Palladium-Catalyzed Arylation and Vinylation of 1,4-Dienes

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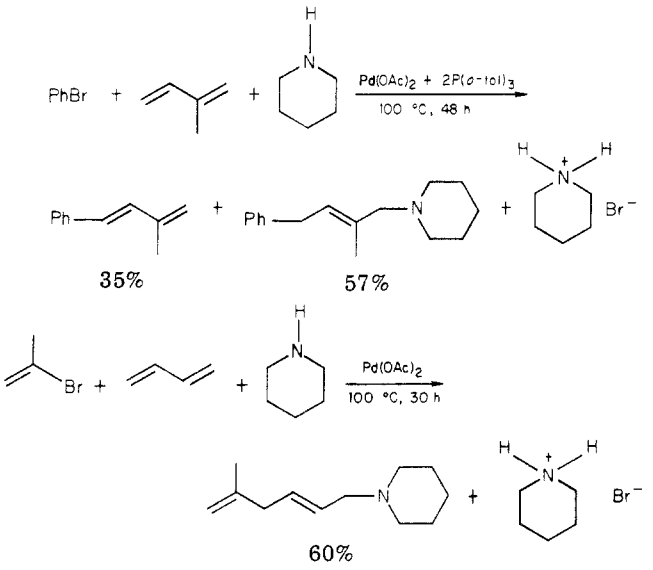
Bromo- or iodobenzene has been reacted with 1,4-pentadiene, (*Z*)- or (*E*)-1,4-hexadiene, and 2-methyl-1,4-pentadiene in the presence of piperidine and a palladium acetate–tri-*o*-tolylphosphine catalyst. 1-Phenyl-5-piperidino-3-alkenes are major reaction products along with minor amounts of 1-phenyl-3-piperidino-4-alkenes, 2-phenyl-5-piperidino-3-alkenes, and varying amounts of phenylalkadienes. *N*-(2,5-Hexadienyl)piperidine reacts with bromobenzene and piperidine to give 55% *N*-(6-phenyl-2,4-hexadienyl)piperidine. Vinylic bromides react with simple 1,4-dienes and piperidine to form mixtures of dienyl amines. The reactions are quite specific if symmetrical intermediate σ-palladium alkyls are formed, but mixtures are obtained in other cases. (*E*)- and (*Z*)-1-Bromo-1-butene react with either *N*-(1,4-pentadienyl)piperidine or *N*-(2,4-pentadienyl)piperidine and piperidine with the palladium catalyst to form enamines which hydrolyze to 2,6-nonadienal in 20–28% yield.

The palladium-catalyzed arylation[1] and vinylation[2] of conjugated dienes are useful reactions for the preparation of 4-aryl-2-buten-1-yl amines, and 2,5-dienyl amines, respectively. The following examples are typical.



These reactions are believed to proceed by way of π-allylic palladium halide intermediates.[3] We have now investigated the related reaction of 1,4-dienes with aryl and vinylic halides and amines to determine if five-carbon units can be added to the halides in a selective manner. It was anticipated that these reactions also would proceed via π-allylic palladium complexes from our previous work with simple olefins[4] and produce allylic amines and/or trienes. This proved to be the case. In some examples, mixtures of products were observed because two different π-allylic intermediates were formed. The identity of the products produced provides insight into the behavior of organopalladium complexes. Some useful synthetic applications were found as well.

Results and Discussion

Arylations. The reaction products obtained from bromobenzene or iodobenzene with 1,4-pentadiene, *trans*-1,4-hexadiene, and 2-methyl-1,4-pentadiene, and piperidine with a palladium acetate–tri-*o*-tolylphosphine catalyst are listed in Table I, along with reaction conditions. The structures of the products formed in these and other reactions listed in this report have been determined by high-resolution mass spectroscopy for molecular weights and from NMR spectra at 250 MHz with decoupling where essential. We have not determined stereochemistry in most examples because it can be confidently predicted usually on the basis of the few examples where it has been determined. In these and other reactions studied in this investigation, the reaction products were determined to be stable under the reaction conditions. No major products such as diaddition products were found other than those listed in the tables. Mixtures of phenylpentadienes and (phenylpentenyl)amines were obtained. The phenyl group adds to the least substituted double bond in all cases. The amines predominated in the bromobenzene reactions, while the same reaction with iodobenzene, in one case, gave a higher yield of dienes than amines. The dienes were mixtures of three to five isomers and were not studied further. The amine products were mixtures of two or three isomers. The major amine in all reactions was the 1-phenyl-5-amino derivative arising from the 1-(β-phenylethyl)-π-allylic palladium intermediate. (See Scheme I.) The allylic isomer, the 1-phenyl-3-amino derivative, is also formed in at least two cases but in much smaller amount. The third isomer observed in all cases is the 2-phenyl-5-amino derivative formed by addition of the phenyl group to the second carbon of the diene rather than the first, with formation of an 1-α-phenylethyl)-π-allylic complex as the intermediate. The addition of bromobenzene to 1-hexene produced about 20% of 2-phenyl adducts[5] also; therefore the 2-phenyl isomers are not unexpected in the present examples. The probable mechanism of the reaction is shown in Scheme I.

It is notable that the palladium hydride elimination from the initial, terminal phenyl diene adduct significantly prefers to occur to form the conjugated diene π complex rather than the phenyl conjugated olefin π complex (at least in the bromobenzene reactions). The 1,4-hexadiene reaction gave the same products in the same yields at 140 °C as it did at 100 °C.

The last example in Table I, the reaction of bromobenzene with *N*-(2,5-hexadienyl)piperidine, gave a single product, *N*-(6-phenyl-2,5-hexadienyl)piperidine in 55% yield, resulting from elimination of the hydridopalladium group to form the phenyl conjugated olefin. No other

(1) B. A. Patel, J. E. Dickerson, and R. F. Heck, *J. Org. Chem.*, **43**, 5018 (1978).
(2) B. A. Patel, L-C. Kao, N. A. Cortese, J. V. Minkiewicz, and R. F. Heck, *J. Org. Chem.*, **44**, 918 (1979).
(3) F. G. Stakem and R. F. Heck, *J. Org. Chem.*, **45**, 3584 (1980).
(4) B. A. Patel and R. F. Heck, *J. Org. Chem.*, **43**, 3898 (1978).
(5) R. F. Heck, *Acc. Chem. Res.*, **12**, 146 (1979).

