

Palladium-Catalyzed Reactions of Organic Halides with Olefins

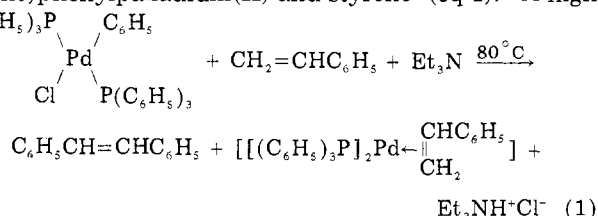
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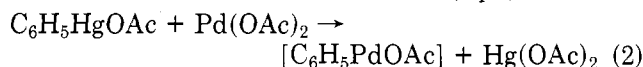
Palladium compounds are useful reagents for producing carbon-carbon bonds.¹ That organopalladium species probably are involved in these reactions can be shown from the chemistry of isolated organopalladium compounds.

A useful synthetic reaction which exemplifies the carbon-carbon bond formation step is the production of *trans*-stilbene from chlorobis(triphenylphosphine)phenylpalladium(II) and styrene² (eq 1). A high



yield of the product is obtained if a base such as triethylamine is present to neutralize the HCl formed, since HCl otherwise destroys the unreacted organopalladium complex.

The detailed mechanism of this reaction is not known, and the product in brackets has not been proven to be formed. A wide variety of closely related reactions have been carried out without isolation of the organopalladium reagent. This was done initially by producing the organopalladium compound in the presence of the olefin by a metathesis reaction of a main group organometallic, usually a mercurial, with a palladium(II) salt such as the acetate or chloride³ (eq 2).

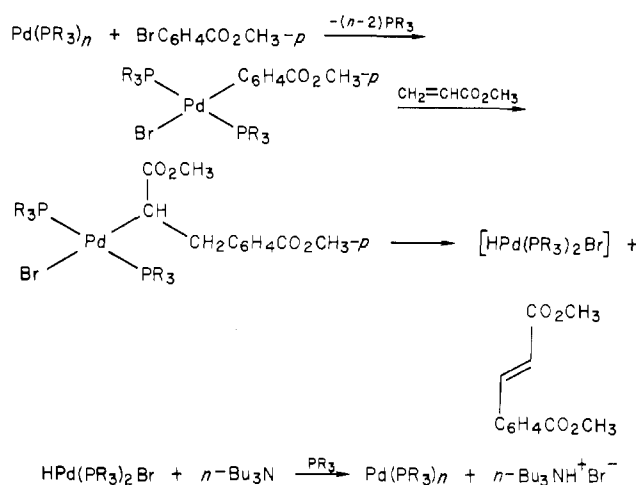


The resulting organopalladium salts were shown to react with olefins in the presence of a wide range of substituents. In most cases the reactions were selective under convenient laboratory conditions.³ Since replacement of a vinylic hydrogen by an organic group cannot be accomplished as easily in any other way, the reaction is of considerable potential value. However, the use of stoichiometric amounts of the main group organometallic and the palladium salt were serious problems as far as the synthetic organic chemist was concerned.

Catalytic Reactions

It was soon found that the reaction could be carried out catalytically in palladium in the presence of a stoichiometric quantity of cupric chloride, as had been done in other palladium reactions.³ This was an im-

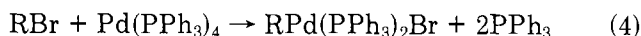
Scheme I



provement, but the presence of thick slurries of salts and still the need for a stoichiometric amount of the organometallic made the reaction relatively unattractive for general synthetic purposes. Discovery that the organopalladium species could be generated from organic iodides and palladium metal^{4,5} (eq 3) or organic



bromides and palladium-triarylphosphine complexes² at around 100 °C (eq 4) enabled the reaction to be



carried out under convenient conditions with readily available reagents. Presumably palladium(II) is always coordinated to four groups, but in many instances it is not known what the neutral ligands are, as in reaction 3, so these ligands are not shown.

The reaction is generally best carried out by combining the organic halide, a slight excess of the olefin, a slight excess of the amine, usually triethylamine, and 1 mol % of palladium acetate and 2 mol % of the triarylphosphine, usually tri-*o*-tolylphosphine. The palladium acetate-phosphine complex formed initially is reduced under the reaction conditions to the palladium(0)-phosphine catalyst. The homogeneous solution is either refluxed under nitrogen or heated in a capped bottle in the steam bath. At completion of the reaction, the mixture is usually a nearly solid mass of amine salt crystals. Addition of water dissolves the salt,

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(1) J. Tsuji, *Acc. Chem. Res.*, **2**, 151 (1969).
 (2) H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.*, **96**, 1133 (1974).
 (3) R. F. Heck, *J. Am. Chem. Soc.*, **90**, 5518 (1968).
 (4) R. F. Heck and J. P. Nolley, Jr., *J. Org. Chem.*, **37**, 2320 (1972).
 (5) T. Mizoroki, K. Mori, and A. Ozaki, *Bull. Chem. Soc. Jpn.*, **44**, 581 (1972).

leaving the product which if solid can be separated and crystallized or if liquid can be extracted and distilled.

