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Some Aspects of Palladium-Catalyzed Reactions of Aryl and Vinylic Halides with Conjugated Dienes in the Presence of Mild Nucleophiles

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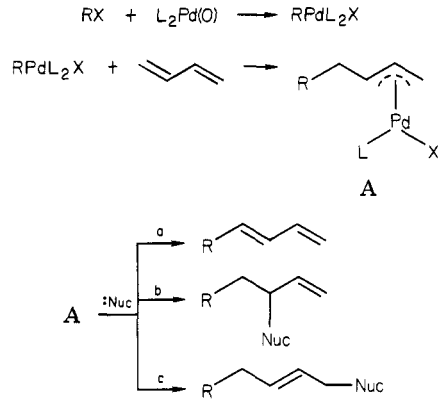
Certain aspects of reactions involving the catalytic formation of π-allylic palladium complexes via addition reactions to conjugated dienes and the subsequent reaction of these complexes with mild nucleophiles were investigated.

Introduction

π-Allylic palladium complexes are known to undergo reactions with mild nucleophiles such as amines[1] and stabilized carbanions[2] to yield allylated products.[3] Reactions involving the formation and reactions of such complexes under catalytic conditions have generally employed allylic esters, ethers, or alcohols as starting materials in reactions with phosphine–palladium catalyst systems.[3-6]

An alternate route to π-allylic palladium intermediates could involve reaction of an initially formed σ-palladium complex with a conjugated diene (Scheme I). The σ complex could be formed by oxidative addition of an aryl or vinylic iodide or bromide (the same restrictions as those found for the Heck vinylic hydrogen substitution reaction[7] should apply here) to a Pd(0) species. The π-allylic complex could then undergo elimination of hydride to form substituted diene or reaction with the nucleophile to form allylated products. Indeed, Heck has reported such reactions employing secondary amines[8] that in reactions with aryl halides and conjugated dienes yield primarily substituted diene and allylic amine resulting from attack by the amine nucleophile on that terminus of the allyl moiety, which is further from the aryl group.[8a,d] For example, the reaction of bromobenzene, isoprene, and piperidine using a $Pd(OAc)_2{\cdot}2(o\text{-}CH_3C_6H_4)_3P$ catalyst precursor was reported to produce (*E*)-1-phenyl-3-methyl-1,3-butadiene and *N*-(4-phenyl-2-methyl-2-buten-1-yl)piperidine in yields of 35% and 57%, respectively[8a] (Scheme I, paths a and c). We had independently discovered this method of generation and reaction of π-allylic intermediates[9] and present some of our results that we feel complement those already reported. In particular we have found (1) that primary amines will also participate in these reactions and that they show enhanced tendencies to attack the internal π-allylic terminus (Scheme I, path b), (2) that these reactions may be used to form heterocyclic compounds, and (3) that dimethyl sodiomalonate may be used as the nucleophilic species.

Scheme I



Results and Discussion

Table I shows the results of reactions of iodobenzene and isoprene in the presence of various amines with phosphine–$Pd(OAc)_2$ catalyst precursors. Our results with secondary amines parallel those reported by Heck, with products corresponding to paths a and c in Scheme I being formed. That path c is favored over path b is not surprising since attack of the amine at the secondary terminus of the π-allylic moiety should be sterically less favorable. The amine products are believed to possess the *E* configuration about the double bond on the basis of the assumption that $PhPdL_2I$ should react with diene in the more stable and predominant s-trans conformation and on the observation that reaction of iodobenzene, butadiene, and piperidine (115–120 °C, 104 h) yields *trans*-*N*-(4-phenyl-2-buten-1-yl)piperidine (53%) as evidenced by the presence of absorption bands at 965 and 1295 cm^{-1} in the out-of-plane bending region of the infrared spectrum of this product.

Reactions using the primary amines are extremely sluggish at 100 °C but proceed at reasonable rates at 125–130 °C. Reactions using *n*-butyl- and ethylamine show enhanced tendencies of amine to attack the secondary carbon of the π-allylic system (Scheme I, path b) due to the lessened steric requirements of these amines. When the bulkier *tert*-butylamine is used, only product resulting from attack at the primary terminus is obtained.

