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Palladium-Catalyzed Vinylic Substitution with Highly Activated Aryl Halides

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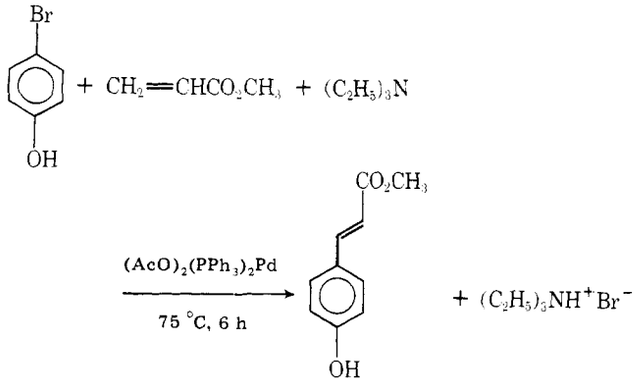
Aryl bromides with strongly electron-donating substituents generally do not undergo the triphenylphosphine–palladium acetate catalyzed vinylic substitution reaction in acceptable yields. Competing formation of tetraarylphosphonium salts from the aryl bromide and, in some cases, reduction of the aryl bromide to the arene occur. Significant improvements in yield are often obtained when tri-*o*-tolylphosphine is used in place of triphenylphosphine. In general, however, as good or even better results are obtained using the corresponding aryl iodide instead of the bromide when palladium acetate without a phosphine can be employed as the catalyst.

The palladium-catalyzed vinylic substitution reaction is a useful synthetic reaction.[1] Subsequent attempts by us to extend this reaction to aryl bromides containing strongly electron-donating substituents such as hydroxyl and amino groups, however, were generally unsuccessful. The synthetic value of the reaction obviously would be considerably enhanced if these reactants could be employed. Accordingly, we undertook a detailed study of the reaction to determine reasons for the lack of success and to find ways to promote it. This paper reports the results of the study.

Results and Discussion

Typical of the results obtained with highly activated aryl bromides is the 3% yield of (*E*)-methyl 4-hydroxycinnamate obtained from the reaction of 4-bromophenol with methyl acrylate catalyzed by 1 mol % of $(AcO)_2(PPh_3)_2Pd$ based upon the aryl bromide used. The reaction proceeds at 75 °C in 6 h



and no further increase in the yield occurs up to 48 h. The same low yield is found at a 100 °C reaction temperature. The reaction mixture is initially homogeneous, but soon begins to deposit black palladium metal. The reaction ceases because the required, soluble catalyst decomposes. Gas chromatographic analyses of the reaction mixture revealed that nearly all of the 4-bromophenol and methyl acrylate had not reacted and that a possible side product, phenol, was not formed in significant quantities. Two reasonable explanations for the deposition of palladium metal appeared possible: (1) the triphenylphosphine underwent a reaction leaving weakly solvated palladium atoms which rapidly formed insoluble metal; and (2) the palladium(0)–phosphine intermediate dissociated under the reaction conditions and the weakly complexed palladium atoms (e.g., $S_3Pd(PPh_3)$ or $S_2Pd(PPh_3)_2$, where S = solvent) agglomerated to form the metal. We already had evidence for the first possibility, since tetraphenylphosphonium bromide forms from triphenylphosphine and bromobenzene in the palladium-catalyzed reaction of bromobenzene and 3-buten-2-ol with a large excess of the phosphine.[2] We have now investigated the quaternization reaction independently of the vinylic substitution. The reaction is clearly palladium-catalyzed and very probably similar to the known nickel, zinc, and cadmium salt catalyzed quaternizations of phosphines with aryl halides.[3] A detailed kinetic analysis of the palladium-catalyzed reaction was not made, but a comparison of half lives of a series of reactions with a variety of substituents present revealed that the quaternization is facilitated by electron-donating groups para in either the aryl halide or triarylphosphine and retarded by at least one electron-withdrawing group in the aryl halide, the *m*-CF_3 group. The data are summarized in Table I. We only investigated triarylphosphines because earlier work had shown they were the most useful in our reaction.[1]

The substituent effects are not very large, but are in the direction required if this reaction is the cause of the low yield obtained in the reaction of *p*-bromophenol with methyl acrylate. The magnitude of the effect, the *p*-bromophenol being only 3.2 times more readily quaternized than the bromobenzene, appears to be too small to account for the total decrease in yield compared with the bromobenzene–methyl acrylate reaction where an 85% yield of methyl cinnamate was obtained.[1] Very probably the 4-bromophenol undergoes the vinylic substitution reaction more slowly than bromobenzene does, making the quaternization relatively more serious for it than the difference in quaternization rates would indicate.

3-Bromopyridine was very unreactive in the quaternization.

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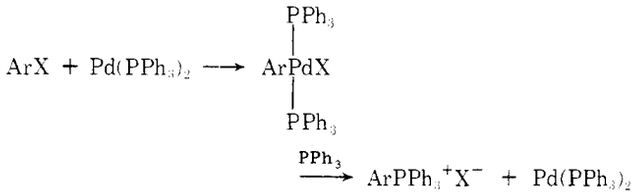
Table I. Relative Rates of Phosphonium Salt Formation at 100 °C[a]

aryl halide	registry no.	triarylphosphine	solvent	relative rate based on $T_{1/2}$
4-HOC_6H_4Br	106-41-2	PPh_3	CH_3CN	3.2
4-$H_2NC_6H_4Br$	106-40-1	PPh_3	CH_3CN	3.2
4-$CH_3C_6H_4Br$	106-38-7	PPh_3	CH_3CN	2.0
C_6H_5Br	108-86-1	PPh_3	CH_3CN	1.0
3-$CF_3C_6H_4Br$	401-78-5	PPh_3	CH_3CN	0.2
3-bromopyridine	626-55-1	PPh_3	CH_3CN	<0.1
$(CH_3)_2C{=}CHBr$	3017-69-4	PPh_3	CH_3CN	0.5
C_6H_5Br		P(*o*-tol)$_3$	DMAA	<0.1
4-HOC_6H_4Br		P(*o*-tol)$_3$	DMAA	<0.1
C_6H_5Br		P(4-$(CH_3)_2NC_6H_4)_3$	DMAA	6.4