The reaction is carried out under nitrogen to prevent oxidation of the triarylphosphine, but small amounts of air can be tolerated. Reactions of organic iodides do not require the phosphine and therefore can be carried out in the presence of air. In the absence of a phosphine, acetonitrile is preferred as a solvent to keep the amine salt in solution. If the salt is allowed to crystallize from the reaction mixture it often removes the finely divided palladium metal catalyst with it and the reaction becomes very slow. A typical reaction (Scheme I) is the formation of methyl *trans*-*p*-carbomethoxy-cinnamate in 81% yield in 7 h at 100 °C from methyl *p*-bromobenzoate and methyl acrylate.²

The organic halides which can be employed must not contain β hydrogens, for they are easily eliminated. If they do, only olefins will be formed from the organic halide. In general, aryl, benzylic heterocyclic, and vinylic iodides and bromides undergo the reaction. Chlorides, except for benzyl chlorides, normally do not react. Terminal, internal, 1,1-disubstituted, and some trisubstituted olefins react, although the rates decrease with increasing substitution. The reaction is remarkably selective, and almost any functional groups can be present in the organic halide or the olefin.⁶ A problem does arise with aryl halides containing strongly electron-releasing substituents such as hydroxyl and amino groups. In these instances some triarylphosphines are readily quaternized in palladium-catalyzed reactions with the organic halides. In many instances the use of tri-*o*-tolylphosphine, rather than less hindered phosphines, eliminates this side reaction.⁷

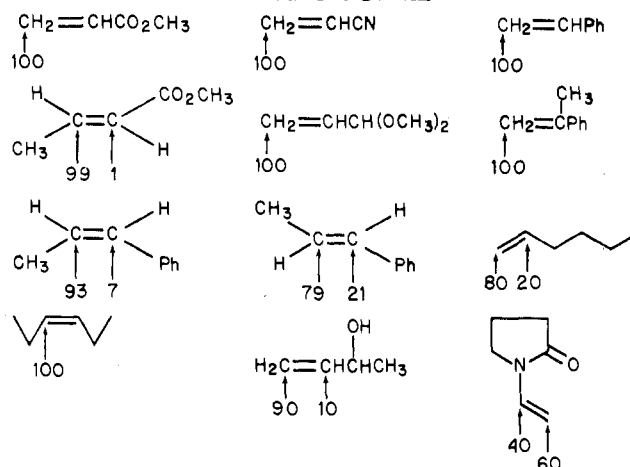
The direction of addition of the organopalladium intermediate to the olefin is generally predictable on the basis of steric effects: the organic group prefers the less substituted carbon of the double bond regardless of the substituents present in either reactant. However, electronic effects are also significant in some instances. Electron-releasing groups on the double bond or attached to the carbon bearing the halogen tend to produce more addition to the most electron-deficient double bond carbon. Nevertheless steric effects generally dominate. The percent of substitution at each of the double bond carbons on palladium-catalyzed reaction with bromobenzene at 100 °C is shown for several olefins in Chart I.⁸

The orientation of addition of iodobenzene is the same as for bromobenzene within experimental error. Orientation is not significantly altered by the absence of a triarylphosphine or by the substituents present in the triarylphosphine. Even the presence of *o*-isopropyl groups or *p*-methoxyl groups has no appreciable effect. Chelating diphosphines, trialkylphosphines, and phosphite esters in general do not produce useful catalysts.

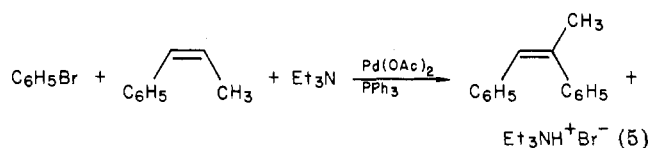
Stereochemistry

The stereochemistry of the reaction seems best explained as the result of a syn addition of the organopalladium compound followed by a syn elimination of the palladium hydride.² For example, bromobenzene

Chart I
Orientation of Addition of Bromobenzene to Various Olefins



and (*Z*)-1-phenyl-1-propene produce 73% (*Z*)-1,2-diphenyl-1-propene (eq 5), while the *E* olefin gave 79%

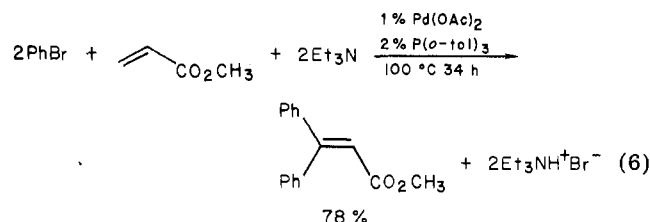


of the (*E*)-1,2-diphenyl-1-propene. Consistent with these results is the fact that bromobenzene and cyclohexene form largely 3-phenylcyclohexene.