The reactions involving piperidine and *n*-butylamine were also investigated by using $(Ph_2PCH_2)_2$ and (*o*-

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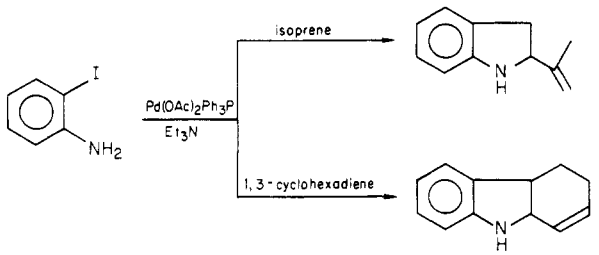
Table I. Reactions of Iodobenzene, Isoprene, and Amines[a]

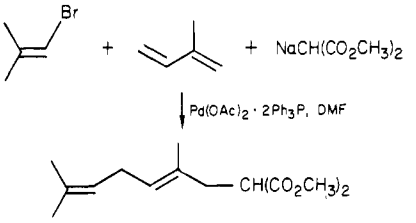
amine	phosphine	reaction temp, °C	reaction time	products, % yield (GLC)
diethylamine	Ph_3P	115-120	48 h	(*E*)-1-phenyl-3-methyl-1,3-butadiene, (I), 17; *N*-(4-phenyl-2-methyl-2-buten-1-yl)-*N*,*N*-diethylamine, 35
pyrrolidine	Ph_3P	115-120	63 h	I, 10; *N*-(4-phenyl-2-methyl-2-buten-1-yl)pyrrolidine, 56
piperidine	Ph_3P	115-120	40 h	I, 11; *N*-(4-phenyl-2-methyl-2-buten-1-yl)piperidine (II), 51
piperidine	Ph_3P	125-130	28 h	I, (15); II, (66)
piperidine	Ph_3P	100-105	168 h	I, (18); II, (68)
piperidine	$(o\text{-}CH_3C_6H_4)_3P$	125-130	14 h	I, (35); II, (36)
piperidine	$(Ph_2PCH_2)_2$[b]	125-130	30 h	I, (14); II, (64)
n-butylamine	Ph_3P	125-130	55 h	I, (16); *N*-(4-phenyl-2-methyl-1-buten-3-yl)-*N*-*n*-butylamine (III), (12); *N*-(4-phenyl-2-methyl-2-buten-1-yl)-*N*-*n*-butylamine (IV), (37)
n-butylamine	Ph_3P	100-105	90 days	I, (13); III, (8); IV, (23)
n-butylamine	$(o\text{-}CH_3C_6H_4)_3P$	125-130	130 h	I, (23); III, (2); IV, (20)
n-butylamine	$(Ph_2PCH_2)_2$[b]	125-130	65 h	I, (13); III, (12); IV, (39)
ethylamine	Ph_3P	125-130	60 h	I, (24); *N*-(4-phenyl-2-methyl-1-buten-3-yl)-*N*-ethylamine (V), (14); *N*-(4-phenyl-2-methyl-2-buten-1-yl)-*N*-ethylamine (VI), (40)
ethylamine	Ph_3P	100-105	63 days	I, (10); V, (12); VI, (32)
tert-butylamine	Ph_3P	125-130	62 h	I, 15 (20); *N*-(4-phenyl-2-methyl-2-buten-1-yl)-*N*-*tert*-butylamine, 28 (40)
aniline	Ph_3P	125-130	96 h	I, 33

[a] Multiples of the following quantities were used: 10 mmol of PhI 15 mmol of isoprene, 10 mL of amine, 0.1 mmol of $Pd(OAc)_2$, 0.2 mmol of phosphine. [b] 1.0 mol % (based on PhI) was used.

Scheme II



Scheme III



$CH_3C_6H_4)_3P$ in place of Ph_3P. Whereas the reactions using $(Ph_2PCH_2)_2$ parallel those with Ph_3P, those using $(o\text{-}CH_3C_6H_4)_3P$ showed enhanced tendencies toward hydride elimination (Scheme I, path a). Also, use of $(o\text{-}CH_3C_6H_4)_3P$ in the catalyst system leads to different distributions of amine products in reactions using *n*-butylamine. Whereas in reactions using Ph_3P or $(Ph_2PCH_2)_2$, *N*-(4-phenyl-2-methyl-2-buten-1-yl)-*N*-*n*-butylamine and *N*-(4-phenyl-2-methyl-1-buten-3-yl)-*N*-*n*-butylamine are produced in ratios of ~3:1, respectively, when the $(o\text{-}CH_3C_6H_4)_3P$ catalyst system is used, this ratio increases to ~9:1. Since attack of nucleophile has been shown to occur on the face of the allylic moiety opposite the palladium,[10] one possible explanation for these results is that the bulkier $(o\text{-}CH_3C_6H_4)_3P$ ligand forces the complex into a conformation in which the phenyl substituent is located on that side of the allyl system opposite the palladium. This would sterically hinder attack by the amine at the secondary terminus of the allyl system, which is closer to the phenyl group than the primary terminus.