[a] A mixture of 10 mmol of the halide and the phosphine with 0.1 mmol of $Pd(OAc)_2$ was heated in 5 mL of solvent. The disappearance of the aryl halide was followed by gas chromatography.

We were unable to measure significant reaction in 2 weeks at 100 °C. 1-Bromo-2-methyl-1-propene was about half as reactive as bromobenzene. The phosphonium salt was isolated in this case and in the reactions of 4-bromophenol and 4-bromotoluene with triphenylphosphine.

The mechanism of the quaternization reaction may involve oxidative addition of the aryl halide to a palladium(0)–phosphine complex, followed by reductive elimination of the phosphonium ion and a final loss of the halide ion from the



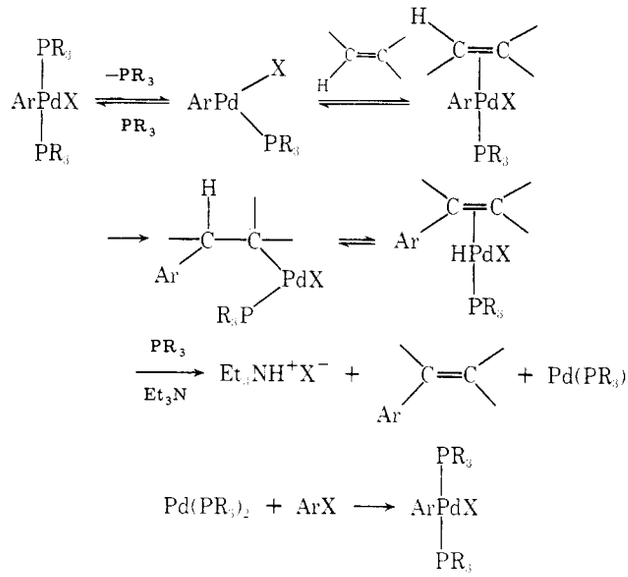
metal. The reductive elimination may require coordination of a third phosphine or another ligand before the phosphonium ion is lost.

A possible solution to the competing quaternization reaction problem may be to use triarylphosphines with electron-withdrawing substituents. Attempts to do this with either tris(3-trifluoromethylphenyl)phosphine or tris(4-carbomethoxyphenyl)phosphine[4] were unsuccessful. These phosphines were slightly better than triphenylphosphine, but still yields were poor even with 6 mol of phosphine per mole of palladium. Either quaternization was still too rapid or these phosphines formed less stable complexes which decomposed to palladium metal during the reaction.

A more successful way to inhibit the quaternization was found by using the hindered tri-*o*-tolylphosphine in the vinylic substitution reactions. The *o*-methyl groups apparently sterically prevent or at least significantly retard the reductive elimination of phosphonium salt, since no quaternization was observed between the *o*-tolylphosphine and bromobenzene or 4-bromophenol over a period of 2 weeks at 100 °C.

Fortunately, the presence of the *o*-methyl groups in the tri-*o*-tolylphosphine did not retard the vinylic substitution; in fact, they seemed to enhance the reaction in some cases. We reported little difference in rate between tri-*o*-tolylphosphine and triphenylphosphine when they were used in the reaction of bromobenzene with propenylbenzene,[1] but bromobenzene and methyl acrylate, for example, appear to react at least ten times faster with the *o*-tolylphosphine–palladium acetate catalyst than with one containing triphenylphosphine. In a large number of cases we find *o*-tolylphosphine is as good as and often superior to triphenylphosphine with respect to both the rate of the reaction and yield of product produced. The only general exception to this statement seems to be in reactions with sterically large aryl halides. 1-Bromo-2,5-diisopropylbenzene reacts with methyl acrylate in much higher yield (79% vs. 6%) with triphenylphosphine in the catalyst than with tri-*o*-tolylphosphine.[5] Apparently in the limited space around the palladium atom, large aryl groups and large phosphines cannot both be accommodated.

Scheme I



The acceleration in rate sometimes observed with the tri-*o*-tolylphosphine may be due to the greater tendency for its palladium complexes to dissociate. In particular, we believe the vinylic substitution reaction involves a dissociation of one triarylphosphine group from the initial oxidative addition product, the halobis(phosphine)arylpalladium(II) species, followed by olefin coordination at the vacant site. This proposal is supported by some preliminary kinetic results we have obtained on the (very complex) reaction of $PhPd(PPh_3)_2Br$ with ethylene, which shows the reaction to be inhibited by excess triphenylphosphine.[6] Thus, tri-*o*-tolylphosphine improves the vinylic substitution by inhibiting the quaternization and promoting dissociation (Scheme I).

The oxidative addition of the aryl halide to the bis(phosphine)palladium(0) complex may be more rapid with the *o*-tolylphosphine complex also, since it only forms a bis complex[7] which need not dissociate before undergoing oxidative addition.