Aryl Halides

A wide variety of substituents may be present in the aryl halide for reaction with methyl acrylate.⁶ The reaction tolerates chloro, cyano, carbomethoxy, carboxy, aldehyde, nitro, dimethylamino, hydroxyl, amino, methylthio, acetamido, acetoxy, and polynuclear aromatic groups. These groups with few exceptions may be ortho, meta, or para to the reacting bromo group. In every case the sole product isolated, in 66–95% yields, is the *trans*-cinnamic ester derivative. It is noteworthy that even the highly hindered 1-bromo-2,5-diisopropylbenzene reacts in 79% yield in 20 h at 120 °C. This reaction proceeded much better with the smaller triphenylphosphine than with tri-*o*-tolylphosphine, presumably because there is not enough room on the palladium for the large aryl group and the large phosphine. Similar results are obtained with ethylene as the olefin; the reactions afford a variety of styrene derivatives.⁹

Diarylation in one operational step is also possible. Methyl acrylate with 2 mol of bromobenzene gave methyl 3,3-diphenylacrylate in 78% yield (eq 6).



When both bromo and iodo groups are present in the reactants, selective reaction is possible.¹⁰ For example,

(6) B. A. Patel, C. B. Ziegler, N. A. Cortese, J. E. Plevyak, T. C. Zebovitz, M. Terpko, and R. F. Heck, *J. Org. Chem.*, **42**, 3903 (1977).

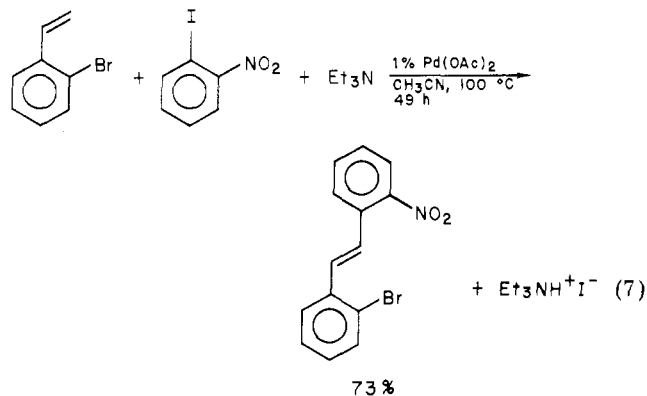
(7) C. B. Ziegler and R. F. Heck, *J. Org. Chem.*, **43**, 2941 (1978).

(8) R. F. Heck, *Pure Appl. Chem.*, **50**, 691 (1978).

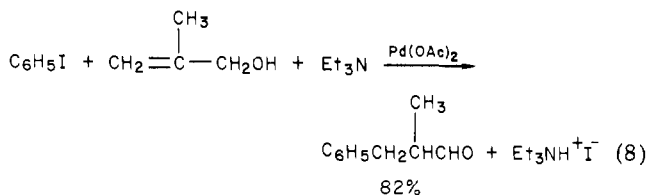
(9) J. E. Plevyak and R. F. Heck, *J. Org. Chem.*, **43**, 2454 (1978).

(10) Unpublished results of J. E. Plevyak.

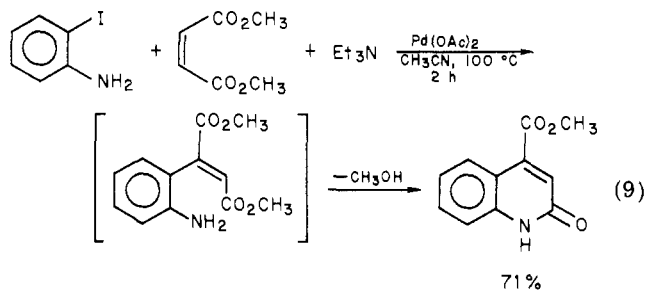
p-bromiodobenzene reacts with methyl acrylate and a palladium acetate catalyst to form methyl 4-bromocinnamate in 68% yield. Reaction of this product with styrene and a palladium acetate-tri-*o*-tolylphosphine catalyst produced (*E,E*)-methyl 4-styrylcinnamate in 63% yield. Similar selectivity is found if the halo groups are on different reactants, as in the reaction of *o*-bromostyrene with *o*-iodonitrobenzene¹⁰ (eq 7).



