

## PALLADIUM-CATALYZED SYNTHESSES OF CONJUGATED POLYENES

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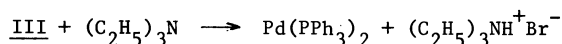
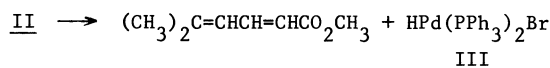
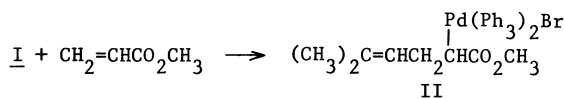
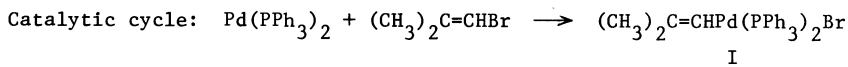
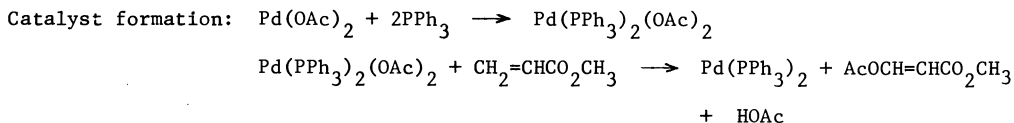
**Abstract** - Conjugated dienoic acid derivatives are stereospecifically prepared in good to excellent yields by the palladium-catalyzed reaction of vinylic bromides with acrylic acid derivatives in the presence of triethylamine. Aryl bromides or iodides and 2,4-pentadienoic acid derivatives yield 5-arylpentadienoic acid derivatives. Other types of conjugated dienes are obtained by a two-step procedure from the Hofmann elimination on the tertiary amines obtained from the palladium-catalyzed reaction of vinylic bromides with dienes and secondary amines. Conjugated trienoic acids or esters are obtained analogously by either method in good yields from vinylic bromides, conjugated dienes and amines. Conjugated tetraenedioate esters are obtained in modest yields by the double vinylation of conjugated dienes with E-methyl 3-bromo-2-methylpropenoate.

### INTRODUCTION

The palladium-catalyzed synthesis of various styrene derivatives from aryl halides (bromides and iodides) and a wide variety of olefinic compound is well documented (1). The same reaction with vinylic halides and olefinic compounds has been found to give conjugated dienes in some instances (2) and the corresponding reaction with a conjugated diene has given a conjugated triene in one instance (3). Aryl halides and conjugated dienes in certain cases produce arylated conjugated dienes (4). In this report we shall summarize the earlier work and discuss recent results extending the scope of the reaction to demonstrate its utility as a general method for the synthesis of a variety of conjugated polyenes.

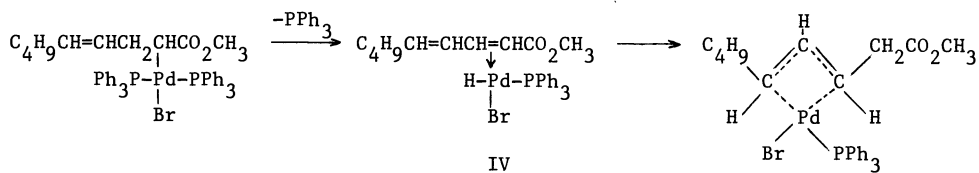
### CONJUGATED DIENES

The palladium-catalyzed direct synthesis of conjugated dienes from vinylic halides (bromides and iodides) and alkenes in practical yields generally occurs only when a carboxylic acid, ester, amide, or nitrile group is conjugated with either the double bond in the vinylic halide and/or in the olefinic reactant (5,6). For example, 2-methyl-1-bromo-1-propene and methyl acrylate with a palladium acetate--triphenylphosphine catalyst and triethylamine as an acid acceptor, at 100° form E-methyl 5-methyl-2,4-hexadienoate in 60% yield (2). The reaction is believed to occur by way of a vinylic palladium bromide intermediate by a mechanism analogous to that proposed for the arylation of alkenes (6).

