Palladium-Catalyzed Vinylic Substitution Reactions with Carboxylic Acid Derivatives

Babu A. Patel, Carl B. Ziegler, Nicholas A. Cortese, Joseph E. Plevyak, Thomas C. Zebovitz, Marc Terpko, and Richard F. Heck*

Chemistry Department, University of Delaware, Newark, Delaware 19711

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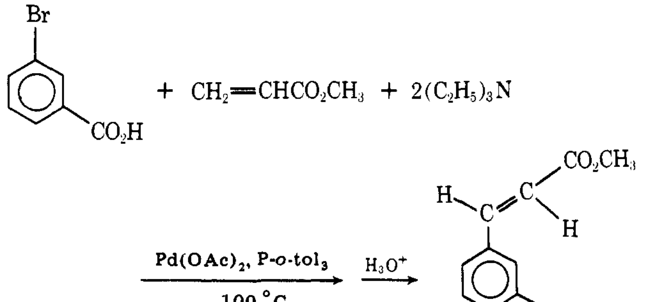
Palladium-catalyzed vinylic substitutions occur normally with both *m*- and *p*-bromobenzoic acid in the presence of 2 equiv of a tertiary amine. The ortho acid does not react. Its methyl ester does, however. Free carboxylic acid groups may also be present in the olefinic reactant. Acrylic, crotonic, and methacrylic acids were successfully reacted. As little as 0.05 mol % catalyst could be used with reaction temperatures of 150 °C in these homogeneous reactions. The reaction was also shown to proceed normally in the presence of aldehyde, cyano, thiomethyl, amide, and phenanthryl groups. Even the highly hindered 2-bromo-1,4-diisopropylbenzene reacted well with methyl acrylate at 125 °C.

Organopalladium compounds are highly selective reagents. They react with double bonds in the presence of a wide variety of functional groups. They are generally unreactive toward carbomethoxyl,[1] nitro,[1] chloro,[1] cyano,[2] methoxyl,[2] thenyl,[2] pyridyl,[2] acetoxyl,[3] phenolic,[4] and aromatic amino[4] groups. We now report examples of palladium-catalyzed vinylic substitutions with reactants containing free carboxylic acid groups and other related functional groups not used previously.

Results and Discussion

Both *m*- and *p*-bromobenzoic acids reacted normally with alkenes. Using 1 mol % of palladium acetate and 4 mol % of tri-*o*-tolylphosphine based upon the organic halide as catalyst and 2 equiv of triethylamine, the meta acid and methyl acrylate formed (*E*)-methyl *m*-carboxycinnamate (triethylammonium salt) in 67% yield in 5.5 h at 100 °C. The *p*-bromobenzoic acid and styrene reacted under similar conditions to form *p*-carboxystilbene in 74% yield. The data are given in Table I. *o*-Bromobenzoic acid, however, failed to react with methyl acrylate even at temperatures up to 125 °C. Very probably a stable chelated organopalladium complex is formed. An attempt to prepare this complex from the *o*-bromo acid and $(PPh_3)_4Pd$ led to the formation of at least six products as determined by the ^{31}P NMR spectrum of the reaction product. Recrystallization failed to separate pure fractions. Some support for proposing formation of a stable chelate with the free acid is the fact that the methyl ester of *o*-bromobenzoic acid did react normally and produce methyl *o*-carbomethoxycinnamate in 69% yield in only 3 h at 100 °C.

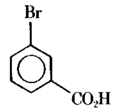
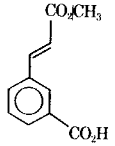
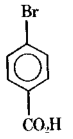
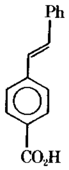
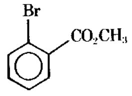
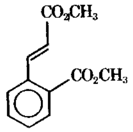
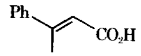
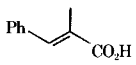
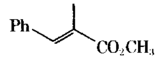
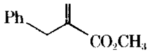
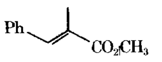
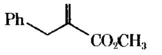