The advantage of tri-*o*-tolylphosphine over a variety of other phosphines in the 4-bromophenol–methyl acrylate reaction is shown in Table II. The 2:1 tri-*o*-tolylphosphine–palladium acetate catalyst gave a nearly quantitative yield of methyl 4-hydroxycinnamate in the reaction, while under the same condition the 2:1 triphenylphosphine catalyst gave only a 3% yield.

Table II. Influence of the Organophosphine on the Palladium-Catalyzed Reaction of 4-Bromophenol with Methyl Acrylate[a]

phosphine	registry no.	P/Pd	reaction temp, °C	time, h	% yield (GLC)
Ph_3P	603-35-0	2	75	6[b]	3
Ph_3P		6	75	50[b]	5
$(o\text{-tol})_3P$	6163-58-2	2	75	22	98
$(o\text{-tol})_3P$		6	75	49	95
$(p\text{-tol})_3P$		2	100	45	26
$(\alpha\text{-nap})_3P$	3411-48-1	2	100	45	8
$(4\text{-}CH_3OCOC_6H_4)_3P$	66417-54-7	2	75	50	4
$(4\text{-}(CH_3)_2NC_6H_4)_3P$	1104-21-8	2	75	50	~0
$[2,3,4,5\text{-}(CH_3)_4C_6H]_3P$	66417-52-5	2	75	90	37
$[2,3,4,5\text{-}(CH_3)_4C_6H]_3P$		6	75	100	8
$(2\text{-}C_2H_5C_6H_4)_3P$	50777-27-0	2	75	51	43
$(2\text{-}C_2H_5C_6H_4)_3P$		6	75	50	95
$(2,5\text{-}i\text{-}Pr_2C_6H_3)_3P$	63600-29-3	2	75	53	27
$(2,5\text{-}i\text{-}Pr_2C_6H_3)_3P$		6	75	50	68
$[2\text{-}CH_3\text{-}5\text{-}t\text{-}BuC_6H_3]_3P$	66417-48-9	2	75	51	87
$[2\text{-}(CH_3\text{-}5\text{-}t\text{-}BuC_6H_3]_3P$		6	75	49	95
$(2\text{-}CH_3\text{-}4\text{-}(CH_3)_2NC_6H_3)_3P$	66417-47-8	2	75	50	20
$[2\text{-}CH_3\text{-}5\text{-}CF_3C_6H_3]_3P$	66417-45-6	2	75	35	29
$[2\text{-}CH_3\text{-}5\text{-}CF_3C_6H_3]_3P$		6	75	49	95
$2,6\text{-}(CH_3O)_2C_6H_3PPh_2$	66417-43-4	2	75	8[b]	1
$(NCCH_2CH_2)_3P$	4023-53-4	2	75	4[b]	~0

[a] Carried out with 1 mol % of palladium acetate based upon the aryl halide. [b] No further increase in yield was observed with longer reaction time.

The use of more than 2 mol of phosphine per mole of palladium often improves yields because any phosphine quaternized is replaced by the excess. Addition of electron-donating groups to the *o*-tolylphosphine [tris(2,3,4,5-tetramethylphenyl)phosphine, tris(2-methyl-5-*tert*-butylphenyl)phosphine, or tris(2-methyl-4-dimethylaminophenyl)-phosphine] or electron-withdrawing groups [tris(2-methyl-5-trifluoromethylphenyl)phosphine] did not produce phosphines that formed catalysts as good as tri-*o*-tolylphosphine. Likewise, increasing the size of the ortho group to ethyl [tris(*o*-ethylphenyl)phosphine] or isopropyl [tris(2,5-diisopropylphenyl)phosphine] did not give phosphines that were as good as tri-*o*-tolylphosphine. The larger ortho groups are less effective because the intermediate bis(phosphine)palladium(0) complexes are less stable than the *o*-tolyl complex[7] and dissociation with precipitation of palladium metal becomes a serious side reaction.

$$Pd(PR_3)_2 \rightarrow \underline{Pd} + 2\,PR_3$$

The results of the application of the tri-*o*-tolylphosphine catalyst in reactions of various halophenols and halophenyl acetates with methyl acrylate or styrene are shown in Table III. The reaction of 4-bromophenol with styrene is also significantly improved by use of the tri-*o*-tolylphosphine catalyst. 2-Bromophenol does not react as readily with methyl acrylate as does the 4-bromo isomer even with the 6:1 *o*-tolylphosphine catalyst (24% product yield vs. 98%). Similarly, 3-bromophenol only gives low yields of product with methyl acrylate. For unknown reasons, 3-bromophenol is exceptional and the tri-*o*-tolylphosphine is inferior to triphenylphosphine as a ligand.

The acetate of 2-bromophenol reacts better with methyl acrylate than the free phenol, giving a 66% yield of product, and if 2 mol % of palladium acetate is used rather than one, an almost quantitative yield of (*E*)-methyl 2-acetoxycinnamate is obtained.

The 2,4-, 3,4-, and 2,5-dihydroxybromobenzenes, as might have been anticipated from the above results, gave none of the vinylic substitution products on reaction with methyl acrylate even with 6:1 tri-*o*-tolylphosphine–palladium acetate catalysts. Diacetylation was helpful, although yields were still very poor to moderate (3–47%). The use of more electron-withdrawing ester substituents in the phenols did not raise the yields. The dimethanesulfonate and bis(trifluoro)acetate of 2,4-dihydroxybromobenzene did not even undergo the desired reactions. Palladium precipitation occurred very quickly in both of these cases and neither of the expected products was obtained.