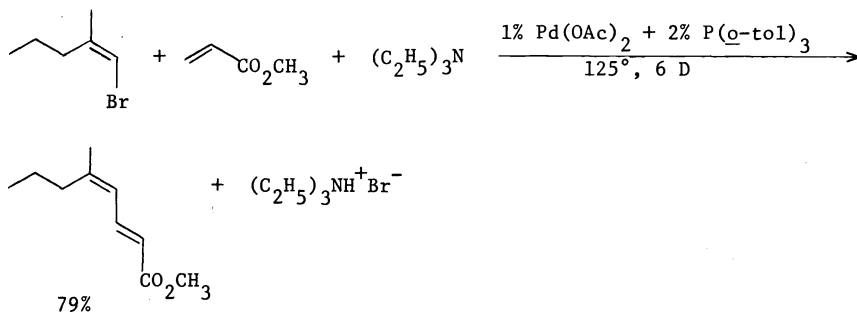


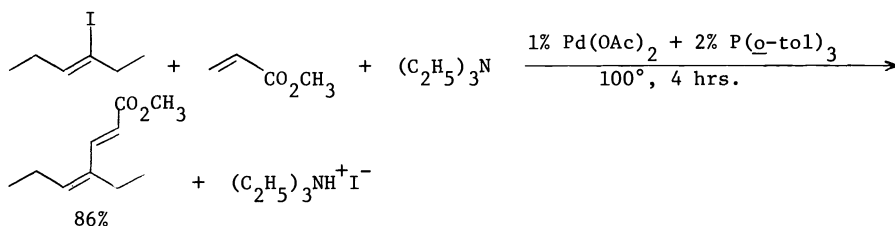
The stereochemistry of the  $\alpha,\beta$ -double bond in the diene product is trans as it is in all other palladium-catalyzed reactions of acrylic acid and its esters. If trans-crotonic acid or its esters are reacted, the carboxyl and methyl group on the double bond become cis in the product because the vinylic palladium species adds syn to the double bond and the final palladium hydride elimination occurs syn, also. The stereochemistry in the double bond of the vinylic bromide is usually retained. How stereospecific the reactions is, however, depends upon the reaction conditions and the structure of the reactants.

The reactions of E- and Z-1-bromo-1-hexene with methyl acrylate and triethylamine with the usual one mole percent catalyst at 100° produce mixtures of the E,E- and E,Z-dienoate esters (6). The loss of stereochemistry in the reaction is due to three problems: ① the formation of  $\pi$ -allylic palladium intermediates which equilibrate isomers by way of  $\sigma$ -forms, ② isomerization of the 1-bromo-1-hexene under the reaction conditions, and ③ isomerization of the product under the reaction conditions. The formation of the pi-allylic palladium species is due to the readdition of the palladium hydride to the diene product in the reverse direction. Actually, the hydride probably never leaves the diene, but merely forms a pi-complex directly in the elimination and then readdition occurs from within the pi-complex. The pi-allylic complex equilibrates isomers through sigma forms which can rotate

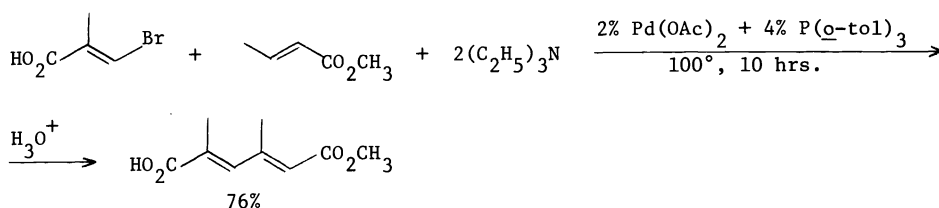


and reclose to pi-allylic complexes with altered stereochemistry. The formation of pi-allylic complexes can be suppressed in some instances, at least, by adding additional triphenylphosphine to the reaction mixtures. Probably, the high concentration of ligand causes displacement of the diene from IV before readdition of the hydride group occurs. The extent of isomerization of the vinylic bromide and product ester in the reaction can be significantly reduced by increasing the catalyst concentration, thereby reducing the reaction time. Therefore, by increasing the amount of triphenylphosphine to 6 mol % of the vinylic bromide and the palladium acetate to 3 mol %, the reaction rate increased by a factor of ~38 and the selectivity to form the E,Z-isomer increased from 57% to 89%. Other types of vinylic bromides are stereochemically stable under the reaction conditions as are their dienoate products formed with methyl acrylate. For example, E- and Z-1-bromo-2-methyl-1-pentene and E- and Z-3-iodo-3-hexene all react totally stereospecifically with methyl acrylate to give dienoate esters with the  $\alpha,\beta$ -double bond in the E-configuration and the  $\gamma,\delta$ -double bond with the same configuration that was present in the reactant vinylic bromide (6).

