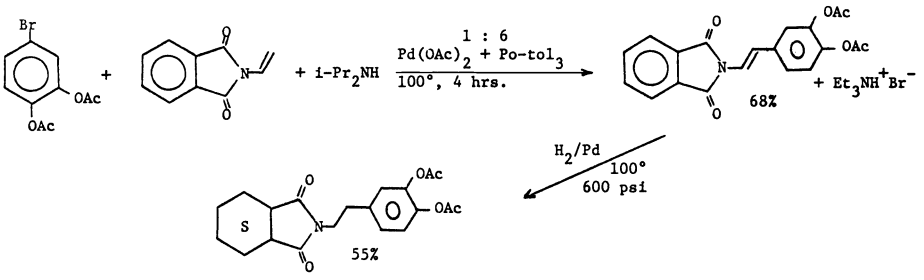
The third major class of halides which is useful in the vinylic substitution reaction is the heterocyclic halides. A variety of these halides now have been investigated and many undergo the reaction in high yield. For example, 2-bromothiophene, methyl 5-bromo-2-furanoate, 3-bromopyridine and 4-bromoiisoquinoline react well. 2- and 4-Bromopyridine, however, react only very slowly and in poor yield, with styrene. The desired products are obtainable in good yields, however, by reacting the appropriate vinylpyridine with bromobenzene. 3-Bromoindole apparently decomposes under our reaction conditions. However, the N-acetyl derivative does react in 50% yield with methyl acrylate.



The formation of heterocyclic rings by palladium catalyzed reactions of appropriately 2-substituted-vinylic or aryl halides also appears to be a useful reaction, at least, in some instances. Palladium-catalyzed cyclizations of 2-bromo-N-acryloylaniline, 2-bromo-N-3-cyclohexenylaniline and similar compounds do not proceed in high yield, presumably because it is difficult for the intermediate palladium complex to achieve the required geometry for the insertion to occur. On the other hand, quinolones are obtained easily from a variety of α,β-unsaturated esters, acids, or amides and 2-iodoaniline. Products with trans aryl and ester groups are expected from these reactions if the palladium has a choice of two α-hydrogens for elimination. These should not cyclize under the reaction conditions. Surprisingly, trans-cinnamate esters appear to be significant products only in the reactions of 2-iodoaniline with various substituted acrylate esters which have terminal vinyl groups. Even reactions of trans-3-substituted acrylic esters which should give trans-aryl esters in the vinylic substitution give appreciable amounts of cyclized products and no detectable amounts of trans aryl esters. We know that the stereospecificity of the addition-elimination sequence if low in the absence of a phosphine as in these cases, but still a substantial amount of the trans isomer would have been expected to have been formed. Cyclization probably is occurring before the palladium hydride elimination takes place. Even though the reactions of trans esters do yield cyclized products, higher yields have been obtained by reacting the corresponding cis esters. These should give cis aryl esters which would cyclize directly. Some examples of the reaction are shown below.

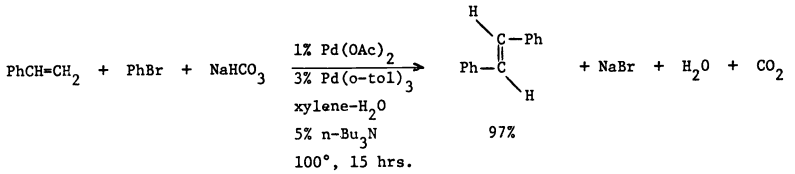


The potential applications of the vinylic substitution in organic syntheses, based upon the above examples and a great many more which I do not have time to mention, are very numerous. I will describe only one more, the vinylic substitution with N-vinylamides. As briefly noted before, N-vinylpyrrolidinone gives a 40:60 mixture of the N-1- and -2-styrylpyrrolidinones with bromobenzene and is therefore not a very useful reactant. However, N-vinylphthalimide reacts much more selectively and the only products isolated are the N-2-styryl derivatives. Since the products can be readily hydrogenated and hydrolyzed, this reaction provides a new route to 2-arylethylamines. For example, we have prepared N-2-(3',4'-diacetoxyphenyl)ethyl-tetrahydrophthalimide by this route starting with 3,4-diacetoxybromobenzene. The protected phenol is necessary in this case since free phenolic groups react with the N-vinyl group under the reaction conditions.

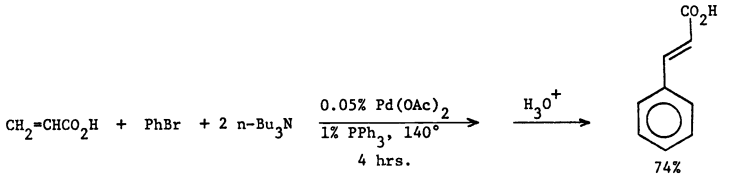


Hydrolysis of the product will yield dopamine, It is interesting that the phthalimide aromatic ring reduced at a rate comparable to that of the double bond with a palladium on charcoal catalyst.

The reactions described so far have generally been carried out with one mole percent of catalyst. While the cost of this amount of catalyst is easily tolerable in the laboratory for small scale preparations and would be acceptable for the commercial production of relatively valuable products, the reaction would find wider application if this cost could be reduced. Of course, the palladium can be recovered easily and recycled but this is time consuming and inconvenient. Some partial solutions to the problems are available. In the situation where reactants and products are stable to hydrolysis and the product has low solubility in the reaction solvent, continuous operation of the vinylic substitution reaction is possible with the use of very little palladium. Thus, stilbene can be made from styrene and bromobenzene in a two phase system of a xylene solution of the reactants and catalyst with 5% tri-n-butylamine and an aqueous phase containing sodium bicarbonate. After a few minutes reaction at 100°, crystals of stilbene appear at the interface and these can be removed continuously by filtration. Reactants can be added as they are used and the aqueous bicarbonate replaced as needed. The palladium and amine remain in the xylene phase for continuous reuse.



The question of how much palladium is really necessary to cause the reactions to occur is difficult to answer because it depends upon how fast the reaction must be. Reaction rates vary significantly with structure and, of course, with temperature. Substantial reductions in the amount of catalyst required over the 1% level appear possible in most reactions if higher temperatures than 100° are used. For example, acrylic acid and bromobenzene can be reacted in only 4 hrs. to form cinnamic acid (amine salt) in 74% yield with only 0.05 mole percent catalyst if the temperature is raised to 140-150°. The reaction remains homogeneous at this temperature.



This type of reaction can be made even more economical in palladium since the product may be selectively removed from amine, catalyst and solvent (xylene) by a base extraction and the catalyst-amine solution can be used again. We have reused the above solution three times. Palladium precipitation begins to occur with reuse because the triphenylphosphine is slowly quaternized. Even with this problem, the equivalent of about 6000. g of cinnamic acid were prepared per gram of palladium used and the palladium was still recoverable. Thus, in some cases, at least, catalyst costs can be reduced to relatively low amounts.

The vinylic substitution reaction, therefore, is a very convenient and versatile method for introducing unsaturated groups into molecules. The four major advantages of this reaction over others which produce the same products are:

(1) The reaction cannot be done in one step any other way.

(2) The reaction occurs under mild conditions and is not effected by water or air. (If a phosphine is used, an inert atmosphere is preferred, however.)

(3) The reaction is usually regioselective and stereospecific.

(4) The reaction is tolerant of almost every functional group.

In closing, I wish to acknowledge the assistance of many coworkers in this study. The main contributors to the new results reported in this lecture were:

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