The major reason for failure of the vinylic substitution reaction with 2,4-dihydroxybromobenzene, and presumably the other dihydroxy compounds also, is that reduction of the halide to the dihydroxybenzene occurs preferentially under the reaction conditions. The reducing agent was not discovered, but large amounts (60%) of resorcinol were produced from the bromide.

Reactions of highly activated aryl halides with olefins less reactive than methyl acrylate or styrene give lower yields or none of the expected vinylic substitution products. For example, 2-bromoaniline does not yield the usual product on reaction with dimethyl maleate, only a dark polymeric oil, while bromobenzene reacts normally, although in poor yield.[8]

In many instances the best solution to the problem of obtaining vinylic substitution products with highly activated aromatics is to use aryl iodides where the addition of phosphines to the catalyst is unnecessary. Thus, as shown in Table III, 2-iodophenol reacts with methyl acrylate without a phosphine present with acetonitrile as solvent to form (*E*)-methyl 2-hydroxycinnamate in 95% yield compared with only 24% in the best reaction with 2-bromophenol. The addition of phosphines to the 2-iodophenol reaction offers no advantage; in fact the reactions are slowed and product yields are decreased when either triphenyl- or tri-*o*-tolylphosphine is added. The presence of phosphines promotes reduction of the iodides to phenol. 3-Iodophenol also reacts in 95% yield with methyl acrylate in the absence of a phosphine. 2-Hydroxy-4-benzoxyiodobenzene does not yield the expected product with methyl acrylate under the same conditions. However, 2,4-dibenzoxyiodobenzene reacts with methyl acrylate in 48% yield to give a mixture of mono- and dibenzoates of methyl

Table III. Vinylic Substitution Reactions with Halophenols and Halophenyl Acetates[a]

aryl halide	registry no.	olefin[i]	triarylphosphine	P/Pd	time, h, at 100 °C	product (% yield)	registry no.
4-HOC_6H_4Br		$C_6H_5CH=CH_2$	$(o\text{-tol})_3P$	2	43	4-$HOC_6H_4CH=CHC_6H_5$ (44)	6554-98-9
4-HOC_6H_4Br		$C_6H_5CH=CH_2$	$(o\text{-tol})_3P$	6	19	4-$HOC_6H_4CH=CHC_6H_5$ (76)	
2-HOC_6H_4Br	95-56-7	$CH_2=CHCO_2CH_3$	Ph_3P	6	28[b]	(*E*)-$CH_3OCOCH=CHC_6H_4OH$-2 (7)	6236-69-7
2-HOC_6H_4Br		$CH_2=CHCO_2CH_3$	$(o\text{-tol})_3P$	6	28[b]	(*E*)-$CH_3OCOCH=CHC_6H_4OH$-2 (24[c])	
3-HOC_6H_4Br	591-20-8	$CH_2=CHCO_2CH_3$	Ph_3P	2	21[b]	(*E*)-$CH_3OCH=CHC_6H_4OH$-3 (2)	66417-53-6
3-HOC_6H_4Br		$CH_2=CHCO_2CH_3$	Ph_3P	6	7[b]	(*E*)-$CH_3OCH=CHC_6H_4OH$-3 (24)	
3-HOC_6H_4Br		$CH_2=CHCO_2CH_3$	$(o\text{-tol})_3P$	2	6[b]	(*E*)-$CH_3OCH=CHC_6H_4OH$-3 (4)	
3-HOC_6H_4Br		$CH_2=CHCO_2CH_3$	$(o\text{-tol})_3P$	6	6[b]	(*E*)-$CH_3OCH=CHC_6H_4OH$-3 (6)	
2-$AcOC_6H_4Br$	1829-37-4	$CH_2=CHCO_2CH_3$	$(o\text{-tol})_3P$	8	18	(*E*)-$CH_3OCOCH=CHC_6H_4OAc$-2 (66)	6286-83-5
2-$AcOC_6H_4Br$		$CH_2=CHCO_2CH_3$	$(o\text{-tol})_3P$	8[d]	18	(*E*)-$CH_3OCOCH=CHC_6H_4OAc$-2 (95)	
2-4-$(AcO)_2$-C_6H_3Br	66417-41-2	$CH_2=CHCO_2CH_3$	$(o\text{-tol})_3P$	8	4	(*E*)-$CH_3OCOCH=CHC_6H_3(OAc)_2$-2,4 (26)	66417-51-4
2,4-$(AcO)_2$-C_6H_3Br		$CH_2=CHCO_2CH_3$	$(2,5\text{-}i\text{-}Pr_2C_6H_3)_3P$	6	48	(*E*)-$CH_3OCOCH=CHC_6H_3(OAc)_2$-2,4 (25)	
3,4-$(AcO)_2$-C_6H_3Br	66373-95-3	$CH_2=CHCO_2CH_3$	Ph_3P	6	20[e]	(*E*)-$CH_3OCOCH=CHC_6H_3(OAc)_2$-3,4 (5)	66417-50-3
3,4-$(AcO)_2$-C_6H_3Br		$CH_2=CHCO_2CH_3$	$(o\text{-tol})_3P$	6	7	(*E*)-$CH_3OCOCH=CHC_6H_3(OAc)_2$-3,4 (47)	
2,5-$(AcO)_2$-C_6H_3Br	52376-16-6	$CH_2=CHCO_2CH_3$	$(o\text{-tol})_3P$	6	24	(*E*)-$CH_3OCOCH=CHC_6H_3(OAc)_2$-2,5 (3)	66417-49-0
2-HOC_6H_4I	533-58-4	$CH_2=CHCO_2CH_3$	Ph_3P	6	9	(*E*)-$CH_3OCOCH=CHC_6H_4OH$-2 (83)	
2-HOC_6H_4I		$CH_2=CHCO_2CH_3$	$(o\text{-tol})_3P$	6	9	(*E*)-$CH_3OCOCH=CHC_6H_4OH$-2 (68)	
2-HOC_6H_4I[f]		$CH_2=CHCO_2CH_3$			3	(*E*)-$CH_3OCOCH=CHC_6H_4OH$-2 (95)	
3-HOC_6H_4I[f]	626-02-8	$CH_2=CHCO_2CH_3$			5	(*E*)-$CH_3OCOCH=CHC_6H_4OH$-3 (95)	66417-46-7
2,4-$(BzO)_2C_6H_3I$[f]	66417-40-1	$CH_2=CHCO_2CH_3$			24	(*E*)-$CH_3OCOCH=CHC_6H_3(OBz)_2$-2,4 (48[h])	66417-44-5
2,4-$(CH_3O)_2C_6H_3Br$[g]	17715-69-4	$CH_2=CHCO_2CH_3$	$(o\text{-tol})_3P$	6	41	(*E*)-2,4-$(CH_3O)_2C_6H_3CH=CHCO_2CH_3$ (13[b])	66417-42-3