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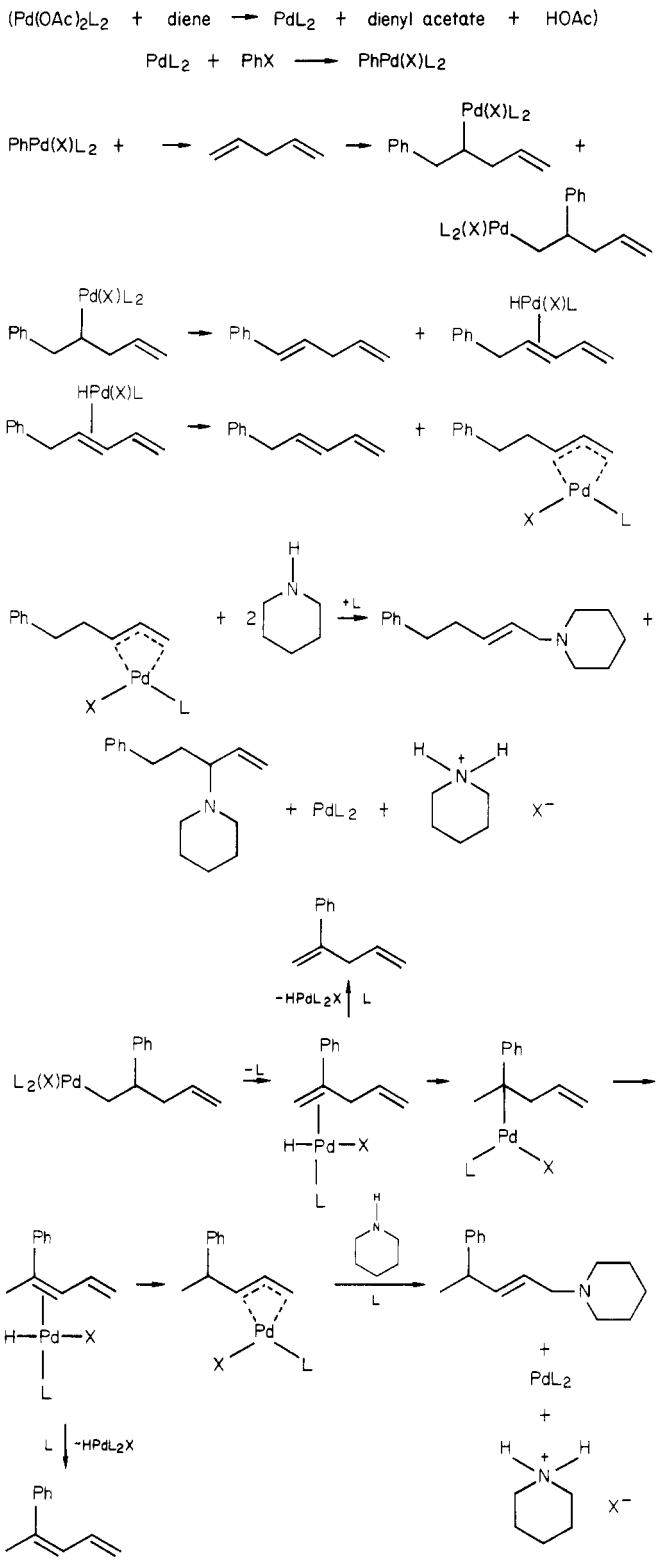
Scheme I [a]



[a] L = P(*o*-tol)$_3$ or piperidine.

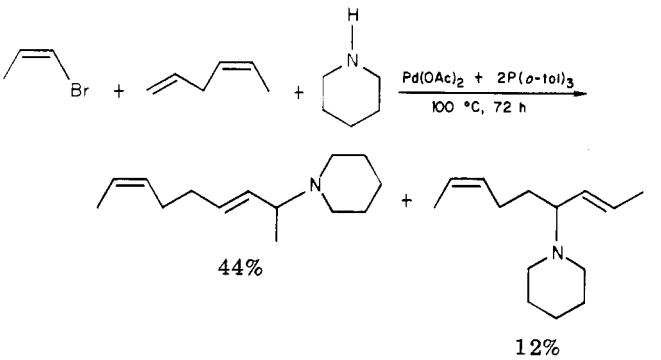
volatile products were formed, although diamines could have been present in the "nonvolatile" material formed. It is clear that the piperidine group present in the diene is influencing the reaction significantly since (*E*)-1,4-hexadiene, the diene without the piperidine substituent, gave mainly (70%) amine adducts and could not have given more than 30% diene compared with the 55% obtained from the dienylpiperidine. Chelation of the amine group to the palladium during the reaction is a probable cause of the different behavior of the dienyl amine.

This aryl halide–1,4-diene reaction provides a very easy method for adding a five-carbon chain to an aromatic ring. In cases where mixtures of products are formed, the major amine products probably could be isolated and purified through their picrates. We have done this in the case of the bromobenzene–1,4-pentadiene–piperidine reaction where we have separated the *N*-(5-phenyl-2-pentenyl)-piperidine (picrate mp 97–99 °C) with 55% recovery of the amount present in the crude reaction product.

Vinylation of 1,4-Dienes Which Form Symmetrical Intermediates. In order to minimize the formation of isomeric products, we studied first the vinylation of 1,4-dienes with examples that should produce symmetrical, initial organopalladium intermediates. These adducts can eliminate and either form trienes or undergo readdition of the metal hydride and form π-allylic palladium complexes. In the symmetrical cases, elimination in either direction will give the same dienes and/or π-allylic complexes. The final S_N2 reaction of the π complexes with piperidine only can form either or both of two possible allylic amine products. The first step of the reaction is the same as in the phenyl halide reaction in Scheme I. The subsequent steps expected to occur are shown in Scheme II.

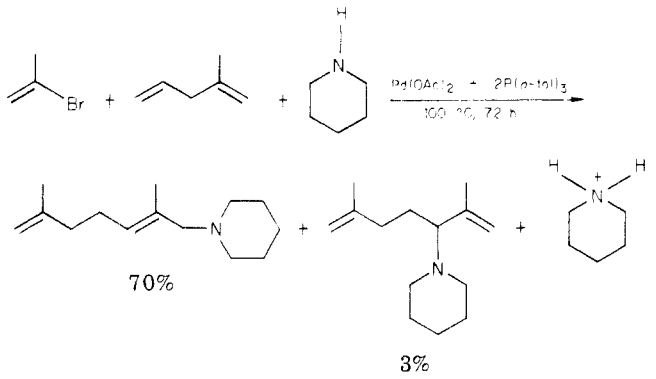
The reactions carried out with vinyl halides and 1,4-dienes which form symmetrical intermediates are listed in Table II. The reaction products were mainly mixtures of two amines, the two allylic isomers expected by the above mechanism. Apparently, the trienes polymerized or reacted in other ways and were not present in significant amounts. In these reactions, as well as the others described in this paper, considerable amounts of high boiling and/or nonvolatile material are present in the reaction mixtures, which account for most of the material not identified in the reactions listed in the tables.