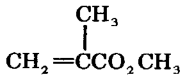
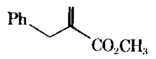
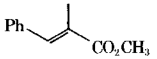
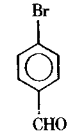
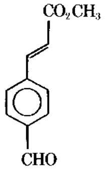
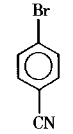
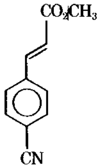
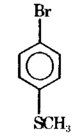
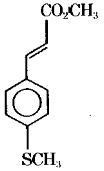
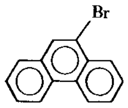
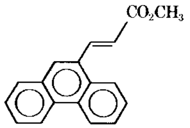
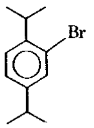
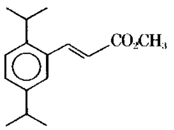
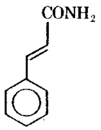
The free carboxyl function may be in the olefinic reactant as well as the organic halide. Acrylic, (*E*)-crotonic, and methacrylic acids all reacted with bromobenzene at 100 °C. Under various conditions acrylic acid gave up to 98% yields of cinnamic acid, crotonic acid gave 60% of (*E*)-3-phenylacrylic acid, and methacrylic acid gave 65% of (*E*)-2-methyl-3-phenylacrylic acid. The methyl esters of acrylic and methacrylic acids reacted with bromobenzene at essentially the same rates as the acids did. Analyses by GLC, however, in the methyl methacrylate example, revealed the presence of about 8% of an isomeric product, methyl 2-benzylacrylate, the acid of which was not observed in the isolation of products from the methacrylic acid reaction. It was very probably produced, but separated in the purification step. The use of the tris(2,5-diisopropylphenyl)phosphine in place of tri-*o*-tolylphosphine in the methyl methacrylate reaction had only a minor effect upon the yields of the two esters produced. Likewise the reaction with iodobenzene in the absence of a phosphine produced only a minor change in the product composition.

It occurred to us that in the above reactions, where the products are carboxylic acid trialkylamine salts, that a simplified procedure for isolation of products would be to extract the products from the reaction mixture with aqueous sodium bicarbonate. Acidification of the extract then would cause precipitation of the product. This procedure works very well and has the added advantage of liberating the tertiary amine so that the amine–catalyst phase can be separated and used again. The same amine–catalyst solution with a little xylene added was reused twice more. The reaction times in the bromobenzene–acrylic acid reaction increased with each cycle from 1.5 to 2.0 to 10.0 h because palladium began to precipitate in the second cycle. Palladium precipitation is very probably due to depletion of the phosphine in the solution through quaternerization with the aryl halide.[4] We also investigated the minimum amount of catalyst necessary to promote the bromobenzene–acrylic acid reaction. It was found that as little as 0.05 mol % palladium acetate based upon the bromobenzene and 1 mol % of triphenylphosphine were sufficient to give a 74% yield of cinnamic acid in 2 h at 150 °C. The reaction mixture remained homogeneous at this temperature. Smaller amounts of catalyst gave significantly lower reaction rates at 150 °C. Crotonic acid reacted similarly at 125 °C, although the product yield of a single isomeric acid was only 60%.

Attempts were made to use aqueous sodium bicarbonate rather than a tertiary amine as the acid acceptor in the bromobenzene–methyl acrylate reaction in xylene solution. The reaction was very slow unless a catalytic amount of a tertiary amine was added. However, ester hydrolysis was very rapid in the presence of a catalytic amount of tertiary amine and little cinnamate could be detected. On the other hand, this procedure worked very well with hydrolytically stable reactants. Thus, bromobenzene and styrene reacted at 100 °C in this two-phase reaction system and colorless crystals of the relatively insoluble *trans*-stilbene soon appeared at the interface of the phases. After 15 h reaction a 97% yield of stilbene was obtained under our best conditions. Presumably the reaction solution could be used again for the same reaction. The

Table I. Vinylic Substitution Reactions at 100 °C[a]