[a] Mixtures of 10 mmol of the aryl halide, 12.5 mmol of olefin, 12.5 mmol or more of triethylamine, and 0.10 mmol of palladium acetate or chloride were used in these reactions. [b] The yield did not increase with longer reaction times. [c] Also formed, 13% phenol. [d] With 2 mol % $Pd(OAc)_2$. [e] At 140 °C. [f] Acetonitrile, 4 mL added. [g] DMF (3 mL) added. [h] After rebenzoylation. [i] Registry no.: $C_6H_5CH=CH_2$, 100-42-5; $CH_2=CHCO_2CH_3$, 96-33-3.

2,4-dihydroxycinnamate. Even 2,4-dimethoxybromobenzene with the tri-*o*-tolylphosphine catalyst did not give a high yield of product in the reaction with methyl acrylate (13%).

The bromoanilines are similar, in their behavior in the vinylic substitution reaction, to the bromophenols. Table IV gives the results of various vinylic substitutions carried out with *p*- and *o*-bromoaniline. 4-Bromoaniline reacted with methyl acrylate with an 8:1 triphenylphosphine–palladium acetate catalyst to form (*E*)-methyl 2-aminocinnamate in only 4% yield, while the same reaction with the *o*-tolyl catalyst gave the product in 73% (isolated) yield in one-tenth the time. Similarly styrene and 4-bromoaniline gave (*E*)-4-aminostilbene in 45% (isolated) yield with the *o*-tolyl catalyst and in 23% yield with triphenylphosphine. Tris(*o*-ethylphenyl)-phosphine was slightly better than tri-*o*-tolylphosphine in this reaction, giving a 53% yield. 2-Bromoaniline reacted well with styrene (73% product) and acrylic acid (65% yield) but not with acrylonitrile, using the tri-*o*-tolylphosphine catalyst in each case. Acetylation of 4-bromoaniline and reaction with methyl acrylate gave an 83% (isolated) yield of (*E*)-methyl 4-acetamidocinnamate as compared with a 48% yield (GLC) obtained with the free amino compound under the same conditions. As with the phenols, 2-iodoaniline reacts in higher yield in the vinylic substitution than the bromo compound does. 2-Iodoaniline and acrylonitrile gave 53% (*E*)-2-amino-cinnamonitrile, while 2-bromoaniline gave none of this product under our usual conditions. 2-Iodoaniline and acrylic acid formed the expected 2-aminocinnamic acid in 72% (isolated) yield compared with 65% from the bromo compound. Surprisingly, the highly activated 2-amino-5-hydroxyiodobenzene and styrene reacted to form 2-amino-5-hydroxystilbene in 50% yield.

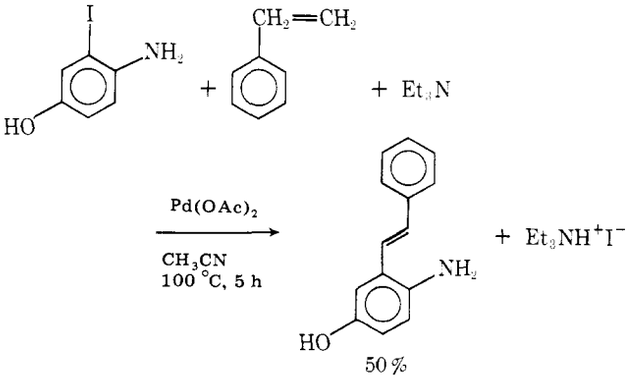


Table IV. Vinylic Substitution Reactions with Haloanilines and Acetanilides[a]