The reaction of vinyl bromide with 1,4-pentadiene gave the same ~3:1 mixture of the two amines in the same yields when reacted at 100 or 140 °C. A similar mixture was obtained from the reaction of (*Z*)-1-bromo-1-propene and (*Z*)-1,4-hexadiene whether carried out at 60 or 100 °C. Relatively more of the 3-amino isomer was obtained at 140 °C (39:21 compared with 44:12 at 100 °C). It is surprising

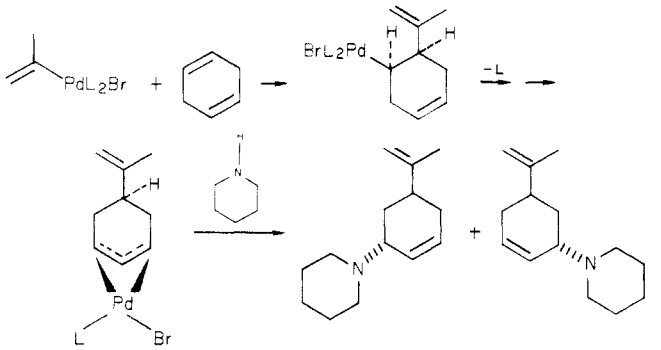


that little or none of the amine formed from addition of the propenyl group to the second carbon of the diene was produced since 1-hexene and 1-bromo-1-propene produce a significant amount of the 2-propenyl adduct.[4] The third example forming a symmetrical intermediate was the reaction of 2-bromopropene with 2-methyl-1,5-pentadiene and piperidine. This reaction produced 70% of the 1-amino 2,6-diene and only 3% of the allylic isomer.

The reaction of 1,4-cyclohexadiene with 2-bromopropene and piperidine is different from the other examples in Table II because the symmetry of the intermediate arises from the cyclic nature of the diene rather than the symmetry of the initial adduct. Only one π-allylic intermediate



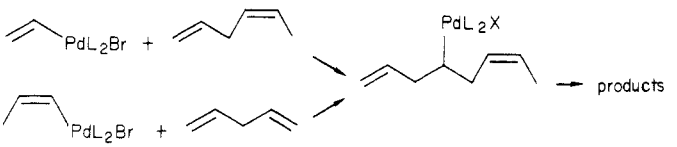
is formed in this reaction because there is no syn hydrogen available for elimination to form the other possible π-allylic complex. Attack at either of the terminal π-allylic carbons in the intermediate gives rise to enantiomeric forms of the same, presumably trans, product. (Trans stereochemistry has been confirmed in the related palladium-catalyzed addition of bromobenzene to 1,3-cyclohexadiene with piperidine.[13]) Unfortunately, the reaction is very slow and the yield of product is low (20%).



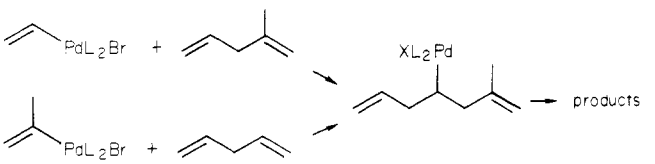
Vinylation of 1,4-Dienes Which Form Unsymmetrical Intermediates. The combination of vinylic halides with 1,4-dienes which do not form symmetrical intermediates was expected to yield more complex reaction mixtures because the palladium hydride elimination in the initial adduct can occur in both possible directions and each of these isomers can produce different trienes and different π-allylic palladium complexes. Four isomeric allylic amines are possible from the two π complexes. In addition to these four amines, other amines can be formed from addition of the vinylic group to the second carbon of the terminal dienes. As anticipated, complex reaction mixtures were usually obtained. It was of interest to investigate how the structure of the initial organopalladium adducts influenced the direction of elimination of the palladium hydride group.

A variety of reactions between vinylic bromides and 1,4-dienes with unsymmetrical intermediates were carried out and the results are summarized in Table III. Five vinylic bromides were used: vinyl bromide, (*Z*)-1-bromo-1-propene, 2-bromopropene, 1-bromo-2-methyl-1-propene, and 2-bromo-3-methyl-2-butene. These bromides were reacted with one or more of the following 1,4-dienes: 1,4-pentadiene, (*Z*)- or (*E*)-1,4-hexadiene, 2-methyl-1,4-pentadiene, and *N*-(1,4-pentadienyl)piperidine. Both possible π-allylic complexes were apparently formed in all instances expect the 1,4-cyclohexadiene and *N*-(1,4-pentadienyl)piperidine reactions, and products of addition of the vinylic group to C-2 of the diene were also seen in some reactions. The reaction of vinyl bromide with 2-methyl-1,4-pentadiene produced an additional product, 4-methyl-7-piperidino-1,5-heptadiene, apparently arising from addition of the vinyl group to the 1,2-disubsitituted diene double bond. This usual type of product was obtained in only about 4% yield. The analogous product was also obtained when morpholine was used as the base.

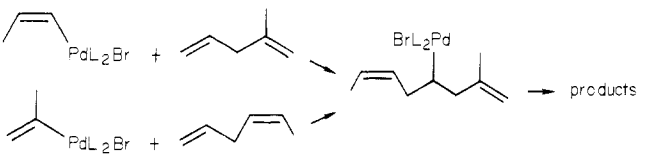
Three sets of reciprocal reactions were carried out to determine if the same intermediate organopalladium adduct was formed in each set. The first set was the reaction of vinyl bromide with (*Z*)-1,4-hexadiene compared with the reaction of (*Z*)-1-bromo-1-propene with 1,4-pentadiene with morpholine and with piperidine as the bases. Only small differences in yields within experimental error of the various products obtained were seen. It could be imagined that coordination of the nonreacting double bond of the 1,4-diene in the transition state could give rise to different products from the two reactions. Since the product yields are similar in this and the following two cases, the two reactions probably proceed by way of the same initial adduct. In the second set, the reaction of vinyl bromide



with 2-methyl-1,4-pentadiene was compared with the reaction of 2-bromopropene with 1,4-pentadiene, employing both piperidine and morpholine as bases. The similarity of the ratios of products obtained again suggests the same major intermediate is involved in both reactions. The



third reciprocal set consisted of the reaction of (*Z*)-1-bromo-1-propene with 2-methyl-1,4-pentadiene compared with the reaction of 2-bromopropene with (*Z*)-1,4-hexadiene with piperidine as the base. The differences are clearly outside of the experimental error in this case, but since we could account for only 60–65% of the products, different side reactions of the products could easily account for them. It is not clear, therefore, whether these reactions also are proceeding by way of a common intermediate as formulated below or by some other route.



