Catalytic arylation of carbon-carbon double bond followed by N- or O-cyclization

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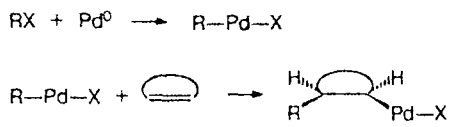
Under the catalytic action of palladium, *o*-hydroxy- or *o*-amino-substituted aryl iodides oxidatively add to palladium(0), insert strained or rigid olefins, and close the ring between the aliphatic carbon and the *ortho*-functional group. This reaction occurs under mild conditions in the absence of phosphine ligands in a DMF solution and affords fused dihydrofurans or -pyrroles.

Key words: palladium complexes, catalysis; formation of C—C, C—O, and C—N bonds, cyclization.

It is well known that alkylation or arylation of rigid olefins with organic halides RX (X = Br, I) and palladium(0) complexes leads to norbornylpalladium species containing *cis*-oriented alkyl (or aryl) and PdX groups.[1] For steric reasons, these complexes do not undergo reductive elimination of the hydrogen atom from the generally favored *anti*-position[2] (Scheme 1, the ligands are omitted for simplicity).

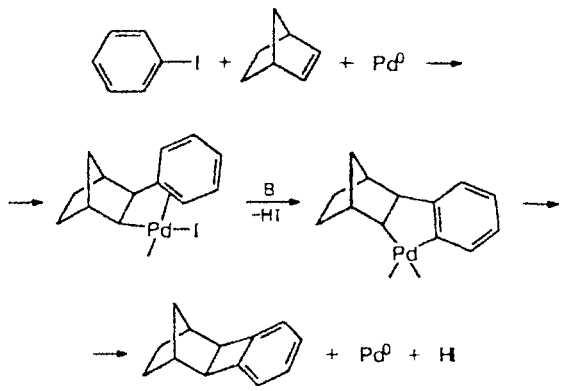
Scheme 1



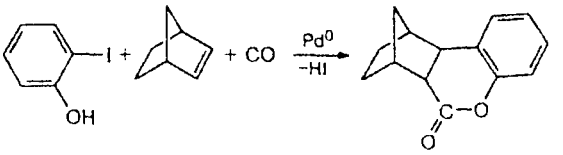
Some years ago we showed that the substituted norbornyl group attached to palladium can be trapped in several ways, for example, by hydride transfer.[3] Later, we studied the behavior of the arylnorbornylpalladium complexes obtained from aryl halides, norbornene, and palladium(0). These complexes gave palladacycles, which are converted into hexahydromethanobiphenylenes upon reductive elimination. A catalytic cycle, which is shown in Scheme 2 for iodobenzene and norbornene,[4] was also worked out.

We further observed that the palladium-bonded arylalkyl intermediates can be trapped by carbon monoxide and nucleophiles.[5] Using *o*-iodophenol we were able to trap also the Pd-bonded arylacyl intermediate, which resulted in the formation of a dihydrocoumarin derivative (reaction (1)).[6] An analogous behavior was observed with *o*-iodoaniline, although the yield was low.[7]

Scheme 2



B is a base



(1)

The present paper deals with the direct trapping of the arylalkyl Pd-intermediates using OH and NH_2 functional groups in the absence of carbon monoxide.

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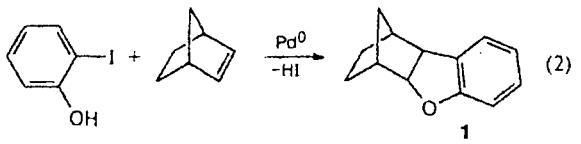
Results and Discussion

The palladium-catalyzed reaction of *o*-iodophenol with norbornene to form methanohexahydrodibenzofuran (**1**) (reaction (2)) proved to be not so simple as expected.