A useful variation of the reaction occurs with allylic alcohols. In most instances, the palladium hydride elimination produces vinylic alcohols which isomerize to β -arylcaryl derivatives.^{11,12} Methallyl alcohol and iodobenzene, for example, produce 2-methyl-3-phenylpropanal in 82% yield (eq 8).



Another variation combines the reaction with a ring closure to form 2-quinolones.¹³ *o*-Iodoaniline and dimethyl maleate, for example, react to form 4-carbomethoxy-2-quinolone in 71% yield (eq 9). The (*E*)-cinnamic ester is presumably an intermediate in the reaction.

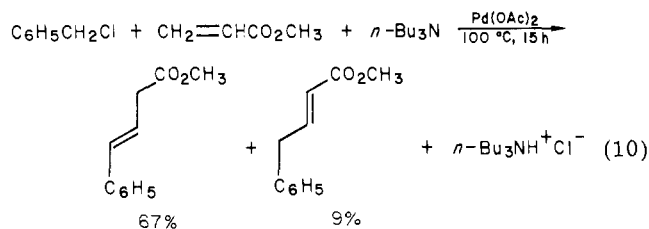


(*E*)-cinnamic ester is presumably an intermediate in the reaction.

Benzylic Halides

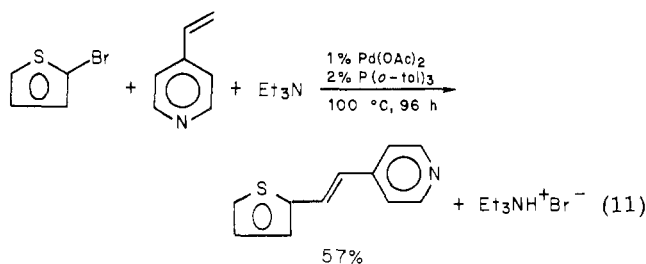
Relatively little work has been done with benzylic halides, but it is clear that they react analogously to the aryl halides in at least some instances.⁴ For example, benzyl chloride is reactive enough to combine with methyl acrylate even in the absence of a triaryl-

phosphine in 15 h at 100 °C to give 69% methyl 4-phenyl-3-butenate and 9% methyl 4-phenyl-2-butenate (eq 10).



Heterocyclic Bromides

2-Bromothiophene, methyl 2-bromofuranoate, 3-bromopyridine, 3-bromoquinoline, 4-bromoisquinoline, 5-bromoindole, and *N*-acetyl-3-bromoindole all undergo palladium-catalyzed addition to olefins.¹⁴ It is a simple matter to synthesize exotic molecules such as (*E*)-1-(2-thenyl)-2-(4-pyridyl)ethylene (57% yield) (eq 11).

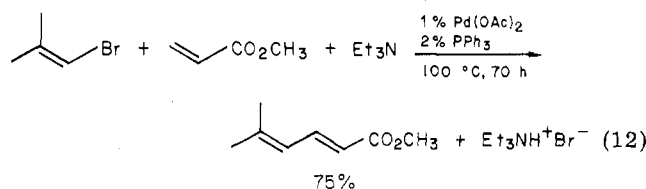


Nornicotine was also produced from 3-bromopyridine in four steps, starting with the addition of the halide to 3-butenylphthalimide.¹⁴

Vinylic Halides

Employing vinylic halides in the palladium-catalyzed addition to olefins allows the synthesis of a wide variety of purely aliphatic compounds. This area is still under active investigation, but it is already clear that the reaction is of considerable value in the preparation of unsaturated, functionalized compounds.^{15,16}

Vinylic bromides, in some instances, react analogously to aryl bromides. For example, 2-methyl-1-bromo-1-propene and methyl acrylate readily form (*E*)-methyl 5-methyl-2,4-hexadienoate in 75% yield under the usual reaction conditions (eq 12).



The stereoselectivity of the reaction with (*E*)- and (*Z*)-1-bromo-1-hexene and methyl acrylate is low under the usual conditions. The loss of stereochemistry is believed to be due to the formation of intermediate π -allylic palladium complexes which isomerize. The cis compound isomerizes to trans through σ -allylic palladium species. It is well-known that substituents in π -allylic palladium complexes easily move from anti (same side as the metal) to the more stable syn (op-

(11) J. B. Melpolder and R. F. Heck, *J. Org. Chem.*, **41**, 265 (1976).

(12) A. J. Chalk and S. A. Magennis, *J. Org. Chem.*, **41**, 273 (1976).

(13) N. A. Cortese, C. B. Ziegler, B. J. Hrnjez, and R. F. Heck, *J. Org. Chem.*, **43**, 2952 (1978).

(14) W. C. Frank, Y. C. Kim, and R. F. Heck, *J. Org. Chem.*, **43**, 2947 (1978).