aryl halide	registry no.	olefin	triarylphosphine	P/Pd	time, h, at 100 °C	product (% yield)[b]	registry no.
4-$H_2NC_6H_4Br$		CH_2=$CHCO_2CH_3$	Ph_3P	8	22	(*E*)-CH_3OCOCH=$CHC_6H_4NH_2$-4 (4)	66417-26-3
4-$H_2NC_6H_4Br$		CH_2=$CHCO_2CH_3$	(o-tol)$_3P$	4	3	(*E*)-CH_3OCOCH=$CHC_6H_4NH_2$-4 (48)	
4-$H_2NC_6H_4Br$		CH_2=$CHCO_2CH_3$	(o-tol)$_3P$	8	2	(E)-CH_3OCOCH=$CHC_6H_4NH_2$-4 (73[c])	
4-$H_2NC_6H_4Br$		CH_2=CHC_6H_5	Ph_3P	6	24	(*E*)-C_6H_5CH=$CHC_6H_4NH_2$-4 (23)	4309-66-4
4-$H_2NC_6H_4Br$		CH_2=CHC_6H_5	(o-tol)$_3P$	6	2	(*E*)-C_6H_5CH=$CHC_6H_4NH_2$-4 (45)	
4-$H_2NC_6H_4Br$		CH_2=CHC_6H_5	(o-EtPh)$_3P$	6	2	(*E*)-C_6H_5CH=$CHC_6H_4NH_2$-4 (53)	
2-$H_2NC_6H_4Br$	615-36-1	CH_2=CHC_6H_5	(o-tol)$_3P$	8	2	(*E*)-C_6H_5CH=$CHC_6H_4NH_2$-2 (73[c,d])	27652-35-3
2-$H_2NC_6H_4Br$		CH_2=CHC_6H_5	(o-tol)$_3P$	6	12	(*E*)-$HOCOCH$=$CHC_6H_4NH_2$-2 (65[c,f])	22469-15-4
2-$H_2NC_6H_4Br$		CH_2=$CHCO_2H$[e]	(o-tol)$_3P$	4	100	(*E*)-$NCCH$=$CHC_6H_4NH_2$-2 (~0[f])	58106-57-3
4-$CH_3CONHC_6H_4Br$	103-88-8	CH_2=$CHCN$[g]	(o-tol)$_3P$	4	3	(*E*)-CH_3OCOCH=$CHC_6H_4NHCOCH_3$-4 (83[c])	66417-25-2
2-$H_2NC_6H_4I$	615-43-0	CH_2=$CHCN$			40	(*E*)-$NCCH$=$CHC_6H_4NH_2$-2 (53[c,f])	
2-$H_2NC_6H_4I$		CH_2=$CHCO_2CH_3$			80	(*E*)-$HOCOCH$=$CHC_6H_4NH_2$-2 (72[c,f])	
2-H_2N-5-HOC_6H_3I	66416-73-7	C_6H_5CH=CH_2			5	(*E*)-C_6H_5CH=$CHC_6H_3NH_2$-2,OH-5 (50[c])	66417-31-0

[a] Reaction mixtures contained 10 mmol of aryl halide, 12.5 mmol of olefin, 0.10 mmol of palladium salt, and 5 mL of triethylamine. [b] GLC yields except where noted. [c] Yield of isolated product. [d] 10 mL of triethylamine used rather than 5 mL. [e] 30 mmol of triethylamine used. [f] Results of M. Terpko. [g] Registry no.: 107-13-1.

Cyclization products of the *o*-hydroxy- and *o*-aminocinnamate esters, coumarin or quinoline derivatives, were not observed in any of the reactions described above. If cyclization were fast compared with palladium hydride elimination in the intermediate arylpalladium complex–olefin adduct, cyclic products could have been formed. Reaction of 2-iodoaniline with a variety of substituted acrylic acid derivatives, however, does produce cyclic products, 2-quinolines, in moderate to good yields. The cyclization reactions will be reported in detail elsewhere.[9]

Experimental Section

Table V, containing the melting points, molecular weights, and NMR spectra of the products prepared, will appear only in the microfilm edition of the journal. (See note on supplementary material at the end of this paper.)

Reagents. The isomeric bromo- and iodophenols and -anilines were commercial products, used as received. Methyl acrylate, acrylic acid, acrylonitrile, and styrene were also used as obtained from industrial sources. Triethylamine and acetonitrile were dried with molecular sieves before use. Triphenylphosphine was a product of the Aldrich Chemical Co., Inc., and tris(4-dimethylaminophenyl)phosphine was from the Strem Chemical Co. Other phosphines were prepared as described below. Bromoresorcinol and bromohydroquinone were obtained from Aldrich, also, and 4-bromocatechol was prepared by the method shown in "Organic Syntheses".[10] Acetylation of the phenols was done with acetic anhydride and pyridine at 100 °C. 2-Hydroxy-4-benzoxyiodobenzene was prepared as described by Nicolet:[11] mp 160–164 °C dec; reported 153–155 °C dec.[11] This compound was benzoylated with benzoyl chloride at 130 °C to give the dibenzoate: mp 176–178 °C; mol wt 443.992 (calcd 443.985). 4-Hydroxy-2-iodoaniline was prepared as described by Kvalnes.[12] 4-Bromoresorcinol dimethyl ether was made by the method of Buu-Hoi.[13]

Tri-*o*-tolylphosphine. The Grignard reagent was prepared under nitrogen from 100 g (0.585 mol) of *o*-bromotoluene and 15.4 g (0.644 mol) of magnesium in 200 mL of dry THF. It was necessary to add 0.5 mL of ethylene dibromide to initiate the reaction. After heating the Grignard solution under a reflux condenser for 2 h the solution was allowed to cool and 15.7 mL (0.185 mol) of phosphorus trichloride in 50 mL of dry THF was added dropwise in about 30 min. The resulting solution was boiled for 15 h, after which time the mixture was cooled and excess saturated ammonium chloride solution was added. The product was extracted with three portions of ether. After drying the ether was removed under reduced pressure and the solid remaining was recrystallized from ethanol to give 40 g (71%) of tri-*o*-tolylphosphine: mp 123–125 °C (reported 125 °C).[14] The ^{31}P NMR spectrum had a single peak at −29.32 ppm in $CDCl_3$.