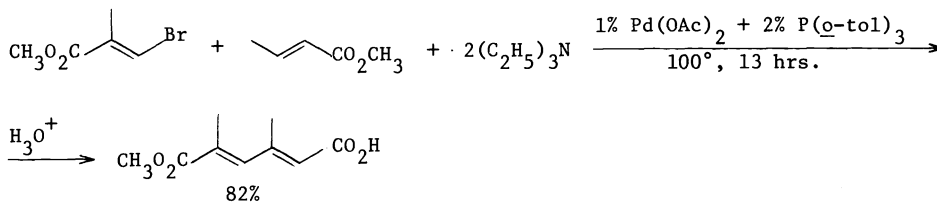




This reaction is particularly useful for preparing polyfunctional acids and acid derivatives since most functional groups are stable to the organopalladium reactants. Conjugated dienonitriles may also be prepared from acrylonitrile, but acrylonitrile tends to give significant amounts of product with a *cis*  $\alpha,\beta$ -double bond in contrast to methyl acrylate which gives little or none of this type of product (6). Acrylamide is similar to methyl acrylate in its reaction with *Z*-1-bromo-1-hexene (6). Crotonate esters undergo the reaction stereospecifically with *E*-3-bromo-2-methylpropenoic acid and its esters. In these examples the stereochemistry of the crotonate double bond is inverted while the vinylic bromide retains its structure (6).



There is no ester-acid interchange during the reaction. Reaction of the bromovinyl ester with *E*-crotonic acid occurs selectively also producing the isomeric half ester in 82% yield (6).

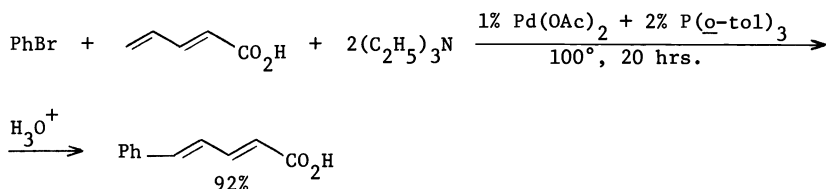


The related reactions with both reactants esterified or with both as the carboxylic acids occur equally well (6).

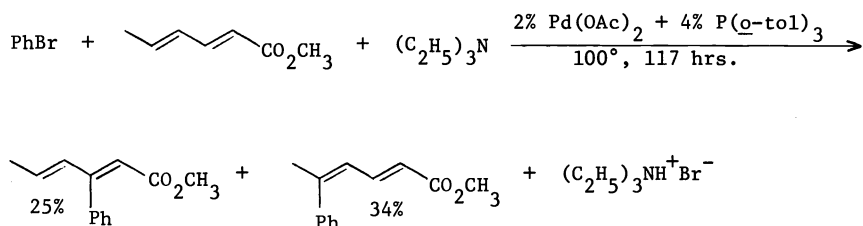
Methyl methacrylate is similar to methyl acrylate in that isomerization occurs in the reaction with 1-bromo-1-hexene and mixtures of *E,E*- and *E,Z*-nonadienoates are the major products. Since the reactions are slower than with methyl acrylate, the thermal isomerization is somewhat more serious. Minor amounts of the *Z,E*-isomer are observed in the methyl methacrylate reactions, also (6).

A limitation of the conjugated dienoic acid or ester synthesis is that unsubstituted and some mono-substituted pentadienoic acid derivatives cannot be made efficiently from vinylic bromides or iodides and acrylic acid derivatives because the Diels-Alder reaction of the dienoic acid derivative with the unreacted acrylate is competitive or faster than formation of the dienoic acid derivative. Vinyl bromide (2), 2-bromopropene (2), and 2-bromo-1-hexene (6), for example, give mainly Diels-Alder products when they are reacted with methyl acrylate.