The reaction of the 1,4-dienamine, *N*-(1,4-pentadienyl)piperidine, with (*Z*)-1-bromo-1-butene and piperidine was studied with the hope of preparing an adduct that would hydrolyze to (*E*,*Z*)-2,6-nonadienal (violet leaf aldehyde), a natural product found in the violet plant which is of value in perfumery. Previous results indicated the need to keep the reaction time as short as possible to minimize isomerization of the 1-bromo-1-alkene.[6] Therefore, we used 3% palladium acetate with 6% tri-*o*-tolylphosphine as catalyst rather than the usual amounts (one-third as much). The reaction was complete in less than 2 h at 100 °C, but even so, there was about 20% of the *E*,*E* isomer in the product dienal after acidic hydrolysis. The desired *E*,*Z* isomer was formed in 19% yield and

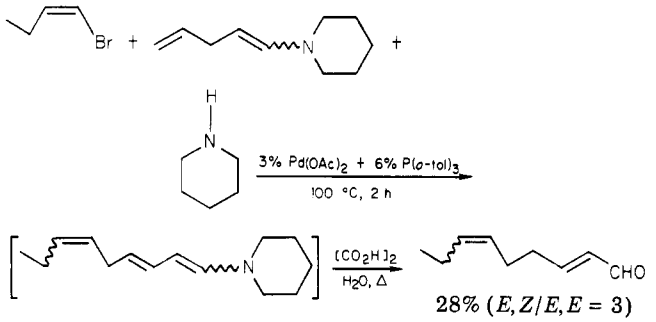
(6) F. Sondheimer, *J. Am. Chem. Soc.*, 74, 4040 (1952).

Table I. Arylation of 1,4-Dienes[a]

aryl halide	1,4-diene	rctn time, h	temp, °C	products, % yield by GLC: phenylalkadienes[b]	1-phenyl 5-amine	1-phenyl 3-amine	3-phenyl 5-amine
C_6H_5Br	CH_2=$CHCH_2CH$=CH_2	18	100	24	49	3	8
	(*E*)-CH_2=$CHCH_2CH$=$CHCH_3$	20	100		59	4	7
		1.5	140		56	5	8
	CH_2=$CHCH_2C(CH_3)$=CH_2	18	100	32	37[b]		<1
C_6H_5I	CH_2=$CHCH_2C(CH_3)$=CH_2	20[c]	100	40	29[b]		5[b]
C_6H_5Br	CH_2=$CHCH_2CH$=$CHCH_2NC_5H_{10}$	18[c]	100	55[d]			

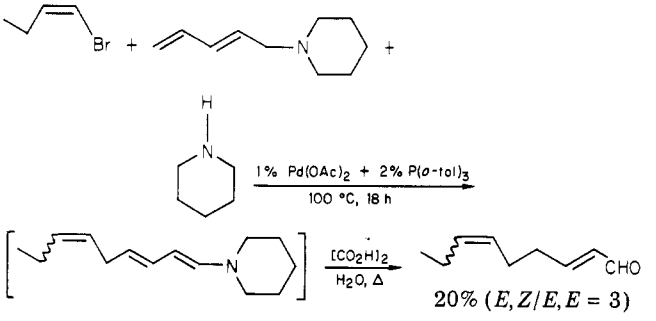
[a] Catalyst: 1 mol % of $Pd(OAc)_2$ + 2 mol % of P(*o*-tol)$_3$ based upon the aryl halide. Piperidine was the amine present. Yields are based upon the aryl halide employed. [b] Isolated yield. [c] Only 1 mol % of $Pd(OAc)_2$ used as catalyst. [d] *N*-(6-Phenyl-2,4-hexadienyl)piperidine.

the *E,E* isomer in 9% yield based upon the 1-bromo-1-butene. No other volatile, acid-insoluble products were found. The intermediate, presumably a trienamine, was not isolated. The remaining 72% of product was polymer and various amines which were not characterized.



28% (*E,Z/E,E* = 3)

We also studied the (*Z*)-1-bromo-1-butene reaction with *N*-(2,4-pentadienyl)piperidine and piperidine to determine if this diene might give a better yield of the 2,6-nonadienal enamine. The yield of 2,6-nonadienal from hydrolysis of the enamine was only 20% from this combination and the stereochemical result was similar to that of the previous reaction whether we used 1% or 3% catalyst. (*E*)-1-

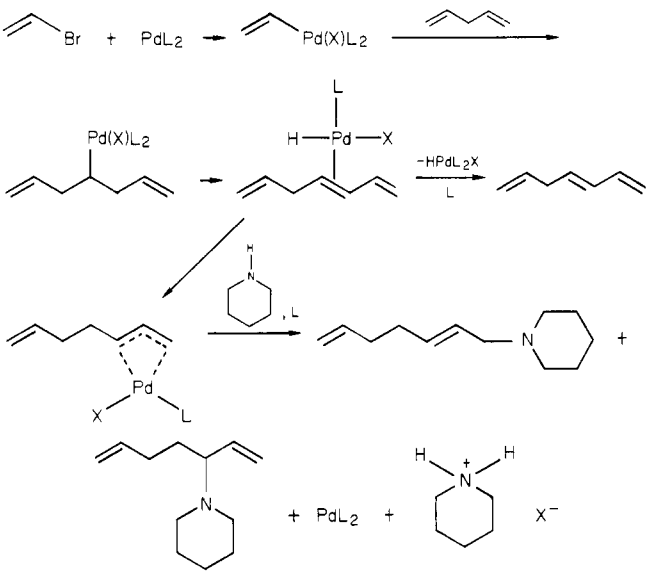


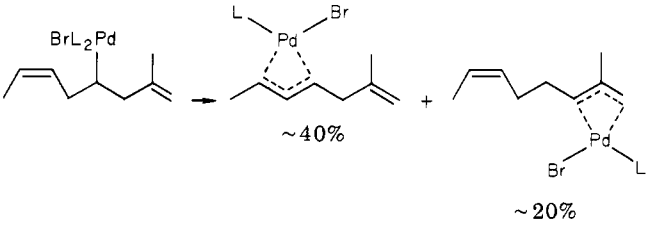
20% (*E,Z/E,E* = 3)

Bromo-1-butene reacted similarly to give 19% of dienal which had the isomer ratio *E,E/E,Z* = 4. A related reaction of *N*-(2,4-pentadienyl)piperidine with 1-bromo-2-methyl-1-propene failed to give identifiable products under similar conditions. Likewise, the quaternary salt of this amine with ethyl bromide and 1-bromo-2-methyl-1-propene did not give the expected vinylation product. *N*-(1,3-Butadienyl)piperidine did not give tractable products either with the same vinylic bromide. An attempt to form citral from *N*-(3-methyl-1,4-pentadienyl)piperidine and 2-bromopropene with piperidine also failed to give any of the desired product.