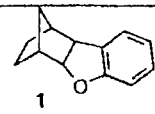
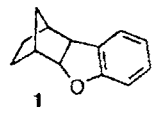
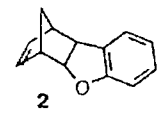
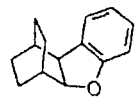
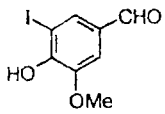
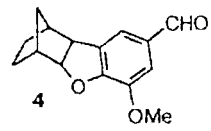
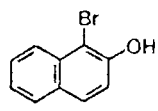
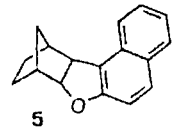
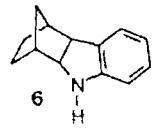


(2)

1

Triphenylphosphine as well as other strong ligands did not allow the reaction to proceed satisfactorily probably because they prevented the OH group from approaching the reaction center. Thus we resorted to working with palladium acetate in DMF in the presence of K_2CO_3 as a base and tetra-*n*-butylammonium bromide as a phase transfer catalyst[8] (palladium(0) is formed under these conditions) and obtained satisfactory results provided that the excess of norbornene and *o*-iodophenol with respect to palladium was not too high ((10—20) : 1). Under these conditions, the yield of compound **1** was 89% over a period of 4 h at 80 °C (Table 1, run *1*). The reaction occurred even at room temperature; however, the reaction time was much longer (72 h), and the target product **1** was formed in a lower yield (61%) at complete conversion. The reaction of 2-bromophenol with norbornene required a higher temperature (105 °C) and gave only 30% yield at 80% conversion (run *2*). This has to be attributed to the slower oxidative addition of the

Table 1. Palladium-catalyzed reactions of aryl halides, containing *ortho*-OH or *ortho*-NH_2 groups, with olefins (DMF, 24 h, complete conversion)

Run	Aryl halide	Olefin	*T*/°C	Product	Yield (%)[a]
1	2-IC_6H_4OH [b]	Norbornene	80	 **1**	89
2	2-BrC_6H_4OH	Norbornene	105	 **1**	30 [c]
3	2-IC_6H_4OH	Norbornadiene	80	 **2**	46
4	2-IC_6H_4OH	Bicyclooctene	80	 **3**	52
5		Norbornene	105	 **4**	74
6		Norbornene	105	 **5**	47 [d]
7	2-$IC_6H_4NH_2$	Norbornene	105	 **6**	53

[a] Isolated yield (based on the aryl halide).
[b] The reaction time was 4 h.
[c] For 80% conversion of 2-BrC_6H_4OH.
[d] For 60% conversion of 1-$BrC_{10}H_6OH$.

bromoarene to Pd^0, which allows secondary reactions leading to unidentified heavy products to prevail.

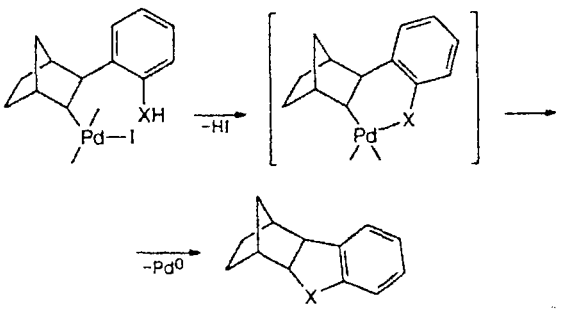
Norbornadiene reacted with *o*-iodophenol (run *3*) in a moderate yield (45%) probably because of the ready polymerization process that takes place with the resulting methanotetrahydrofuran.[9] Bicyclooctene reacted analogously to norbornene (run *4*), thus showing that the main requisite for the success of the reaction is not the "strained" character of the olefin but its rigidity which does not allow the elimination of β-hydrogen. Accordingly *cis*-cycloheptene, which is strained to a small extent, gave the product of the Heck reaction[10] (an isomeric mixture which was not further investigated).

Reaction (2) was extended to substituted *o*-iodophenols. Thus 5-iodovanillin reacts with norbornene without affecting the aldehyde function (run *5*). Furthermore, 1-bromo-2-hydroxynaphthalene reacts with norbornene to give the corresponding methanohexahydrobenzonaphthofuran (5) (run *6*). Substituted anilines can also be used in place of phenols. Thus *o*-iodoaniline readily reacts with norbornene to give methanohexahydrocarbazole (run *7*).