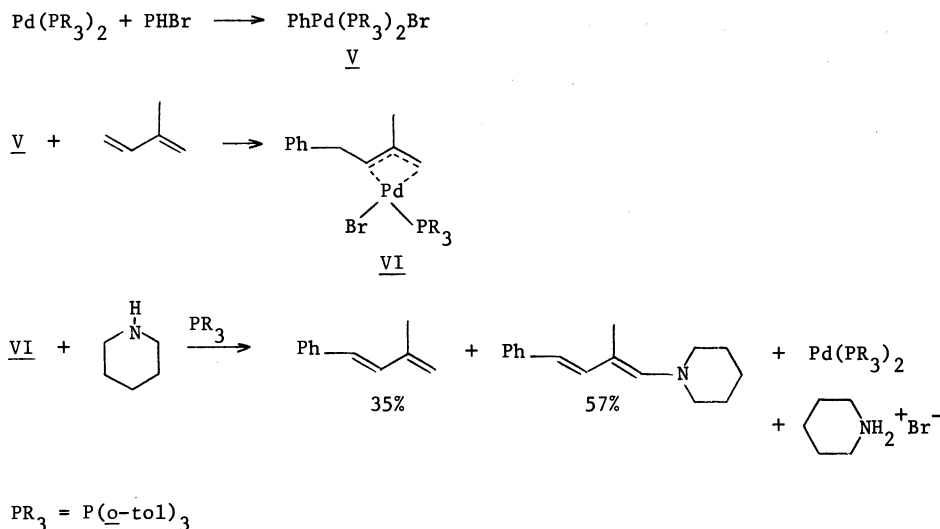
Conjugated 5-arylpentadienoic acids also can be formed easily from aryl bromides or iodides and the dienoic acid by the palladium-catalyzed reaction. Bromobenzene and *E*-2,4-pentadienoic acid and triethylamine give the *E,E*-5-phenyl-2,4-pentadienoic acid in 92% yield (4).



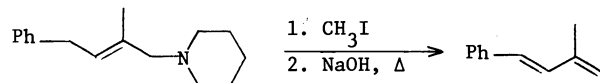
Piperic acid, the 3,4-methylenedioxy derivative of the same acid, was obtained in 60% yield from 4-bromomethylenedioxybenzene and E-2,4-pentadienoic acid (4). Methyl sorbate and bromobenzene, however, yield a mixture of the 3- and 5-phenyl-2,4-pentadienoic acid esters (7).



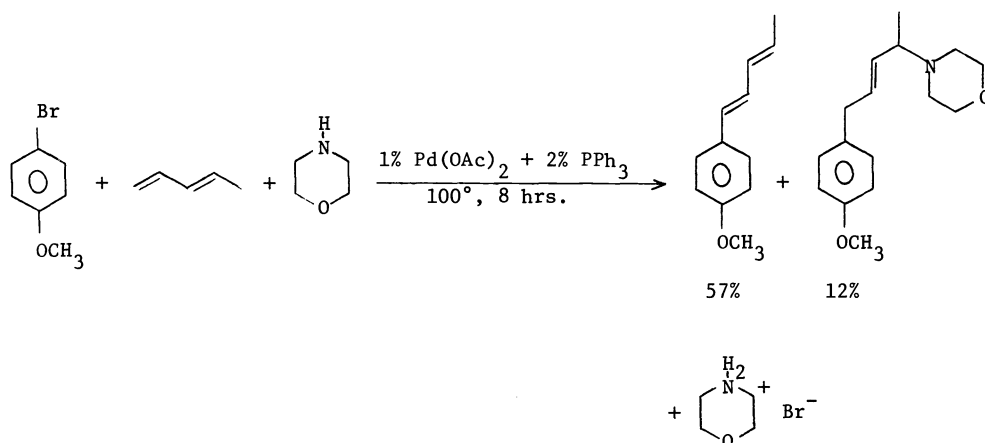
Other types of conjugated dienes can be made in two steps involving related palladium chemistry, with aryl bromides or vinylic bromides and alkenes. In the absence of carboxylic acid (or derivative) substituents on the double-bond carbon of one of the reactants, the palladium reactions appear to produce relatively stable  $\pi$ -allylic palladium complexes which do not easily decompose to dienes in the presence of triethylamine, even at 150°. We have found that catalytic reactions occur in these cases if nucleophilic secondary amines are used as the acid acceptors and as a reactant to decompose the  $\pi$ -allylic complexes by nucleophilic substitution. This reaction produces tertiary allylic amines as major products, generally in good yields. For example, isoprene and bromobenzene with piperidine react as follows (4):



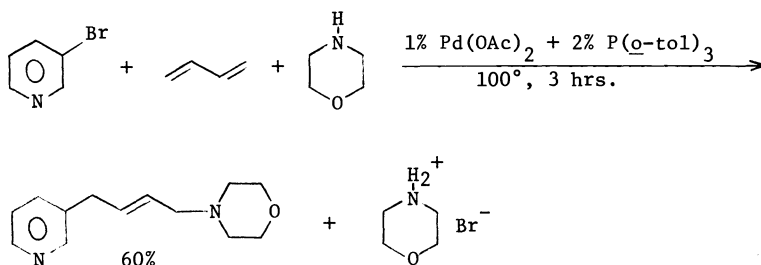
The allylic amines formed are easily converted into the conjugated diene by the Hofmann elimination (4).