Some generalizations can be made from the data in Table III regarding the preferred direction of elimination of the palladium hydride group in the unsymmetrical adducts. The elimination is not very selective in any case, but it is apparent that elimination toward the less substituted end of the molecule is preferred. Elimination toward a 2-methyl-substituted double bond is less favorable than elimination toward a 1-methyl-substituted double bond. Thus, the products from the reactions in the third reciprocal set above probably arise mainly from the 1,3-disubstituted π-allylic intermediate rather than the other possible one, the 2,3-disubstituted π-allylic isomer.

Scheme II





~20%

Unfortunately, these reactions are often not of much value preparatively because of low yields or the difficulty of separating the isomeric mixtures of products formed or both. Some of the products, however, may be of sufficient complexity and value that it would be worthwhile separating them. The 2,6-nonadienal preparation is of value since the alternative synthesis is much longer and the overall yield is comparable.[6] We have demonstrated that the major amine product in a mixture can be isolated in one instance through recrystallization of the amine picrate. The example is the reaction of vinyl bromide with 1,4-pentadiene and piperidine which gave the mixture of amines shown in Table II. Recrystallization of the picrates of the mixtures gave the pure derivative of *N*-(2,6-heptadienyl)piperidine (mp 60–61 °C) in about 26% yield based

Table II. Vinylation of 1,4-Dienes Which Form Symmetrical Intermediates[a]

vinylic bromide	1,4-diene	rctn time, h	temp, °C	products, % yield by GLC: 1-amino 2,6-diene	products, % yield by GLC: 3-amino 1,6-diene
CH_2=CHBr	CH_2=$CHCH_2CH$=CH_2	16	100	47[b]	15[b]
		5	140	46	14
Z-CH_3CH=CHBr	Z-CH_2=$CHCH_2CH$=$CHCH_3$	216	60	47	14
		72	100	44	12
		2.5	140	39	21
$CH_3C(Br)$=CH_2	CH_2=$CHCH_2C(CH_3)$=CH_2	72	100	70	3[c]
	1,4-cyclohexadiene	240	100	20	

[a] Catalyst: 1 mol % of $Pd(OAc)_2$ + 2 mol % of tri-*o*-tolylphosphine based upon the vinylic bromide. The amine employed was piperidine except in the vinylic bromide reactions where morpholine was used. Yields are based upon the vinylic halide employed. [b] If piperidine was employed as the base rather than morpholine, the yields were 37% and 7%, respectively. [c] Structure uncertain. [d] $Pd(OAc)_2/P(o\text{-tol})_3$ = 4:8.

Table III. Vinylation of 1,4-Dienes Which Form Unsymmetrical Intermediates[a]

					% yields of products: from π complex with vinylic halide double bond		from π complex with 1,4-diene double bond		from addn of vinyl group to C-2,	
vinylic bromide	1,4-diene	amine[b]	rctn time, h	temp, °C	1-amino-2,6-diene	3-amino-1,6-diene	1-amino-2,6-diene	3-amino-1,6-diene	1-amino-2,5-diene	other
CH_2=CHBr	(*Z*)-CH_2=$CHCH_2CH$=$CHCH_3$	P*H	19	100	45	0	12	8		
			2	140	56	0	11	12		
		MH	19	100	23	0	19	19		
		P*H	16[c]	100	56	0	7	11		
	CH_2=$CHCH_2C(CH_3)$=CH_2	P*H	43	100	18	1	9	4	5	4[d]
			5	140	19	2	9	4	6	4[d]
		MH	21	100	21	3	6	11	5	5[d]
(*Z*)-CH_3CH=CHBr	CH_2=$CHCH_2CH$=CH_2	P*H	24	100	14	10	46	0		
		MH	24	100	19	21	21	0		
	CH_2=$CHCH_2C(CH_3)$=CH_2	P*H	43	100	34	13	14	3		
CH_2=C(Br)CH_3	CH_2=$CHCH_2CH$=CH_2	P*H	18	100	13	~4	32	~3		
		MH	21	100	8	8	28	4		
CH_2=C(Br)CH_3	(*Z*)-CH_2=$CHCH_2CH$=$CHCH_3$	P*H	22	100	20	2	30	8		
(*Z*)-C_2H_5CH=CHBr	CH_2=$CHCH_2CH$=$CHNC_5H_{10}$	P*H	2[e]	100						28[f]
$(CH_3)_2C$=CHBr	CH_2=$CHCH_2CH$=CH_2	P*H	22	100	7	15	17	<2[g]	17	
	(*E*)-CH_2=$CHCH_2CH$=$CHCH_3$	P*H	16	100	15	5	18		17	
	CH_2=$CHCH_2C(CH_3)$=CH_2	P*H	65	100	39	8	19	6[g]		
$(CH_3)_2C$=C(Br)CH_3	CH_2=$CHCH_2CH$=CH_2	P*H	26 days[h]	60		17	24	4	5	
		P*H	12[e]	100		15	33	3	4	
		P*H	1[e]	125		4	30	4	4	
		P*H	213[e]	140		3	31	4	4	

[a] Catalyst: 1 mol % of $Pd(OAc)_2$ + 2 mol % of $P(o\text{-tol})_3$ based upon the vinylic halide. Yields are estimated to be ±2% and are based upon the vinylic halide employed. [b] P*H = piperidine; MH = morpholine. [c] No tri-*o*-tolylphosphine used. [d] 4-Methyl-7-piperidino-1,5-heptadiene. [e] $Pd(OAc)_2/P(o\text{-tol})_3$ = 3:6. [f] 2,6-Nonadienal (*Z*/*E* = 3) formed by the hydrolysis of the presumed product, *N*-(1,3,6-nonatrienyl)piperidine. [g] Structure uncertain. [h] $Pd(OAc)_2/P(o\text{-tol})_3$ = 4:8.

upon the amount of that amine present.