The reactions shown in Table 1 are accompanied by the formation of heavy by-products probably resulting from polymerization initiated by the arylpalladium complex.[11]

The mechanism we propose for the formation of the main products is depicted in Schemes 1—3 for the case of norbornene and *o*-iodophenol or *o*-iodoaniline (unreactive ligands are omitted). It is based on the following steps: (a) oxidative addition of the aryl halide to Pd^0 (see Scheme 1); (b) norbornene coordination and insertion into the Pd—C bond (see Scheme 2); (c) reductive elimination with final cyclization and elimination of Pd^0 (see Scheme 3). This step is likely to involve the oxapalladacycle[12] (shown in brackets), which, however, has not yet been detected.

Scheme 3



Thus, intramolecular etherification or amination at a Pd-bonded carbon atom with formation of fused dihydrofurans or -pyrroles can be readily achieved under mild conditions using Pd^0 as a catalyst and DMF as a solvent and a ligand.

Experimental

All reagents were commercially available and were used without further purification. DMF was distilled under reduced pressure and stored under nitrogen over 4 Å molecular sieves. Reactions were run under inert atmosphere (N_2) using conventional Schlenk-type techniques. Column chromatography was performed on silica gel (Merck silica 70—230 mesh) using a hexane—ethyl acetate mixture as the eluent. TLC analyses were carried out on precoated plates (Merck silica gel 60). GLC analyses were carried out with a Carlo Erba HRGC 5300 instrument equipped with a 30-m-long capillary column (SE-30 as the stationary phase). Mass spectra (EI) were obtained with a Finnigan Mat SSQ 710 spectrometer (70 eV). IR spectra were run on a Nicolet 5PC FT-IR instrument. ^1H NMR spectra were recorded on Bruker AC 300 (300.13 MHz) and AMX 400 (400.13 MHz) instruments, and ^{13}C NMR spectra were measured on a Bruker AC 300 spectrometer (75.48-MHz). All spectra were obtained for solutions in $CDCl_3$ using the solvent peak referred to $SiMe_4$ as the internal standard (δ ^1H: 7.28; δ ^{13}C: 77.0). Assignments of protons and carbons were based on COSY, NOESY, proton decoupling, and C—H correlation experiments;* Satisfactory elemental analyses were obtained for all compounds.

Palladium-catalyzed reaction of olefins with aryl halides (general procedure). Palladium acetate (15 mg, 0.067 mmol), K_2CO_3 (93 mg, 0.67 mmol), and Bu_4NBr (250 mg, 0.80 mmol) were introduced into a Schlenk-type flask and kept under nitrogen. A solution of the olefin (0.79 mmol) and aryl halide (0.68 mmol) in DMF (8 mL) was then added, and the resulting mixture was stirred at 80—105 °C for 4—24 h. After cooling, the mixture was diluted with CH_2Cl_2 (50 mL) and extracted twice with 2 *N* H_2SO_4 (40 mL). The organic layer was extracted with water (40 mL) and dried over Na_2SO_4. The solvent was removed on a rotary evaporator and the resulting crude was purified by column chromatography using hexane—ethyl acetate mixtures as eluents. A different extraction procedure was followed for compound **6**: the mixture was diluted with diethyl ether (50 mL) and washed with water (5×40 mL). All compounds were colorless viscous oils.