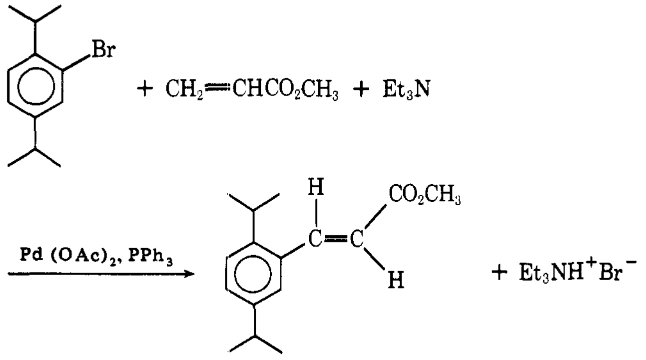
Organic halide (10 mmol)	Registry no.	Alkene (12.5 mmol)	Registry no.	Mol % PR_3	Mol % $Pd(OAc)_2$	Reaction time, h	Product (% yield)	Registry no.
	585-76-2	$CH_2{=}CHCO_2CH_3$	96-33-3	4 P-*o*-tol$_3$	1	5.5	 (67)	63600-26-0
	586-76-5	$CH_2{=}CHPh$	100-42-5	4 P-*o*-tol$_3$	1	3.5	 (74)	7329-77-3
	610-94-6	$CH_2{=}CHCO_2CH_3$		4 P-*o*-tol$_3$	1	3	 (69)	63600-27-1
PhBr	108-86-1	$CH_2{=}CHCO_2H$[b]	79-10-7	4 P-*o*-tol$_3$	1	4.5[c]	E-PhCH=CHCO$_2$H (98)	621-82-9
PhBr		$CH_2{=}CHCO_2CH_3$[b]		4 P-*o*-tol$_3$	1	1.5[c]	E-PhCH=CHCO$_2$CH$_3$ (95)[g]	
PhBr		$CH_2{=}CHCO_2H$[b]		1 PPh$_3$	0.05	2[d]	E-PhCH=CHCO$_2$H (74)	
PhBr		E-$CH_3CH{=}CHCO_2H$[b]	107-93-7	1 PPh$_3$	0.05	12[e]	 (60)	1199-20-8
PhBr		$CH_2{=}\overset{CH_3}{C}CO_2H$[b]	79-41-4	2 PPh$_2$	1	24[f]	 (65)	1199-77-5
PhBr		$CH_2{=}\overset{CH_3}{C}CO_2CH_3$	80-62-6	2 P-*o*-tol$_3$	1	22	 (86)[g,h]	25692-59-5
							 (8)[g]	3070-71-1
PhBr		$CH_2{=}\overset{CH_3}{C}CO_2CH_3$		2 P-(2,5-*i*-Pr$_2$Ph)$_3$	1	22	 (83)[g,i]	
							 (15)[g]	

PhI	591-50-4	 $CH_2{=}C(CH_3)CO_2CH_3$			1	18[j]		(19)[g]	
								(78)[g]	
	1122-91-4	$CH_2{=}CHCO_2CH_3$		4 P-*o*-tol$_3$	1	18		(72)	7560-50-1
	623-00-7	$CH_2{=}CHCO_2CH_3$		4 P-*o*-tol$_3$	1	2		(70)	51116-83-3
	104-95-0	$CH_2{=}CHCO_2CH_3$		4 P-*o*-tol$_3$	1	72[f]		(77)	51953-89-0
	573-17-1	$CH_2{=}CHCO_2CH_3$		4 P-*o*-tol$_3$	1	3.5		(72)	7470-23-7
	42196-29-2	$CH_2{=}CHCO_2CH_3$		4 PPh$_3$	1	20[f]		(79)	63600-28-2
PhBr		$CH_2{=}CHCONH_2$	79-41-4	4 P-*o*-tol$_3$	1	1.5[j]		(70)	621-79-4