Experimental Section

Materials. Halides. Bromobenzene (Fisher), iodobenzene (Aldrich), vinyl bromide (Aldrich), (*Z*)-1-bromo-1-propene (Pfaltz and Bauer), and 2-bromo-1-propene (Aldrich) were commercial products and were used as received. 1-Bromo-2-methyl-1-propene[7] and 2-bromo-3-methyl-2-butene[8] were prepared according to the literature. (*E*)- and (*Z*)-1-Bromo-1-butene were obtained by fractionation of a commercial sample of a mixture (Columbia Organic Chemicals, Inc.). The *Z* isomer had the following: bp 88 °C (lit.[9] bp 86.15 °C); NMR ($CDCl_3$) δ 1.03 (t, 3 H), 1.91–2.45 (m, 2 H), 6.12 (m, 2 H). The *E* isomer had the following: bp 96 °C (lit.[9] bp 94.7 °C; NMR ($CDCl_3$) δ 1.00 (t, 3 H), 1.75–2.30 (m, 2 H), 6.10 (m, 2 H).

Dienes. 1,4-Pentadiene, (*E*)- and (*Z*)-1,4-hexadiene, 2-methyl-1,4-pentadiene, and 1,4-cyclohexadiene were commercial samples obtained from the Chem Samples Co. and were used as received. *N*-(1,3-Butadienyl)piperidine was prepared by the procedure of Mannich et al.[10] The methods of preparation of the other dienes are given below.

Miscellaneous. Morpholine (Fisher) and piperidine (Aldrich) were used as received. Palladium acetate and tri-*o*-tolylphosphine were obtained as described previously.[4]

***N*-(2,5-Hexadienyl)piperidine.** A mixture of 25 mL (250 mmol) of piperidine, 0.224 g (1 mmol) of palladium acetate, and 0.608 g (2 mmol) of tri-*o*-tolylphosphine was prepared in an 80-mL stainless-steel bomb. After the mixture was cooled to −78 °C in a good hood, 7.05 mL (100 mmol) of vinyl bromide and 13.50 g (250 mmol) of 1,3-butadiene were added, and the bomb was sealed. The bomb was warmed with shaking to dissolve the catalyst and then heated at 100 °C in a steam bath for 22.5 h. After cooling, the bomb was opened in the hood and reaction mixture was diluted with 100 mL of 10% aqueous sodium hydroxide and 100 mL of ether. The aqueous phase was separated and extracted twice more with 100-mL portions of ether. The combined extracts were dried, concentrated, and distilled under reduced pressure. The product was obtained as a colorless liquid: 23.1 g (70%), bp 67–69 °C (0.20 mm). The NMR spectrum and molecular weight are given in Table IV (see note on supplementary material at the end of this paper).

***N*-(1,4-Pentadienyl)piperidine.** A solution of 31.5 g (0.38 mol) of 4-pentenal[11] in 50 mL of ether was cooled to 0 °C and 4A molecular sieves were added equivalent to about half the volume of the liquid. The mixture was stirred and 32 g (0.38 mol) of piperidine in 50 mL of ether was added dropwise. After the addition the mixture was stirred at room temperature for 5 h. At this time a few drops of a second phase was visible on the walls of the flask, so magnesium sulfate was added and the mixture was filtered. The solvent and unreacted starting materials were removed at room temperature under reduced pressure. The crude product remaining was pure judging from its NMR spectrum (Table IV) and it was used directly in the 1-bromo-1-butene reaction since it decomposed on attempted distillation under reduced pressure. The crude yield was 42.5 g (75%).

***N*-(3-Methyl-1,4-pentadienyl)piperidine.** This enamine was prepared in 75% yield from 3-methyl-4-pentenal (obtained in 91% yield by the Claisen rearrangement of crotyl vinyl ether, bp 55–57 °C (90 mm)),[11] using the above procedure for *N*-(1,4-pentadienyl)piperidine.

***N*-(2,4-Pentadienyl)piperidine.** 5-Chloro-1,3-pentadiene was prepared by dissolving 61 g (0.73 mol) of 1,4-pentadien-3-ol in 100 mL of ether and adding this solution slowly with stirring to 128 mL of 12 N hydrochloric acid at 0 °C. The stirring was continued at room temperature for 1.5 h. The layers were then separated, and the aqueous phase was diluted with 200 mL of water and extracted twice more with 100-mL portions of ether. The extracts were combined, washed twice with aqueous sodium bicarbonate and once with water, and dried. The crude product (56% yield) isolated by evaporation of the ether under reduced pressure (80 mm) was used without further purification.

The crude chloride (52.5 g, 0.51 mol) dissolved in 100 mL of ether at 0 °C was stirred, while a solution of 131 g (1.54 mol) of piperidine in 100 mL of ether was added dropwise. The slurry obtained was stirred at room temperature overnight. The solution was then filtered and the filtrate was concentrated, washed with aqueous sodium hydroxide and water, and dried. Evaporation of the solvent and distillation of the residue gave 58 g (75%) of the dienylamine, bp 45–48 °C (1.0 mm).

General Procedure for the Reaction of Aryl Halides or Vinylic Bromides with 1,4-Dienes. A mixture of 0.1 mmol of palladium acetate, 0.2 mmol of tri-*o*-tolylphosphine, 10 mmol of the organic halide, 12.5 mmol of the 1,4-diene, and 30 mmol of the amine was placed in a capped heavy-walled Pyrex tube under nitrogen and heated in a steam bath until GC analysis of a small sample showed that all of the halide had reacted. After cooling, the mixture was treated with 10% aqueous potassium hydroxide and ether. The ether layer was separated, dried over magnesium sulfate, and evaporated. The amines were isolated by preparative gas chromatography on a 20% DC 550/Chromosorb W column. Yields were determined by adding an internal standard such as *p*-xylene, mesitylene, or naphthalene and analyzing by GLC using sensitivity coefficients determined from isolated samples. Alternatively, a mixture of the amines could be isolated by vacuum distillation of the ether extract.

2,6-Nonadienal. From *N*-(1,4-Pentadienyl)piperidine. A solution of 9.44 g (62.5 mmol) of *N*-(1,4-pentadienyl)piperidine, 6.75 g (50 mmol) of (*Z*)-1-bromo-1-butene, and 12.5 mL (125 mmol) of piperidine was prepared in a 250-mL heavy-walled Pyrex bottle. Palladium acetate (0.336 g, 1.5 mmol) and 0.912 g (4.5 mmol) of tri-*o*-tolylphosphine were added, and the bottle was flushed with nitrogen, capped, and heated in a steam bath for 100 min. At this time GLC analysis showed the 1-bromo-1-butene had all reacted. The reaction mixture was cooled to room temperature, 50 mL of ether was added, and it was stirred with a solution of 18 g of oxalic acid in 180 mL of water for 1 h. The aqueous phase was separated and extracted thrice with 100-mL portions of ether. The combined extracts were washed with cold aqueous sodium bicarbonate and then with water and dried. Distillation of the solution gave 1.93 g (28%) of 2,6-nonadienal, bp 43–44 °C (0.30 mm). ^{13}C NMR showed the product to be 80% of the *E,Z* isomer and 20% of the *E,E* isomer.