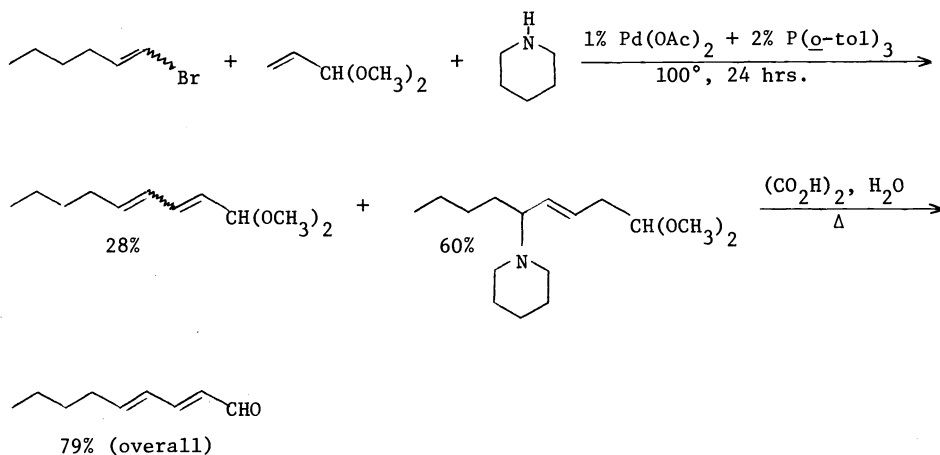
The 4-arylallylic amines produced in the above reactions are generally accompanied by arylated diene as well. The amount of direct elimination depends upon the stability of the diene formed. The more stabilized the diene, the more of it that is formed in the reaction. 4-Bromoanisole and 1,3-pentadiene with morpholine, for example, give 57% diene and 12% amine. (Morpholine is essentially identical to piperidine in these reactions (4).)



3-Bromopyridine, on the other hand, in the related reaction with 1,3-butadiene and morpholine gave only the amine product.

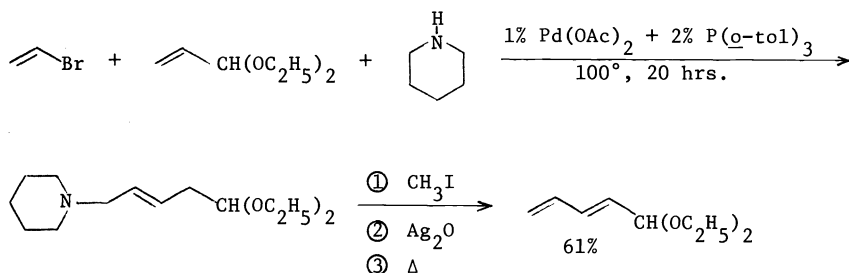


In the vinylic bromide-olefin reactions,  $\pi$ -allylic palladium intermediates are formed as shown previously (Pg. 3). In the absence of carboxylic acid (or derivative) substituents on the double-bond carbons of one or both of the reactants,  $\pi$ -allylic palladium complexes stable to triethylamine are formed. These can be decomposed by utilizing a nucleophilic secondary amine as in the aryl halide-conjugated diene reaction to form allylic tertiary amines as products and as an acid acceptor. This reaction has been used to produce, after acid hydrolysis, 2,4-dienals from vinylic bromides, acrolein acetals and piperidine (8).



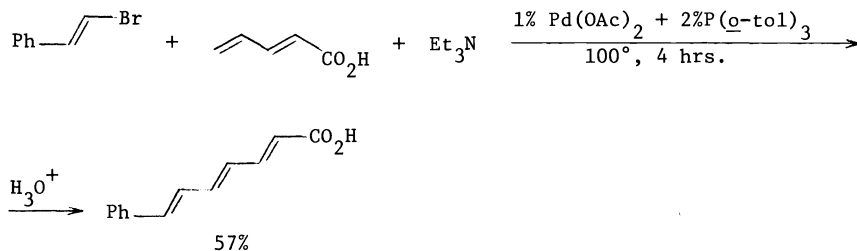
In this reaction, stereochemistry is retained in the bromide double bond, at least in one case studied, the reaction of Z-1-bromo-1-propene with acrolein dimethyl acetal. The  $\alpha, \beta$  double bond in the product dienal acetal is E, while the  $\gamma, \delta$ -double bond from the vinylic halide is Z. The amine derivative, of course, has lost its stereochemistry because it was formed by way of one equilibrating  $\pi$ -allylic intermediate. If the dienal acetal is separated from the amine and hydrolyzed at room temperature, E,Z-sorbic aldehyde can be obtained. Steam distillation of the aldehydes, however, from aqueous acid gives the equilibrated product, ~90% E,E (8).