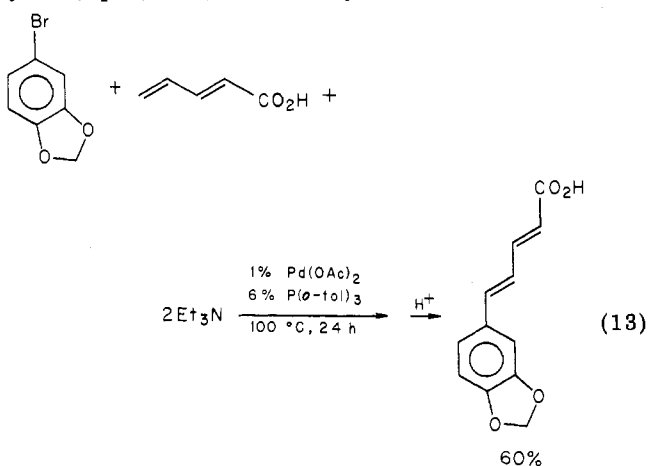
(15) H. A. Dieck and R. F. Heck, *J. Org. Chem.*, **40**, 1083 (1975).

(16) B. A. Patel and R. F. Heck, *J. Org. Chem.*, **43**, 3898 (1978).

posite side to the metal) positions. The mechanism in Scheme II has been proposed.¹⁵

In Scheme II, the initial addition of the vinyl-palladium species and the hydride elimination occur as usual, but the hydride- π complex formed in the elimination, complex I, largely undergoes a readdition of the metal hydride group in the reverse direction. The allylpalladium species so formed then cyclizes to the π -allyl complex, II. Equilibration of isomers now occurs, and ultimately elimination of the palladium hydride occurs to form the conjugated diene. The elimination is believed to be catalyzed by the amine since complexes without the carboxyl group do not undergo the elimination reaction as easily. Addition of more than 2 equiv of triphenylphosphine to the reaction decreases the amount of isomerization observed, presumably because the palladium hydride group in complex I is displaced by the excess phosphine before readdition and isomerization occur. The α,β -double bond formed is always trans.

Similar additions to (*E*)-2,4-pentadienoic acid have been carried out.¹⁷ With 3,4-methylenedioxybromobenzene, for example, piperic acid is obtained in 60% yield (eq 13). (*E*)-2-Bromostyrene in the same reaction

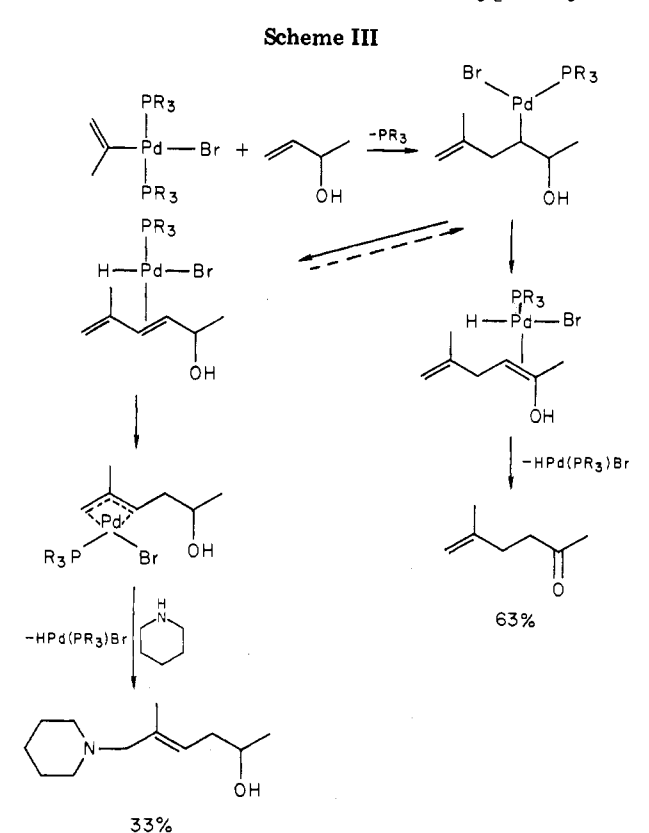
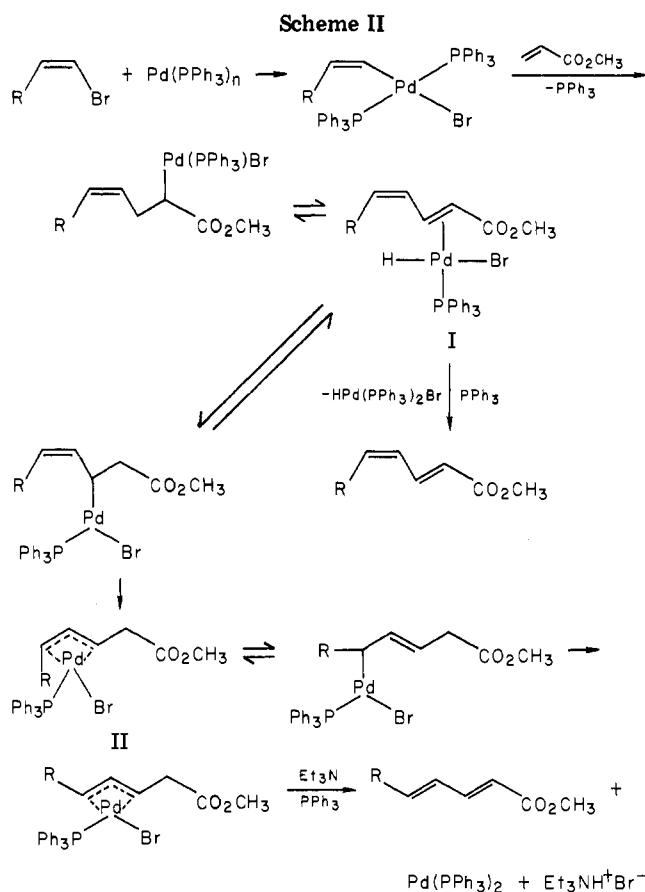