From *N*-(1,3-Pentadienyl)piperidine. The reaction was carried out as in the preceding example, using the 1,3-pentadienylamine in place of the 1,4-diene and with 0.112 g (0.5 mmol) of palladium acetate and 0.304 g (1.0 mmol) tri-*o*-tolylphosphine as catalyst. The reaction time was 18 h and the temperature was 100 °C. Isolation as above gave 1.38 g (20%) of product which was an 80:20 mixture of *E,Z* and *E,E* isomers.

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Registry No. (*N*)-(2,5-Hexadienyl)piperidine, 80719-72-8; piperidine, 110-89-4; vinyl bromide, 593-60-2; 1,3-butadiene, 106-99-0; (*N*)-(1,4-pentadienyl)piperidine, 58369-82-7; 4-pentenal, 2100-17-6; (*N*)-(3-methyl-1,4-pentadienyl)piperidine, 66917-71-3; 3-methyl-4-pentenal, 1777-33-9; *N*-(2,4-pentadienyl)piperidine, 51180-42-8; 5-chloro-1,3-pentadiene, 40596-30-3; 1,4-pentadien-3-ol, 922-65-6; (*Z*)-1-bromo-1-butene, 31849-78-2; (*E,Z*)-2,6-nonadienal, 557-48-2; (*E,E*)-2,6-nonadienal, 17587-33-6; (*N*)-(1,3-pentadienyl)piperidine, 80698-39-1; bromobenzene, 108-86-1; iodobenzene, 591-50-4; 1,4-pentadiene, 591-93-5; (*E*)-1,4-hexadiene, 7319-00-8; 2-methyl-1,4-pentadiene, 763-30-4; 1,4-pentadienylbenzene, 33558-12-2; 2,4-pentadienylbenzene, 1007-52-9; (4-methyl-1,4-pentadienyl)benzene, 58584-25-1; (4-methyl-2,4-pentadienyl)benzene, 80698-40-4; (*N*)-(6-phenyl-2,4-hexadienyl)piperidine, 80698-41-5; (*Z*)-1-bromo-1-propene, 590-13-6; 2-bromo-1-propene, 557-93-7; (*Z*)-1,4-hexadiene, 7318-67-4; 1,4-cyclohexadiene, 628-41-1; 1-bromo-2-methyl-1-

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propene, 3017-69-4; 2-bromo-3-methyl-2-butene, 3017-70-7; morpholine, 110-91-8; 4-methyl-7-piperidino-1,5-heptadiene, 80698-42-6; bis(acetato-*O*)bis[tris(2-methylphenyl)phosphine]palladium, 69073-98-9; (*N*)-(5-phenyl-2-pentenyl)piperidine picrate, 80698-44-8; *trans*-5-(1-methylethenyl)-3-piperidinocyclohex-1-ene, 80698-45-9; $[CH_2{=}CHCH{=}CHCH_2\text{-}P^*\text{-}CH_2CH_3]^+$ Br^-, 80698-46-0; $CH_2{=}CHCH{=}CH\text{-}P^*$, 19352-92-2; $PhCH_2CH_2CH{=}CHCH_2\text{-}P^*$, 80698-43-7; $PhCH_2CH_2CH(CH{=}CH_2)\text{-}P^*$, 80698-47-1; (E)-$PhCH(CH_3)CH{=}CHCH_2\text{-}P^*$, 80698-48-2; $PhCH_2CH_2CH{=}CHCH(CH_3)\text{-}P^*$, 80698-49-3; $PhCH_2CH_2CH(CH{=}CHCH_3)\text{-}P^*$, 80698-50-6; $PhCH(CH_3)CH{=}CHCH(CH_3)\text{-}P^*$, 80698-51-7; $PhCH_2CH_2CH{=}C(CH_3)CH_2\text{-}P^*$, 80698-52-8; $PhCH(CH_3)CH{=}C(CH_3)CH_2\text{-}P^*$, 80698-53-9; $H_2C{=}CHCH_2CH_2CH{=}CHCH_2\text{-}P^*$, 80698-54-0; $H_2C{=}CHCH(\text{-}P^*)CH_2CH_2CH{=}CH_2$, 80698-55-1; $H_3CCH{=}CHCH_2CH_2CH{=}CHCH(CH_3)\text{-}P^*$, 80698-56-2; $H_3CCH{=}CHCH_2CH_2CH(\text{-}P^*)CH{=}CHCH_3$, 80698-57-3; $P^*\text{-}CH_2C(CH_3){=}CHCH_2CH_2C(CH_3){=}CH_2$, 80698-58-4; $H_2C{=}CHCH_2CH_2CH{=}CHCH_2\text{-}M$, 80698-59-5; $H_2C{=}CHCH_2CH_2CH(\text{-}M)CH{=}CH_2$, 80698-60-8; (*X*,*Z*)-$P^*\text{-}CH_2CH{=}CHCH_2CH_2CH{=}CHCH_3$, 80698-61-9; $H_2C{=}CHCH_2CH_2CH{=}CHCH(CH_3)\text{-}P^*$, 80698-62-0; $H_2C{=}CHCH_2CH_2CH(\text{-}P^*)CH{=}CHCH_3$, 80698-63-1; (*E*,*Z*)-$M\text{-}CH_2CH{=}CHCH_2CH_2CH{=}CHCH_3$, 80698-64-2; $H_2C{=}CHCH_2CH_2CH{=}CHCH(CH_3)\text{-}M$, 80698-65-3; $H_2C{=}CHCH_2CH_2CH(\text{-}M)CH{=}CHCH_3$, 80698-66-4; $P^*\text{-}CH_2CH{=}CHCH_2CH_2C(CH_3){=}CH_2$, 80698-67-5; $H_2C{=}CHCH(\text{-}P^*)CH_2CH_2C(CH_3){=}CH_2$, 80698-68-6; $P^*\text{-}CH_2C(CH_3){=}CHCH_2CH_2CH{=}CH_2$, 80698-69-7; $H_2C{=}C(CH_3)CH(\text{-}P^*)CH_2CH_2CH{=}CH_2$, 80698-70-0; $P^*\text{-}CH_2CH{=}C(CH_3)CH_2C(CH_3){=}CH_2$, 80698-71-1; (*E*)-$M\text{-}CH_2CH{=}CHCH_2CH_2C(CH_3){=}CH_2$, 80698-72-2; $H_2C{=}CHCH(\text{-}M)CH_2CH_2C(CH_3){=}CH_2$, 80698-73-3; $M\text{-}CH_2C(CH_3){=}CHCH_2CH_2CH{=}CH_2$, 80698-74-4; $H_2C{=}C(CH_3)CH(\text{-}M)CH_2CH_2CH{=}CH_2$, 80698-75-5; $M\text{-}CH_2CH{=}C(CH_3)CH_2C(CH_3){=}CH_2$, 80698-76-6; (*E*)-$M\text{-}CH_2CH{=}CHCH(CH_3)CH_2CH{=}CH_2$, 80698-77-7; $P^*\text{-}CH(CH_3)CH{=}CHCH_2CH_2C(CH_3){=}CH_2$, 80698-78-8; $H_3CCH{=}CHCH(\text{-}P^*)CH_2CH_2C(CH_3){=}CH_2$, 80698-79-9; $H_3CCH{=}CHCH_2CH_2CH{=}C(CH_3)CH_2\text{-}P^*$, 80698-80-2; $H_3CCH{=}CHCH_2CH_2CH(\text{-}P^*)C(CH_3){=}CH_2$, 80698-81-3; $P^*\text{-}C(CH_3)_2CH{=}CHCH_2CH_2CH{=}CH_2$, 80698-82-4; $(H_3C)_2C{=}CHCH(\text{-}P^*)CH_2CH_2CH{=}CH_2$, 80698-83-5; $(H_3C)_2C{=}CHCH_2CH_2CH{=}CHCH_2\text{-}P^*$, 80698-84-6; $(H_3C)_2C{=}CHCH(CH_3)CH{=}CHCH_2\text{-}P^*$, 80698-85-7; $P^*\text{-}C(CH_3)_2CH{=}CHCH_2CH_2CH{=}CHCH_3$, 80698-86-8; $(H_3C)_2C{=}CHCH(\text{-}P^*)CH_2CH_2CH{=}CHCH_3$, 80698-87-9; $(H_3C)_2C{=}CHCH_2CH_2CH{=}CHCH(CH_3)\text{-}P^*$, 80698-88-0; $(H_3C)_2C{=}CHCH(CH_3)CH{=}CHCH(CH_3)\text{-}P^*$, 80698-89-1; $P^*\text{-}C(CH_3)_2CH{=}CHCH_2CH_2C(CH_3){=}CH_2$, 80698-90-4; $(H_3C)_2C{=}CHCH(\text{-}P^*)CH_2CH_2C(CH_3){=}CH_2$, 80698-91-5; $(H_3C)_2C{=}CHCH_2CH_2CH{=}C(CH_3)CH_2\text{-}P^*$, 80698-92-6; $(H_3C)_2C{=}C(CH_3)CH(\text{-}P^*)CH_2CH_2CH{=}CH_2$, 80698-93-7; $(H_3C)_2C{=}C(CH_3)CH_2CH_2CH{=}CHCH_2\text{-}P^*$, 80698-94-8; $(H_3C)_2C{=}C(CH_3)CH_2CH_2CH(\text{-}P^*)CH{=}CH_2$, 80698-95-9; $(H_3C)_2C{=}C(CH_3)CH(CH_3)CH{=}CHCH_2\text{-}P^*$, 80698-96-0.