[a] Carried out with 21 mmol of triethylamine with reactants containing free carboxyl groups. Only 12.5 mmol employed in the other examples. [b] Tri-*n*-butylamine was used rather than triethylamine. [c] In 2 mL of xylene at 100 °C. [d] Reaction temperature was 150 °C. [e] Reaction temperature was 125 °C. [f] Reaction temperature was 125 °C. [g] Yields obtained by GLC. [h] 6% of another isomer also observed by GLC. [i] 2% of another isomer also observed by GLC. [j] 4 mL of acetonitrile added.

addition of small amounts of triphenylphosphine will probably be necessary with each cycle in order to replace any that had quaternerized in the previous cycle.[4]

Five organic halides which had not been used in the olefin arylation reaction previously were reacted with methyl acrylate to further determine the scope of the reaction. *p*-Bromobenzaldehyde, *p*-bromobenzonitrile, and 9-bromophenanthrene all reacted readily at 100 °C giving 70–77% yields of the expected substituted *trans*-3-arylacrylic esters. *p*-Bromothioanisole and 2-bromo-1,4-diisopropylbenzene required a 125 °C reaction temperature to give 72–79% yields of the expected products. It is notable that the highly hindered bromoisopropyl compound reacted as well as it did.



The reaction of 2-bromo-1,4-diisopropylbenzene with methyl acrylate is unusual in the fact that, in contrast to essentially all other aryl bromides we have studied, it gives a much higher yield of product with triphenylphosphine as the complexing phosphine than it does with tri-*o*-tolylphosphine under the same conditions. The yields were 79% compared with only 6% using the tolylphosphine catalyst. It is probable that serious steric problems inhibit the formation of the intermediate in the reaction involving the large *o*-tolylphosphine and the large bromide.

Finally, the first example employing a reactant with an amide functionality was tried. Bromobenzene and acrylamide were reacted at 100 °C and a 70% yield of (*E*)-cinnamamide was obtained.

The above new examples of the vinylic substitution reaction serve to further emphasize the extraordinary selectivity of organopalladium complexes toward olefins. Essentially every usual functional group except carbon–carbon double and triple bonds, and α,β-unsaturated carbonyl compounds,[5] are inert to these reagents. Highly practical preparations of carboxylic acid derivatives appear possibly by use of this reaction with a simple alkaline extraction to remove the product produced.

Experimental Section

Reagents. With the exceptions noted below, all of the reagents employed were commercial materials used without further purification. Palladium acetate was prepared by the method of Wilkinson.[6] Table II, which will appear only in the microfilm edition of this journal, contains the NMR spectra, melting points, and molecular weights of the compounds prepared in this study.

2-Bromo-1,4-diisopropylbenzene. To a stirred mixture of 3 g of iron powder, 100 g (0.62 mol) of *p*-diisopropylbenzene, and 60 mL of carbon tetrachloride at 0 °C was added over a period of 2 h a solution of 98 g (0.61 mol) of bromine in 60 mL of carbon tetrachloride. The mixture was then allowed to stand at room temperature overnight. The solution was washed twice with 150-mL portions of water, once with 150 mL of 10% sodium hydroxide, and again with water. The carbon tetrachloride was removed by distillation and the crude product refluxed for 30 min with a solution of 6.2 g of sodium metal dissolved in 125 mL of absolute ethanol. The reaction mixture was diluted with 300 mL of water and the product extracted with carbon tetrachloride. The extract was dried over $MgSO_4$ and distilled under reduced pressure, bp 69 °C (0.02 mm). There was obtained 115 g of colorless product (77%): NMR ($CDCl_3$) δ 1.1 (m, 12 H), 2.7 (heptet, 1 H), 3.3 (heptet, 1 H), 7.05 (s, 2 H), 7.4 (s, 1 H).