The potential for using these reactions for the synthesis of certain heterocyclic compounds is exemplified by the reactions (Scheme II) of *o*-iodoaniline with isoprene to yield 2-isopropenyl-2,3-dihydroindole (72%) and with 1,3-cyclohexadiene to yield 1a,3,4,4a-tetrahydrocarbazole (70%). The fact that these syntheses are possible is presumed to be due to the proximity of the amino substituent to the π-allylic moiety in the intermediate complex since the reaction of iodobenzene, isoprene, and aniline yields only (*E*)-1-phenyl-3-methyl-1,3-butadiene (33%) and no amine products. Reactions of *o*-iodobenzylamine with isoprene and 1,3-cyclohexadiene under similar conditions failed to yield heterocyclic products, thus indicating that these reactions may be limited to the synthesis of five-atom heterocycles.

We had also wished to determine if stabilized carbanions could be used as the nucleophile in these reactions. Evidence that this is possible is provided by the reaction (Scheme III) of 1-bromo-2-methylpropene, isoprene, and dimethyl sodiomalonate to yield dimethyl (2,6-dimethylhepta-2,5-dien-1-yl)malonate (22%).

Experimental Section

All chemicals were used as obtained from commercial sources unless otherwise noted.

General Procedure for Reactions of Iodobenzene, Isoprene, and Amines. Iodobenzene (20 mmol), isoprene (30 mmol), and amine (20 mL) were placed in a thick-walled Pyrex reaction bottle containing 0.2 mmol of palladium acetate and 0.4 mmol of triphenylphosphine. The bottle was flushed briefly with nitrogen and then closed with a neoprene gasket and crown cap. The reaction mixture was heated with stirring until GLC analysis indicated that all the iodobenzene had reacted. The reaction mixture was poured into 20% aqueous NaOH and extracted with pentane. The pentane extracts were then extracted with cold 20% HCl. Workup of this pentane solution by drying over $MgSO_4$, filtering, and distilling produced (*E*)-1-phenyl-3-methyl-1,3-butadiene.[8a]

The acidic aqueous solution was made basic with NaOH and extracted with pentane. The pentane solution was dried over $MgSO_4$ and filtered and the pentane removed under reduced pressure. Products were isolated by distillation of the residue. In cases where yield was determined by GLC, the residue was combined with a known quantity of standard (naphthalene or biphenyl) and dissolved in ether. Sensitivity coefficients were

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determined by using known quantities of isolated product and standard. Samples for elemental analyses were obtained by preparative GLC or from center fractions taken during distillation.

***N*-(4-Phenyl-2-methyl-2-buten-1-yl)-*N*,*N*-diethylamine**: bp 91–93 °C (0.75 mmHg); NMR ($CDCl_3$) δ 0.95 (t, 6 H), 1.71 (s, 3 H), 2.41 (q, 4 H), 2.87 (s, 2 H), 3.30 (d, 2 H), 5.45 (t, 1 H), 7.07 (s, 5 H). Anal. Calcd: C, 82.88; H, 10.67; N, 6.45. Found: C, 82.88; H, 10.46; N, 6.08.

***N*-(4-Phenyl-2-methyl-2-buten-1-yl)pyrrolidine**: bp 93–99 °C (0.35 mmHg); NMR ($CDCl_3$) δ 1.77 (br, 7 H), 2.42 (br, 4 H), 2.97 (s, 2 H), 3.35 (d, 2 H), 5.50 (t, 1 H), 7.10 (s, 5 H). Anal. Calcd: C, 83.67; H, 9.83; N, 6.50. Found: C, 83.51; H, 9.91; N, 6.65.

***N*-(4-Phenyl-2-methyl-2-buten-1-yl)piperidine**: bp 115–121 °C (0.80 mmHg); NMR ($CDCl_3$) δ 1.43 (br, 6 H), 1.71 (s, 3 H), 2.25 (br, 4 H), 2.76 (s, 2 H), 3.30 (d, 2 H), 5.50 (t, 1 H), 7.07 (s, 5 H). Anal. Calcd: C, 83.78; H, 10.11; N, 6.11. Found: C, 83.73; H, 10.01; N, 6.20.

***N*-(4-Phenyl-2-methyl-1-buten-3-yl)-*N*-*n*-butylamine (III)**: ^1H NMR ($CDCl_3$) δ 0.62–1.55 (m, 8 H), 1.68 (s, 3 H), 2.37 (br, 2 H), 2.77 (d, 2 H), 3.30 (dd, 1 H), 4.67 (s, 2 H), 7.18 (s, 5 H). Anal. Calcd: C, 82.89; H, 10.66; N, 6.44. Found: C, 82.79; H, 10.71; N, 6.43.