Tris(*o*-ethylphenyl)phosphine. The same procedure as used in the tri-*o*-tolylphosphine preparation was used. The yield in this case was only 24%, however. The product melted at 98–99 °C and the ^{31}P NMR spectrum had a single peak at −34.48 ppm. NMR ($CDCl_3$) δ 7.05 (m, 4 H), 2.85 (q, J = 7 Hz, 2 H), 1.1 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{24}H_{27}P$: C, 83.20; H, 7.86. Found: C, 83.16; H, 7.82.

Tris(2,5-diisopropylphenyl)phosphine. The preparation of this material has been described previously.[5]

Tri-α-naphthylphosphine. This material, mp 261–264 °C (reported 263–265 °C),[15] was prepared by the Grignard procedure described above in 14% yield. The ^{31}P NMR peak was at −33.00 ppm in $CDCl_3$ solution.

Tris(2,3,4,5-tetramethylphenyl)phosphine. The Grignard reagent was prepared from 5-bromo-1,2,3,4-tetramethylbenzene[16] as in the tri-*o*-tolylphosphine reaction and reacted with phosphorus trichloride. Recrystallization from chloroform–heptane gave a 20% yield of the phosphine: mp 258–261 °C. ^{31}P NMR showed a single peak at −26.27 ppm. NMR ($CDCl_3$) δ 6.55 (d, J = 4 Hz, 1 H), 2.3 (s, 3 H), 2.2 (s, 6 H), 2.1 (s, 3 H). Anal. Calcd for $C_{30}H_{39}P$: C, 83.68; H, 9.13. Found: C, 83.45; H, 9.04.

Tris(5-trifluoromethyl-2-methylphenyl)phosphine. *p*-(Trifluoromethyl)benzyl alcohol, bp 79–80 °C (4.5 mm) [reported 49–50 °C (5 mm)],[17] was prepared in 88% yield by the reduction of *p*-(trifluoromethyl)benzoic acid with lithium aluminum hydride in ether solution. The benzylic alcohol was reduced in 3 h in acetic acid solution and a few drops of 70% perchloric acid with 5% palladium on charcoal under 22 psi of hydrogen at room temperature. A 60% yield of *p*-(trifluoromethyl)toluene, bp 129–130 °C (reported 129 °C),[18] was obtained.

A solution of 12.1 g (76 mmol) of bromine in 10 mL of carbon tet-

rachloride was added to 12 g (76 mmol) of 4-(trifluoromethyl)toluene in 20 mL of carbon tetrachloride. A few milligrams of iron was added and the mixture was refluxed for 1.5 h. The reaction mixture was cooled and extracted twice with water. A solution of 0.5 g of sodium metal in 50 mL of ethanol was added and the mixture was allowed to stand at room temperature for 36 h. The sodium bromide formed was removed by washing with water. After drying and distilling there was obtained 12.3 g (66%) of 2-bromo-4-(trifluoromethyl)toluene. NMR ($CDCl_3$) δ 7.5 (m, 3 H) and 2.35 (s, 3 H).

The phosphine was prepared from the above bromide as in the tri-*o*-tolylphosphine example. There was obtained a 29% yield of the phosphine, mp 99–101 °C, after recrystallization from ethanol. The ^{31}P NMR spectrum showed a single peak at −26.71 ppm. NMR ($CDCl_3$) δ 7.4 (m, 3 H) and 2.45 (s, 3 H). Anal. Calcd for $C_{24}H_{18}F_9P$: C, 56.70; H, 3.57. Found: C, 56.62; H, 3.65.

Tris(2-methyl-5-*tert*-butylphenyl)phosphine.[19] 2-Bromo-4-*tert*-butyltoluene was prepared by the bromination of 4-*tert*-butyltoluene.[20] A 57% yield of the bromide, bp 87 °C (0.4 mm), was obtained.

The Grignard reagent was prepared and reacted with phosphorus trichloride as in the tri-*o*-tolylphosphine example. There was obtained a 31% yield of the product: mp 197–198.5 °C. The mass spectrum showed M^+ 473.322 (calcd 473.334). The ^{31}P NMR spectrum showed a peak at −29.09 ppm in $CDCl_3$. NMR ($CDCl_3$) δ 7.15 (s, 2 H), 6.70 (s, 1 H), 2.30 (s, 3 H), 1.00 (s, 9 H).

Diphenyl-2,6-dimethoxyphenylphosphine.[19] To an ice cold solution of 56 mL of 1.8 M *n*-butyllithium dissolved in 400 mL of ether was added 13.82 g (0.1 mol) of resorcinol dimethyl ether in 75 mL of ether. The solution was heated to boiling under nitrogen for 20 h. The solution was cooled to room temperature and 18 mL (0.1 mol) of chlorodiphenylphosphine in 70 mL of ether was added dropwise in 1 h. After boiling for 22 h the solution was cooled and saturated aqueous ammonium chloride was added. The ether layer was separated, dried, and concentrated to a yellow oil. The compound crystallized from ethanol at dry ice temperatures. The solid was collected and recrystallized from ethanol to give 3.05 g (9%) of colorless crystals: mp 110–111.5 °C. The molecular weight by mass spectroscopy was 322.111 (calcd 322.112). The ^{31}P NMR band was at −24.86 ppm in $CDCl_3$. NMR ($CDCl_3$) δ 7.25 (s, 10 H), 6.50 (m, 3 H), 3.45 (s, 6 H).

Tris(*p*-carbomethoxyphenyl)phosphine.[21] This material was prepared by the method of Schiemenz:[22] mp 124–126 °C; ^{31}P NMR peak at −5.27 ppm.