Tris(2,5-diisopropylphenyl)phosphine. A Grignard reagent was prepared from 50 g (0.21 mol) of 2-bromo-1,4-diisopropylbenzene and 5.6 g (0.23 mol) of magnesium in 50 mL of dry THF. It was necessary to add 1 mL of ethylene dibromide to start the reaction. The reaction was very slow. After 48 h only about half of the magnesium had reacted. Then 2.6 mL (0.03 mol) of phosphorus trichloride was added dropwise. The solution was refluxed overnight and saturated aqueous ammonium chloride was added. The product was extracted with three portions of ether. The extracts were dried and the solvent was removed. The residue was recrystallized twice from ethanol to give 13 g of colorless crystals of the phosphine: mp 274–275 °C; NMR ($CDCl_3$) δ 1.0 (t, 12 H, $J = 6$ Hz), 2.6 (heptet, 1 H), 3.7 (heptet, 1 H), 6.6 (d, 1 H), 7.15 (m, 2 H).

Anal. Calcd for $C_{36}H_{51}P$: C, 83.99; H, 9.99. Found: C, 83.85; H, 9.94.

General Procedure for Vinylic Substitution Reactions. Mixtures of 10 mmol of the organic halide, 12.5 mmol of the alkene, solvent if used, 12.5 mmol of triethylamine or tri-*n*-butylamine (25 mmol in reactions with free carboxylic groups present), 0.1 mmol of palladium acetate or less as indicated in Table I, and 0.4 mmol of the triarylphosphine or less as indicated were heated in capped heavy-walled glass tubes under argon in the steam bath or oil baths at the appropriate temperatures. The acrylic acid reactions were done in open flasks as described below. After completion of the reactions as judged by disappearance of one of the reactants by GLC, cold dilute hydrochloric acid was added to the mixtures. Solid products generally crystallized and were separated by filtration and recrystallized. Liquids were extracted with ether and then distilled.

Cinnamic Acid. A mixture of 0.0011 g (0.005 mmol) of palladium acetate, 0.026 g (0.1 mmol) of triphenylphosphine, 1.52 g (10 mmol) of bromobenzene, 0.80 g (11 mmol) of acrylic acid, and 3.9 g (5 mL, 21 mmol) of tri-*n*-butylamine was heated at 150 °C in a round-bottomed flask with magnetic stirring and with a condenser attached, under argon for 2 h. After about 1 h a second phase separated from the solution (n-$Bu_3NH^+Br^-$). After 2 h, 20 mL of water and 2 g of sodium bicarbonate were added. After stirring for a few minutes the aqueous phase was separated and acidified. After cooling to 0 °C the solid precipitate was filtered and air dried. There was obtained 1.1 g (74%) of colorless cinnamic acid, mp 128–130 °C. The NMR spectrum showed the sample to be quite pure. Recrystallization from aqueous methanol gave material of mp 132–133 °C.

Stilbene. A mixture of 1.52 g (10 mmol) of bromobenzene, 1.25 g (12 mmol) of styrene, 2 mL of *p*-xylene, 0.32 g (2.5 mmol) of naphthalene as internal standard, 0.079 g (0.10 mmol) of dichlorobis(tri-*o*-tolylphosphine)palladium,[7] 0.0925 g 0.5 mmol of tri-*n*-butylamine, 1.0 g (12 mmol) of sodium bicarbonate, and 5 mL of water was heated at 100 °C with rapid stirring for 15 h. During this time colorless crystals of stilbene separated from the clear solution. After cooling, ether was added and the organic phase was analyzed by gas chromatography. There was found a 97% yield of *trans*-stilbene.

Acknowledgment. This research was supported by a grant from the National Science Foundation. The palladium used in this study was kindly loaned to us by the Matthey-Bishop Co., Inc.

Supplementary Material Available: Table II, containing complete NMR spectra, melting points, and observed molecular weights for the products prepared in this investigation (3 pages). Ordering information is given on any current masthead page.

Registry No.—*p*-Diisopropylbenzene, 100-18-5; Tris(2,5-diisopropylphenyl)phosphine, 63600-29-3.

References and Notes

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Palladium-Catalyzed Arylation of Unsaturated Acetals and Ketals

Thomas C. Zebovitz and Richard F. Heck*

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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Acetals of α,β-unsaturated aldehydes react readily with aryl bromides and iodides in the presence of triethylamine and a palladium catalyst at 100 °C. The reaction products are mixtures of 3-arylpropenal acetals and 3-arylpropanoate esters. The last products are believed to arise from palladium hydride elimination of the acetal hydrogen to form ketene acetals, which are converted into esters by reaction with the triethylammonium halide present. 3-Buten-2-one ethylene ketal reacts with bromobenzene under the same conditions to produce benzalacetone ethylene ketal in 92% yield.