***N*-(4-Phenyl-2-methyl-2-buten-1-yl)-*n*-butylamine (IV)**: ^1H NMR ($CDCl_3$) δ 0.95–1.39 (m, 8 H), 1.75 (s, 3 H), 2.74 (br, 2 H), 3.02 (s, 2 H), 3.23 (d, 2 H), 5.52 (t, 1 H), 7.22 (s, 5 H); bp (III and IV, mixture) 80–93 °C (0.25 mmHg). Anal. Calcd: C, 82.89; H, 10.66; N, 6.44. Found: C, 82.84; H, 10.79; N, 6.66.

***N*-(4-Phenyl-2-methyl-1-buten-3-yl)-*N*-ethylamine (V)**: ^1H NMR ($CDCl_3$) δ 0.99 (t, 3 H), 1.20 (s, 1 H), 1.72 (s, 3 H), 2.42 (q, 2 H), 2.68 (d, 2 H), 3.32 (t, 1 H), 4.80 (s, 2 H), 7.22 (s, 5 H). Anal. Calcd: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.19, H, 10.24; N, 7.41.

***N*-(4-Phenyl-2-methyl-2-buten-1-yl)-*N*-ethylamine (VI)**: ^1H NMR (neat) δ 0.66 (s, 1 H), 0.99 (t, 3 H), 1.69 (s, 3 H), 2.50 (q, 2 H), 3.07 (s, 2 H), 3.30 (d, 2 H), 5.48 (t, 1 H), 7.07 (s, 5 H); bp (V and VI, mixture) 130–145 °C (30 mmHg). Anal. Calcd: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.42; H, 10.11; N, 7.48.

***N*-(4-Phenyl-2-methyl-2-buten-1-yl)-*N*-*tert*-butylamine**: bp 110–115 °C (0.25 mmHg); ^1H NMR ($CDCl_3$) δ 0.92 (s, 1 H), 1.05 (s, 9 H), 1.77 (s, 3 H), 3.33 (m, 4 H), 5.50 (t, 1 H), 7.13 (s, 5 H). Anal. Calcd: C, 82.89; H, 10.67; N, 6.44. Found: C, 82.70; H, 10.49; N, 6.26.

***N*-(4-Phenyl-2-buten-1-yl)piperidine** was obtained by a procedure similar to that above, substituting 1,3-butadiene for isoprene. All reactants but 1,3-butadiene were placed in the bottle. The bottle was capped, cooled to −78 °C, and then evacuated. Butadiene was added, and the reaction mixture was heated at 115–120 °C for 50 h and then worked up as described above: yield 53%; bp 105–110 °C (0.50 mmHg); ^1H NMR ($CDCl_3$) δ 1.55 (br, 6 H), 2.34 (br, 4 H), 2.89 (d, 2 H), 3.31 (d, 2 H), 5.61 (m, 2 H), 7.12 (s, 5 H). Anal. Calcd: C, 83.67; H, 9.83; N, 6.50. Found: C, 83.68; H, 9.97; N, 6.40.

2-Isopropenyl-2,3-dihydroindole: A mixture of *o*-indoaniline (8.76 g, 40 mmol), isoprene (8.16 g, 120 mmol), $Pd(OAc)_2$ (0.090 g, 0.4 mmol), Ph_3P (0.2096 g, 0.8 mmol), and triethylamine (40 mL) was reacted at 125–130 °C in a capped reaction bottle with magnetic stirring until GLC analysis indicated that all of the *o*-iodoaniline had been consumed (39 h). The cooled reaction mixture was poured into 150 mL of cold 30% HCl and extracted with three 40-mL portions of pentane. The aqueous phase was made basic with NaOH, stirred for 1 h at room temperature, and then extracted with three 50-mL portions of pentane. The pentane extracts were combined, dried over $MgSO_4$, and filtered. Removal of pentane under reduced pressure followed by distillation of the residue yielded 2-isopropenyl-2,3-dihydroindole: 4.60 g (72%); bp 78–83 °C (0.8 mmHg); ^1H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 2.78 (d, 1 H), 2.98 (d, 1 H), 3.50 (s, 1 H), 4.40 (t, 1 H), 4.72 (s, 1 H), 4.92 (s, 1 H), 6.17–7.23 (m, 4 H). Anal. Calcd: C, 82.97; H, 8.23; N, 8.80; mol wt, 159. Found: C, 82.86; H, 8.38; N, 8.82, mol wt (mass spectrum), 159.