gave the conjugated trienoic acid in 57% yield.

Extension of the vinylic halide reactions to olefins not containing the strongly electron-withdrawing carboxyl group often met with failure. For instance, 2-bromopropene and 3-buten-2-ol under the usual conditions or even at 150 °C failed to form more than traces of product after days of reaction. The reactants were largely unaffected and the palladium remained in solution, probably as a very stable π -allylic palladium complex. In the absence of the activating carboxyl group, the amine-catalyzed elimination in the π -allylic complex does not occur.

This problem, of course, severely limits the chemistry which can be done with the vinylic halides. Attempts to use stronger bases to effect the elimination were not successful; however, the use of nucleophilic secondary amines did cause decomposition of the π complexes with incorporation of the amine. Thus, the reaction of 2-bromopropene with 3-buten-2-ol in the presence of piperidine as the amine (Scheme III) was complete in 2 h and two products were formed: 5-methyl-5-hexen-2-one (63%) and 5-methyl-6-piperidino-4-hexen-2-ol (33%). The first product is formed by palladium

(17) B. A. Patel, J. E. Dickerson, and R. F. Heck, *J. Org. Chem.*, **43**, 5018 (1978).



hydride elimination in the initial adduct toward the hydroxyl bearing carbon and the second by elimination in the other direction followed by a reverse readdition of the hydride to form a π -allylic intermediate which finally undergoes nucleophilic attack by the secondary amine.

Table I
Ratios of Terminal to Internal Addition of
Various Organic Groups

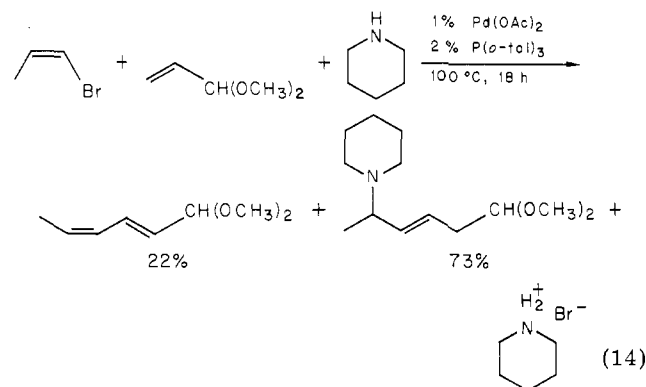
organic bromide	ratio of terminal to internal addition in 1-hexene
PhBr	4
	> 20
	> 20
	1.8
	1.8
	1.7
	4.6

The nucleophilic attack of the amine upon an isolated π -allylic palladium complex was shown to produce the same products as in the catalytic reaction proposed to proceed by way of the same π complex.¹⁸ Other reactions of π -allylic palladium complexes with amines were studied previously by Akermark.¹⁹

Since several convenient methods are available for the conversion of tertiary amines into more useful products, this reaction would appear to be an extremely useful synthetic method. We have confirmed the generality of reaction with numerous vinylic halides and olefins. Attempts to employ other nucleophiles than secondary amines, however, have so far been unsuccessful.

The selectivity of addition of vinylic halides to various olefins considerably determines the utility of the reaction. Table I compares the ratios of terminal to internal substitution obtained for a variety of organic bromides under similar reaction conditions.