2,4-Dienal acetals have been prepared by the Hofmann elimination of the quaternary salts from the acrolein acetal-vinyl bromide-piperidine reaction, also.

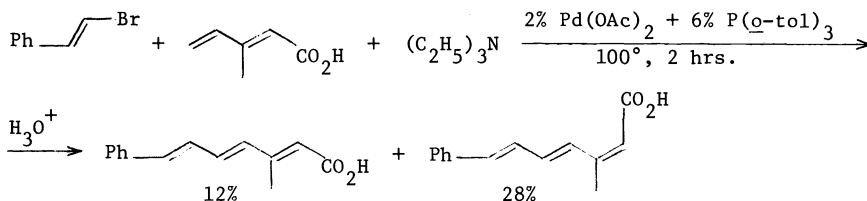


#### CONJUGATED TRIENES

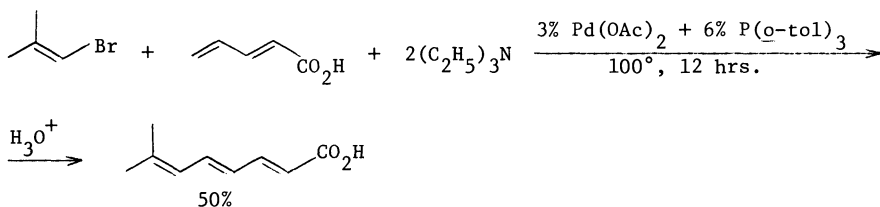
The formation of conjugated trienes from vinyl bromides and conjugated dienes occurs analogously to the olefin reaction and it proceeds best when ester and acid derivative substituents are present on a terminal double bond carbon of one or both of the reactants. For example, E-2-bromostyrene and E-2,4-pentadienoic acid with triethylamine under the usual reaction conditions with the palladium acetate-triphenylphosphine catalyst produce E,E,E-7-phenyl-2,4,6-heptatrienoic acid in 57% yield (3).



A similar reaction with Z-3-methyl-2,4-pentadienoic acid gave 40% of a mixture of two isomeric 3-methyl-7-phenyl-2,4,6-heptatrienoic acids. The reactant acid is stable under the reaction conditions and the selectivity of the reaction is not improved by adding excess triphenylphosphine. Therefore, product isomerization under the reaction conditions appears to be the major source of the loss of stereochemistry.

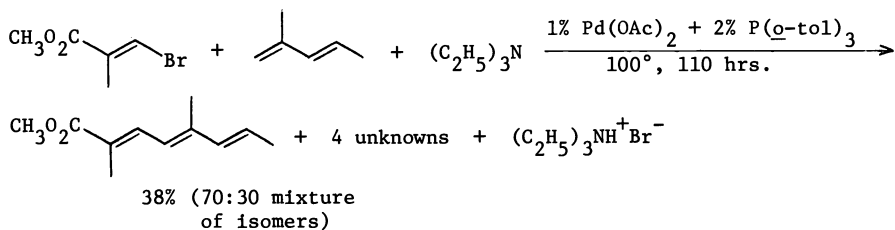


1-Bromo-2-methyl-1-propene reacts with E-2,4-pentadienoic acid and triethylamine to form the triene in 50% yield. Three times the usual amount of catalyst was used in this reaction

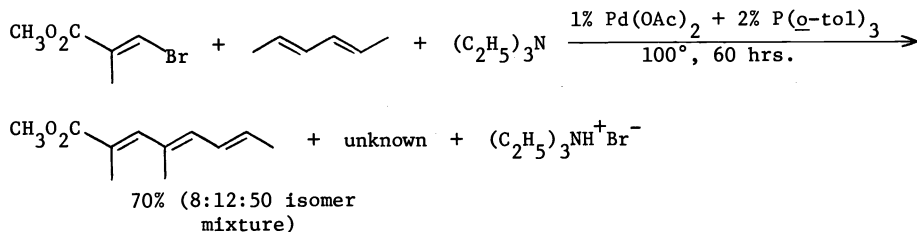


to shorten the reaction time and improve the yield. A similar reaction with Z-1-bromo-1-propene instead of 1-bromo-2-methyl-1-propene failed to give the expected triene. High boiling and polymeric materials were formed instead.