1a,3,4,4a-Tetrahydrocarbazole: A mixture of 2-iodoaniline (8.76 g, 40 mmol), 1,3-cyclohexadiene (9.62 g, 120 mmol), Et_3N (40 mL), $Pd(OAc)_2$ (0.0898 g, 0.40 mmol), and Ph_3P (0.2096 g, 0.80 mmol) was reacted at 120–125 °C in a capped reaction bottle with magnetic stirring until GLC analysis indicated that all of the 2-iodoaniline had reacted (24 h). Excess Et_3N was removed under reduced pressure and the residue combined with 20% aqueous NaOH and extracted with pentane. The pentane extracts were then extracted with cold 20% HCl. The acidic aqueous solution was washed once with pentane, made basic with NaOH, and extracted with pentane. This pentane solution was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, leaving an oil that solidified upon standing. Recrystallization from hexane yielded 4.80 g (70%) of 1a,3,4,4a-tetrahydrocarbazole: mp 63–64 °C; ^1H NMR ($CDCl_3$) δ 1.93 (m, 4 H), 3.40 (m, 2 H), 4.13 (d, 1 H), 5.73 (m, 2 H), 6.90 (m, 4 H). Anal. Calcd: C, 84.17; H, 7.65; N, 8.18; mol wt, 171. Found: C, 83.92; H, 7.88; N, 8.17, mol wt (mass spectrum), 1.71. Reaction of this product with sodium methoxide in methanol produced 1,2,3,4-tetrahydrocarbazole as evidenced by comparison of GLC retention times (10% SE-30, 10% Carbowax, 10% DC-550) with those of commercially obtained material.

Dimethyl (2,6-dimethylhepta-2,5-dien-1-yl)malonate: A mixture of 1-bromo-2-methylpropene[7b] (4.11 g, 30 mmol), isoprene (4.09 g, 60 mmol), dimethyl malonate (16.4 g, 124 mmol), $Pd(OAc)_2$ (0.067 g, 0.3 mmol), and Ph_3P (0.157 g, 0.6 mmol) was added to a thick-walled Pyrex reaction bottle and cooled to 0 °C. A solution of sodium methoxide (6.48 g, 120 mmol) in 50 mL of dimethylformamide was cooled to 0 °C and added to the reaction bottle. The bottle was capped and heated with magnetic stirring at 135–140 °C until GLC analysis indicated that all the halide had reacted (6 h). The reaction mixture was poured into 150 mL of water and extracted with four 100-mL portions of pentane. The pentane fractions were combined, washed with 100 mL of water, dried over $MgSO_4$, and filtered. Pentane was removed under reduced pressure and the residue distilled. Product was obtained at 130–135 °C (0.2 mmHg); yield 1.68 g (22%). ^1H NMR ($CDCl_3$) δ 1.65 (br, 9 H), 2.45–2.88 (m, 4 H), 3.60 (t, 1 H), 3.72 (s, 6 H), 5.13 (br, q, 2 H). Anal. Calcd: C, 66.12; H, 8.72. Found: C, 66.01; H, 8.82. The spectrum was clarified by using $Eu(fod)_3$.

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Registry No. I, 68036-69-1; II, 74312-51-9; III, 84538-63-6; IV, 84538-64-7; V, 84538-65-8; VI, 84538-66-9; Ph_3P, 603-35-0; $(o\text{-}CH_3C_6H_4)_3P$, 6163-58-2; $(Ph_2PCH_2)_2$, 1663-45-2; $Pd(OAc)_2$, 3375-31-3; *N*-(4-phenyl-2-methyl-2-buten-1-yl)-*N*,*N*-diethylamine, 84538-67-0; *N*-(4-phenyl-2-methyl-2-buten-1-yl)pyrrolidine, 84538-68-1; *N*-(4-phenyl-2-methyl-2-buten-1-yl)-*N*-*tert*-butylamine, 84538-69-2; *N*-(4-phenyl-2-buten-1-yl)piperidine, 84538-70-5; 2-isopropenyl-2,3-dihydroindole, 84538-71-6; 1a,3,4,4a-tetrahydrocarbazole, 84558-27-0; dimethyl (2,6-dimethylhepta-2,5-dien-1-yl)malonate, 84538-72-7; diethylamine, 109-89-7; pyrrolidine, 123-75-1; piperidine, 110-89-4; *n*-butylamine, 109-73-9; ethylamine, 75-04-7; *tert*-butylamine, 75-64-9; aniline, 62-53-3; iodobenzene, 591-50-4; isoprene, 78-79-5.