Tris(2-methyl-4-dimethylaminophenyl)phosphine.[21] A mixture of 14.5 mL (0.1 mol) of *N,N*-dimethyl-*m*-toluidine in 50 mL of dry pyridine was stirred rapidly while 3.1 mL of phosphorus tribromide was added. The yellow mixture was then heated at 125 °C for 1 h. After cooling the reaction mixture was diluted with 500 mL of benzene and the solution was extracted with 200 mL of 6 N sodium hydroxide and then with water. After drying the solvent was distilled under reduced pressure. The oil remaining gave crystals on stirring with a little acetone: mp >260 °C. The ^{31}P NMR peak was at −36.16 ppm, and the mass spectrum gave a molecular ion at 433.264 (calcd 433.261).

General Procedure for the Measurement of the Rates of Phosphonium Salt Formation. Mixtures of 10 mmol of the aryl halides and 10 mmol of the triarylphosphine with 0.1 mmol of palladium acetate and an internal GLC standard in 5 mL of solvent (acetonitrile or dimethylacetamide) were heated at 100 °C in capped nitrogen-filled tubes. Samples were withdrawn by syringe periodically and the extent of reaction was determined by noting the disappearance of the aryl halide by GLC. At the completion of the reactions several of the phosphonium salts were isolated by adding acetone to the cooled reaction mixture. The precipitated salt was filtered, washed with acetone, and dried. The following compounds were isolated.

Triphenyl-4-hydroxyphenylphosphonium bromide: 75% yield; mp 293–294 °C (reported 279–280 °C).[23] ^{31}P NMR showed a peak at 22.29 ppm in $CDCl_3$. Anal. Calcd for $C_{24}H_{20}OPBr$: C, 66.22; H, 4.63. Found: C, 66.35; H, 4.70.

Triphenyl-4-aminophenylphosphonium bromide: 62% yield; mp 334–337 °C (reported 316 °C).[24] ^{31}P NMR showed a peak at 23.09 ppm in $CDCl_3$. Anal. Calcd for $C_{24}H_{21}NPBr$: C, 66.37; H, 4.87; N, 3.22. Found: C, 65.52; H, 4.94; N, 3.18.

Triphenyl-*m*-(trifluoromethyl)phosphonium bromide: mp 214–217 °C. ^{31}P NMR showed a peak at 20.65 ppm.

Triphenyl-1-propenylphosphonium bromide: mp 216–218 °C (reported 235 °C).[25] ^{31}P NMR showed a peak at 18.13 ppm.

General Procedure for the Vinylic Substitution Reaction. The procedure was essentially the one described previously.[1] In cases where triarylphosphines were not added, acetonitrile was used as solvent. The progress of the reactions was generally followed by GLC analyses of the remaining organic halide. Phenolic reactants were silylated with bis(trimethylsilyl)acetamide before GLC analysis. When product yields were determined by GLC, internal standards of either naphthalene or benzophenone were used. Two examples of the procedure are given below.

(*E*)-Methyl 4-Hydroxycinnamate. A mixture of 1.73 g (10 mmol) of 4-bromophenol, 1.08 g (12.5 mmol) of methyl acrylate, 0.784 g (0.1 mmol) of $PdCl_2[P(o\text{-tol})_3]_2$,[26] 0.1212 g (0.40 mmol) of tri-*o*-tolylphosphine, and 10 mL of triethylamine was heated in a capped nitrogen-filled tube at 100 °C for 4.5 h. The tube was shaken initially to obtain a homogeneous solution. The cooled reaction mixture was stirred with 100 mL of 1 M hydrochloric acid and the insoluble product was filtered. After washing with water the solid was dissolved in ether and dried, the solvent was removed, and the product was crystallized from heptane to give 1.26 g (71%) of colorless crystals: mp 135.5–137 °C. Other properties are given in Table V.

2-Aminostilbene. A mixture of 3.44 g (20 mmol) of *o*-bromoaniline, 2.6 g (25 mmol) of styrene, 0.045 (0.2 mmol) of palladium acetate, 0.24 g (0.80 mmol) of tri-*o*-tolylphosphine, and 10 mL of triethylamine was heated at 100 °C in a nitrogen-filled capped tube for 2 h. The cooled reaction mixture was broken up in ether and filtered. The amine salt was washed several times with ether, the combined ether extracts were concentrated, and the crude product was sublimed (150 °C, 0.5 mm) and recrystallized from heptane. There was obtained 2.85 g (73%) of product: mp 102–105 °C. Other data are given in Table V.

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Registry No.—(*E*)-4-$HOC_6H_4CH{=}CHCO_2CH_3$, 19367-38-5; *o*-bromotoluene, 95-46-5; phosphorus trichloride, 7719-12-2; 5-bromo-1,2,3,4-tetramethylbenzene, 40101-36-8; *p*-(trifluoromethyl)benzoic acid, 455-24-3; *p*-(trifluoromethyl)toluene, 6140-17-6; 2-bromo-4-(trifluoromethyl)toluene, 66417-30-9; 2-bromo-4-*tert*-butyltoluene, 61024-94-0; 4-*tert*-butyltoluene, 98-51-1; resorcinol dimethyl ether, 151-10-0; chlorodiphenylphosphine, 1079-66-9; *N,N*-dimethyl-*m*-toluidine, 121-72-2; triphenyl-4-hydroxyphenylphosphonium bromide, 22883-70-1; triphenyl-4-aminophenylphosphonium bromide, 22883-72-3; triphenyl-*m*-(trifluoromethyl)phosphonium bromide, 66417-29-6; (*E*)-triphenyl-1-propenylphosphonium bromide, 28691-76-1.

Supplementary Material Available: Table V with properties of the products prepared, melting points, molecular weights, and NMR data (2 pages). Ordering information is given on any current masthead page.

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