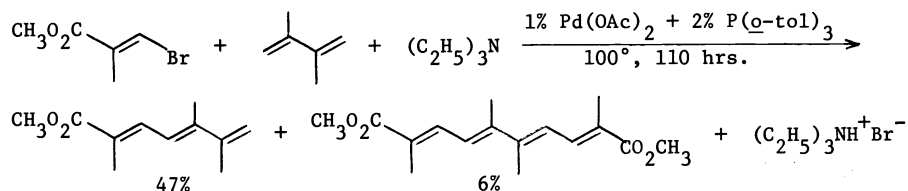




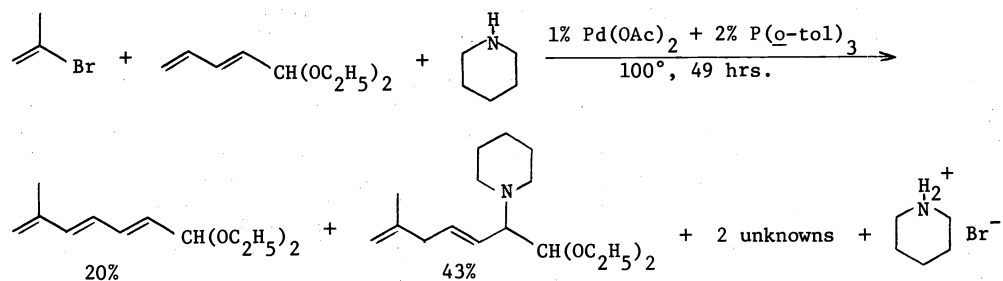
E,E-2,4-Hexadiene likewise produces the expected trienoate ester in ~70% yield, but as an 8:12:50 isomeric mixture.



2,3-Dimethyl-1,3-butadiene produces a single trienoate, but also forms a tetraene from addition of two of ester units to the diene. The ratios of products depends upon the molar ratios of the reactants. With a 250% molar amount of the diene relative to the bromoester, 47% of the trienoate is obtained along with 6% of the yellow crystalline tetraenedioate ester with the probable stereochemistry shown below.

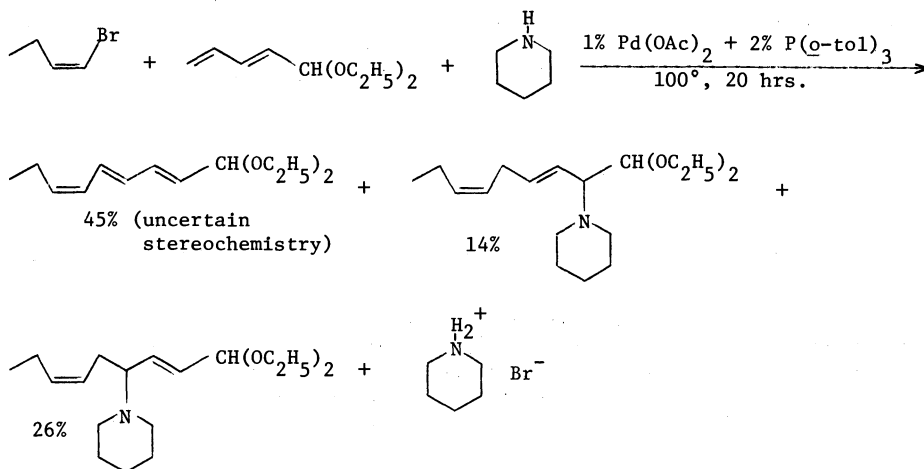


Conjugated trienes may be prepared without the ester or acid derivative function on the conjugated system by the vinylic bromide-conjugated diene--secondary amine reaction which forms the triene along with 2,5-dienylamines. Presumably the amines can be converted into the triene, also, by the Hofmann elimination. For example, the dimethyl acetal of 6-methyl-2,4,6-heptatrienal has been prepared as shown below.



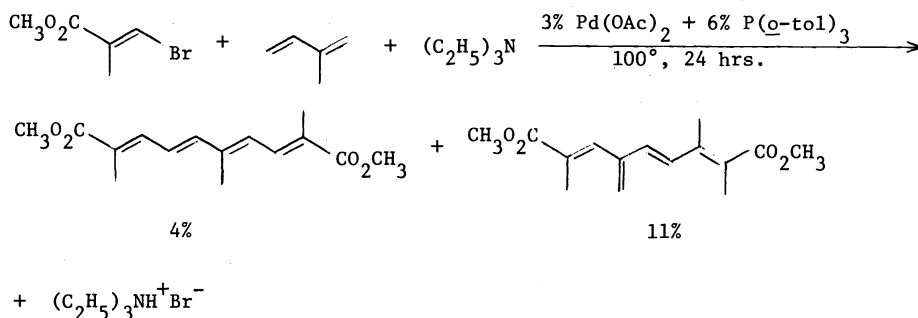
Z-1-Bromo-1-butene reacts similarly.