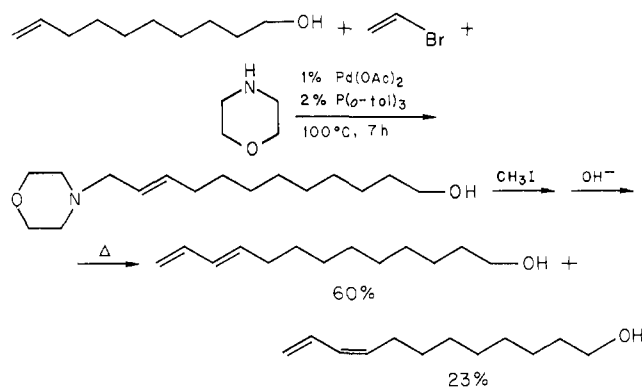
As can be seen from Table I, vinylic halides with β -methyl substituents give mixtures of products in reaction with 1-hexene. All of these halides react selectively at the terminal carbon when electron-withdrawing groups are present on an olefinic carbon, although it is difficult to distinguish electronic and steric effects in some cases. For example, *cis*-1-bromo-1-propene and acrolein dimethyl acetal with piperidine give only terminal addition products: (*E,Z*)-sorbol aldehyde dimethyl acetal (22%) and (*E*)-5-piperidino-3-hexenal dimethyl acetal (73%) (eq 14). It is



(18) Unpublished work of F. G. Stakem.

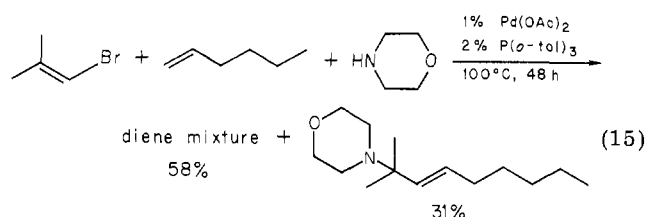
(19) B. Akermark and K. Zetterberg, *Tetrahedron Let.*, 3733 (1975).

Scheme IV



noteworthy that the diene obtained is exclusively the *E,Z* isomer; that indicates that it is formed only before the π -allylic complex is produced.

The idea of a nucleophilic attack of the secondary amine upon the least substituted carbon of the π -allylic complex seems completely reasonable. Therefore, we were very surprised to find that the reaction of 1-bromo-2-methyl-1-propene with 1-hexene and morpholine gave the product in which the tri- rather than the disubstituted end of the allylic system had reacted with the amine (eq 15). The explanation of this may



be that the 1,1-disubstituted π -allylic systems are unsymmetrically bonded with the disubstituted carbon, being only weakly bonded to palladium. In this state the tertiary may be more susceptible to nucleophilic attack than the secondary π -allylic carbon. However, when 1,1-substituents larger than methyl groups are present, the secondary carbon is preferentially attacked. Isolated 1,1-disubstituted π -allylic complexes react similarly.

Numerous applications of the vinylic halide reaction can be imagined. One is synthesis of 9,11-dodecadien-1-ol, a pheromone of the red bollworm moth; see Scheme IV. The readily available 9-decenol reacted with vinyl bromide and morpholine under palladium catalysis to give 12-morpholino-10-dodecen-1-ol in 82% yield. This in turn was subjected to the Hofmann degradation to give a 70:30 mixture of (*E*)- and (*Z*)-dienols in 83% yield.

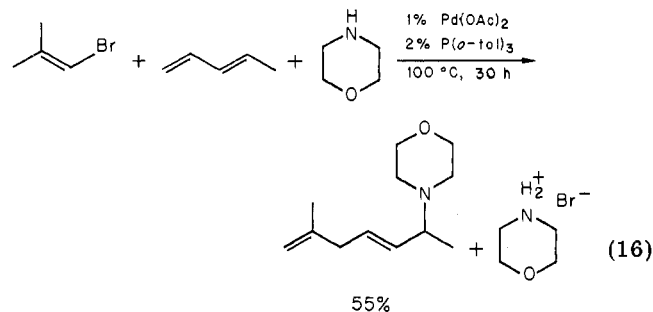
An obvious extension of the vinylic halide-olefin-secondary amine reaction is to conjugated dienes. This has been successfully achieved.²⁰

The addition of an organopalladium group to a conjugated diene produces a π -allylic palladium complex directly, without necessity for palladium hydride elimination and reverse readdition as in reactions of mono enes (Scheme II).