The palladium-catalyzed olefin arylation reaction with organic halides has been shown to be a useful and practical synthetic method. While a variety of reactants have been used,[1–4] no reports of applications of the reaction to unsaturated aldehydes or ketones have appeared. We have now investigated this potentially useful variation and find that product yields are quite low, apparently because the unsaturated carbonyl compounds largely polymerize under the basic reaction conditions and elevated temperatures required. The reaction had previously been shown to take place in moderate yields under less practical conditions with diarylmercury compounds and $LiPdCl_3$ as the arylating combination.[5] In order to effect the reaction under the more practical, newer conditions, we have made the usual modification of carbonyl compounds and used the related acetals and ketals to avoid the polymerization problem. This paper reports the result of a brief study of this reaction.

Results and Discussion

Reactions carried out between bromobenzene and acrolein, crotonaldehyde, and 3-buten-2-one at 60 to 100 °C with triethylamine and a palladium acetate catalyst with various triarylphosphines gave dark viscous reaction mixtures. They never contained more than 5–10% of the 3-phenylcarbonyl product expected or any other volatile product as determined by gas chromatography. Acrolein dimethyl acetal, crotonaldehyde diethyl acetal, and 3-buten-2-one ethylene ketal, however, all reacted normally with bromobenzene at 100 °C under the above conditions in 15–24 h, giving yields of products above 80%. Tri-*o*-tolylphosphine was used in the catalyst in these reactions, since it generally gives somewhat higher yields than the triphenylphosphine used previously.[6] The results are summarized in Table I.

Mixtures of products were obtained from the two aldehyde acetals. Two major products were formed in each case. Isolation of the products from each reaction showed that the expected 3-phenylated acetal was one product and a 3-phenylated ester was the other.

$$PhBr + CH_2{=}CHCH(OCH_3)_2 + Et_3N \xrightarrow[100\ °C]{Pd(OAc)_2/P\text{o-tol}_3} PhCH{=}CHCH(OCH_3)_2 + PhCH_2CH_2CO_2CH_3 + Et_3NH^+Br^-$$

Examination of the intermediate proposed in the arylation reactions reveals the possibility of several isomeric products being formed in our reactions depending upon which of the possible hydrogen groups is eliminated with the palladium. Of the possible *E* and *Z* forms of the 3-phenylacrolein dimethyl acetal expected from acrolein dimethyl acetal the large coupling constant of the vinyl hydrogens (16 Hz) indicates only the *E* form was present. While the 3-phenylcrotonaldehyde diethyl acetal isolated from the crotonaldehyde diethyl acetal reaction was not as easily identified as to isomeric structure, it is probably also the *E* isomer judging by the stereochemistry observed in related reactions.[1]

Elimination of the hydrogen substituent from the acetal group would form a ketene acetal. We initially thought small amounts of water in our reaction mixtures were hydrolyzing the ketene acetals to esters; however, careful drying of all reactants did not alter the products formed, suggesting that amine hydrobromide was involved in the conversion of the ketene acetal into ester. The reactions are believed to occur according to the following equations, where R = H, CH_3 and R′ = CH_3, C_2H_5.

The corresponding reaction of bromobenzene with 3-buten-2-one ethylene ketal produces only one product, *E*-4-phenyl-3-buten-2-one ethylene ketal in over 90% yield.

The usefulness of the last reaction is somewhat diminished by the relative difficulty in obtaining the α,β-unsaturated ketal. This ketal apparently cannot be formed directly from ethylene glycol and the unsaturated ketone. Our sample was prepared by dehydrohalogenation of 4-chloro-2-butanone ethylene ketal.

The usefulness of the acetal arylation is also limited because of the formation of mixtures of products. The direction of palladium hydride elimination in such reactions is believed