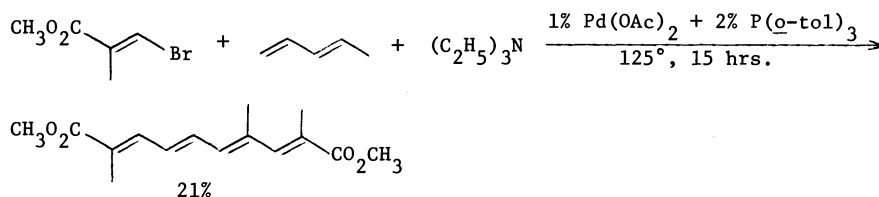
## CONJUGATED TETRAENES

Isoprene reacts with E-methyl 3-bromo-2-methylpropenoate and triethylamine with the usual catalyst to form a mixture of two tetraenes in low yield no matter what ratio of reactants is used. Under the most favorable conditions we found the linear tetraene was formed in only 4% yield and a cross-conjugated isomer in 11% yield. The remainder of the product was non-volatile polymeric material.

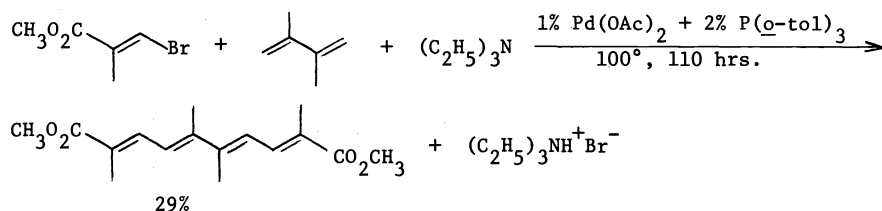


The structures of these products are based upon NMR spectra at 250 MHz. The compounds were easily separated by fractional crystallization. The cross-conjugated tetraene may be formed by the addition of the vinylic group to carbon 3 of the isoprene rather than 4 followed by addition of a second vinylic group at carbon 1. If this is the mechanism, it is surprising that there is so much addition to carbon 3 since we have not observed this mode of addition in any other similar reaction of isoprene. Another possibility for the formation of the cross-conjugated product is that the vinylic group adds to the disubstituted double bond of the isoprene and the second vinylic group is added (partly) in the "abnormal" direction to the other double bond. This explanation is not totally satisfactory either since we do not observe this mode of addition to isoprene either in the other reactions we have studied. Further work is needed to determine which, if either, of these possibilities is correct.

The trienoate ester from piperylene and E-methyl 3-bromo-2-methylpropenoate can be reacted a second time with the same bromoester to form the linear tetraenedioate. This can be done in two steps, but more conveniently in one. In either case, the yield is relatively low, but the product is easily isolated from the polymeric mixture formed with it because of its low solubility in most common solvents.



The yield of the tetraenedioate from 2,3-dimethyl-1,3-butadiene mentioned above (6%) can be increased to 29% by employing a 2:1 molar ratio of vinylic bromide to diene as reactants.



#### CONCLUSIONS

2,4-Dienoic acid derivatives are easily prepared from various vinylic bromides or iodides and acrylic acid derivatives. The reactions are generally stereospecific. Aryl bromides or iodides react with 2,4-pentadienoic acids or esters to form 5-aryl-2,4-pentadienoic acid derivatives. Other conjugated dienes without acid or ester groups can be made by a two-step process involving a palladium-catalyzed reaction of vinylic bromides or iodides, alkenes, and secondary amines to form tertiary allylic amines, followed by a Hofmann elimination. Conjugated trienoic acids and derivatives are made similarly from vinylic bromides and 2,4-pentadienoic acid or derivatives or by a two-step reaction if ester or acid groups are not present, involving a vinylic bromide--conjugated diene--secondary amine reaction followed by a Hofmann elimination. Finally, conjugated tetraenedioates are obtained by a double vinylation of conjugated dienes with E-methyl 3-bromo-2-methylpropenoate.

We understand the factors influencing the stereochemistry in the diene synthesis, but further study is required to learn as much about the triene and tetraene preparations. We are continuing the study of the reactions producing trienes, tetraenes and higher polyenes. It is clear that there are serious limitations to the reaction for preparing the higher, more reactive members of the series, but it is also clear that, at least, some polyenes can be prepared very conveniently by our method.

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