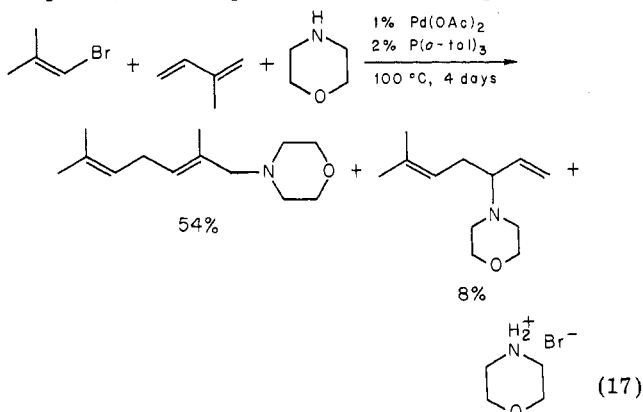
The products formed in the presence of secondary amines clearly stem from the π complex produced directly. For example, 2-bromopropene, (*E*)-1,3-pen-

(20) B. A. Patel, L. Kao, N. A. Cortese, J. V. Minkiewicz, and R. F. Heck, *J. Org. Chem.*, submitted.

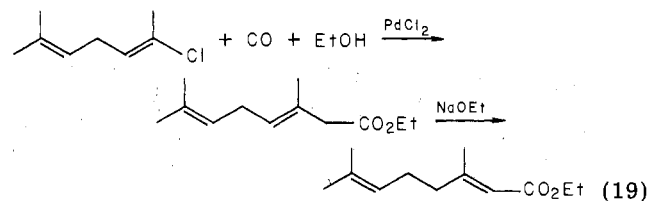
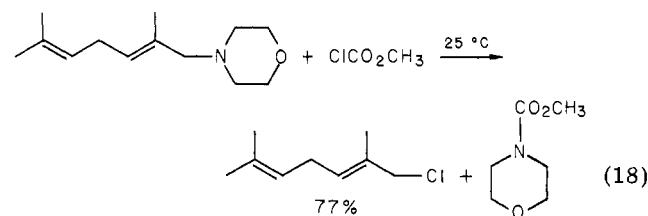
tadiene, and morpholine form 2-methyl-6-morpholino-1,4-heptadiene in 55% yield (eq 16). Other products



are trienes and polymer. Fortunately all vinylic halides add only to the terminal, less substituted double bond of the dienes. Thus 1-bromo-2-methyl-1-propene, isoprene, and morpholine react as in eq 17.



A simple application of this reaction to a terpene synthesis has been made. The adduct of 1-bromo-2-methyl-1-propene, isoprene, and morpholine (eq 17) reacted with methyl chloroformate to give the chloride in 77% yield (eq 18). This reaction, incidentally, is



general and provides an easy method for converting allylic amines into chlorides. A palladium-catalyzed carboxyethylation of the chloride followed by a base-catalyzed double bond isomerization gave ethyl geranate (eq 19).

Summary and Conclusions

The palladium-catalyzed reactions of organic halides with olefins or dienes are broad in scope. These reactions are important because they accomplish transformations not achievable in one operational step by any other method. More than this, these reactions have the advantage of being simple to carry out, not requiring anhydrous conditions or any special techniques. Moreover, they are tolerant of nearly all important functional groups and they are stereospecific and regioselective.

Although these are extremely convenient laboratory reactions, applications in the manufacture of chemicals other than relatively valuable ones are less certain. The use of even 1 mol % of palladium acetate is prohibitively expensive for the commercial synthesis of most chemicals, even if recovery is reasonably efficient. We have made some progress at reducing the amount of catalyst required by increasing reaction temperatures or by devising methods for recycling the catalyst without the necessity of recovery each time it is used. For example, bromobenzene and acrylic acid in the presence of tri-*n*-butylamine react in a closed reactor at 140 °C in 4 h to give 74% yield of cinnamic acid using only 0.05 mol % of palladium acetate (based upon bromobenzene) and 1 mol % of triphenylphosphine. Moreover, the catalyst and amine can be recycled without recovery simply by extracting the reaction mixture with aqueous sodium bicarbonate to remove the product and regenerate the amine from its salt. The amine-catalyst solution then was reused two times after which the equivalent of 6000 g of cinnamic acid had been produced from 1 g of palladium acetate. The palladium could have been used for more cycles if the triphenylphosphine which quaternized slowly in the reactions had been replaced.

In another system a more practical utilization of the catalyst appears possible because the product crystallizes from the reaction mixture and it can be continuously removed. If the acid produced is removed by stirring with a second phase of aqueous sodium bicarbonate a continuous reaction is possible without catalyst recovery. Thus, bromobenzene and styrene in xylene solution with 5% tri-*n*-butylamine, 1% palladium acetate, 3% tri-*o*-tolylphosphine, and aqueous sodium bicarbonate were refluxed at atmospheric pressure. Crystals of stilbene slowly separated from the clear, two-phase solution. After 15 h a 97% yield was obtained by cooling and filtering. Therefore, at least some practical applications for the reaction appear possible.

Another possible solution is the use of polymer-supported catalysts, and those may provide more practical procedures. In any case, there is no question but that these reactions constitute an exceedingly useful laboratory method for the synthesis of a wide variety of substituted olefinic compounds.