Supplementary Material Available: Table IV containing the physical properties, NMR spectral data, and molecular weights of the products prepared (11 pages). Ordering information is given on any current masthead page.

α-Diazophosphonic Acids as Potential Photoaffinity Labeling Reagents: Synthesis, Stability, and Photochemistry

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A series of α-diazophosphonic acid salts ($Et_2NSO_2CN_2PO_3^{2-}$, $i\text{-}Pr_2O_3PCN_2PO_3^{2-}$, and $RR'NCOCN_2PO_3^{2-}$) have been synthesized by diazo transfer to a diester precursor followed by ester cleavage with trimethylsilyl bromide. These compounds show disparate stabilities: the sulfamoyl- and phosphono-substituted derivatives decompose slowly even at pH 6.0 (21 °C, 0.2 M phosphate buffer; $t_{1/2} \approx 5$ h), whereas the *N*,*N*-dimethylcarbamoyl-substituted analogue decomposes rapidly even at pH 9.0 ($t_{1/2} \approx 40$ min). For all three derivatives the decomposition reaction involves initial loss of the PO_3^{2-} group to give the neutral diazo compound, $ZCHN_2$. The photochemical behavior of the α-diazophosphonic diester precursors $ZCN_2PO_3Me_2$ and the dianions $ZCN_2PO_3^{2-}$ (Z = Et_2NSO_2 and $i\text{-}Pr_2O_3P$) was also investigated by using light of $\lambda > 300$ nm. In alcohol or water as solvent, the neutral esters undergo the expected hydroxyl insertion and photoreduction reactions. In contrast, on photolysis in methanol, the anions undergo neither of these reactions; the major products appear to be those of 1,2-migration of one of the phosphate oxygens, leading to the α-hydroxy monoesters $ZCHOHPO_3Me^-$. This represents the first report of a photochemical study of a diazo compound with an anionic substituent. Although it is also the first example of formal Wolff rearrangement of an oxygen substituent from phosphorus to an adjacent carbene, we suggest that the migration proceeds via an oxaphosphirane intermediate instead of the classical Wolff-type mechanism. Unfortunately, the intervention of this transformation means that α-diazophosphonate dianions are unlikely to be useful as photoaffinity labeling reagents.

Since its invention by Westheimer some 20 years ago,[1] the technique of photoaffinity labeling has become an important one for probing macromolecular binding sites and biological targets.[2] The photolabile moieties employed for this purpose have for the most part been α-diazo esters or aryl azides, although diazirine derivatives are finding increasing use.[3] In recent years, a number of steps have been taken to "fine tune" the diazo functionality, modifying the substituents to optimize acid stability, minimize self-destructive Wolff rearrangement of the carbene intermediate, and obtain adequate light absorbance outside the envelope of a biological target.[4] Five years ago, Goldstein, McKenna, and Westheimer[5] and then we[6] reported the synthesis and characterization of several α-diazophosphonic acids as potential photolabile mimics of phosphate derivatives. We report here the full details of

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