1,4-Methano-1,2,3,4,4a,9b-hexahydrodibenzofuran (1). Found (%): C, 83.95; H, 7.56. $C_{13}H_{14}O$. Calculated (%): C, 83.83; H, 7.58; O, 8.59. ^1H NMR, δ: 7.09 (d, 1 H, H(9), J = 7.3 Hz); 7.04 (dd, 1 H, H(7), J = 8.1 and 7.4 Hz); 6.77 (tt, 1 H, H(8), J = 7.4 and 0.8 Hz); 6.67 (br.d, 1 H, H(6), J = 8.0 Hz); 4.65 (br.d, 1 H, H(4a), J = 7.2 Hz); 3.24 (br.d, 1 H, H(9b), J = 7.2 Hz); 2.50 (m, 1 H, H(4)); 2.27 (m, 1 H, H(1)); 1.61—1.48 (m, 2 H, $H(2)_{exo}$, $H(3)_{exo}$); 1.42 (d.quint, 1 H, $H(10)_{syn}$, J = 10.4 and 1.7 Hz); 1.36—1.28 (m, 1 H, $H(2)_{endo}$); 1.18—1.10 (m,** 2 H, $H(3)_{endo}$, $H(10)_{anti}$). ^{13}C NMR, δ: 161.3 (C(5a)); 129.6 (C(9a)); 128.0 (C(7)); 124.7 (C(9)); 120.0 (C(8)); 108.4 (C(6)); 89.2 (C(4a)); 51.6 (C(9b)); 42.6 (C(1)); 42.2 (C(4)); 32.1 (C(10)); 27.9 (C(2)); 23.5 (C(3)). MS, m/z (I_{rel} (%)): 186 $[M]^+$ (81), 157 (40), 145 (48), 131 (67), 118 (100), 107 (35), 91 (37).

1,4-Methano-1,4,4a,9b-tetrahydrodibenzofuran (2). Found (%): C, 84.88; H, 6.63. $C_{13}H_{12}O$. Calculated (%): C, 84.75; H, 6.57; O, 8.68. ^1H NMR, δ: 7.11 (d, 1 H, H(9), J = 7.3 Hz); 7.07 (t, 1 H, H(7), J = 8.0 Hz);*** 6.80 (td, 1 H, H(8),

* Mass and NMR facilities were provided by the Interdepartment Center of Measurements (Centro Interfacoltà di Misure) of the University of Parma.

** Centered at 1.15 ppm.

*** Partly overlaps with the signal of H(9).

J = 7.3 and 1.0 Hz); 6.69 (br.d, 1 H, H(6), J = 8.0 Hz); 6.34 (dd, 1 H, H(2), J = 5.8 and 2.9 Hz); 6.02 (dd, 1 H, H(3), J = 5.8 and 3.1 Hz); 4.84 (dt, 1 H, H(4a), J = 7.1 and 1.1 Hz); 3.45 (br.d, 1 H, H(9b), J = 7.1 Hz); 3.15 (m, 1 H, H(4)); 2.89 (m, 1 H, H(1)); 1.58, 1.53 (2 H, AB-system, $H(10)_{syn}$, $H(10)_{anti}$ in relation to the benzofuran ring). ^{13}C NMR, δ: 163.3 (C(5a)); 141.1 (C(2)); 134.1 (C(3)); 128.3 (C(7), C(9a)); 124.2 (C(9)); 120.1 (C(8)); 109.2 (C(6)); 88.6 (C(4a)); 49.4 (C(9b)); 48.6 (C(4)); 47.5 (C(1)); 42.4 (C(10)). MS, m/z (I_{rel} (%)): 184 $[M]^+$ (3), 118 (100), 66 (12).

8-Formyl-6-methoxy-1,4-methano-1,2,3,4,4a,9b-hexahydrodibenzofuran (3). Found (%): C, 83.90; H, 8.01. $C_{14}H_{16}O$. Calculated (%): C, 83.96; H, 8.05; O, 7.99. ^1H NMR, δ: 9.73 (s, 1 H, CHO); 7.26 (dd, 1 H, H(9), J = 1.5 and 0.9 Hz); 7.22 (d, 1 H, H(7), J = 1.6 Hz); 4.84 (br.dt, 1 H, H(4a), J = 7.2 and 1.2 Hz); 3.87 (s, 3 H, Me); 3.30 (br.d, 1 H, H(9b), J = 7.2 Hz); 2.60 (m, 1 H, H(4)); 2.31 (m, 1 H, H(1)); 1.62—1.49 (m, 2 H, $H(2)_{exo}$, $H(3)_{exo}$); 1.39 (d.quint, 1 H, $H(10)_{syn}$, J = 10.7 and 1.9 Hz); 1.36—1.26 (m, 1 H, $H(2)_{endo}$); 1.18—1.11 (m,* 2 H, $H(3)_{endo}$, $H(10)_{anti}$). ^{13}C NMR, δ: 190.5 (CHO); 155.5 (C(5a)); 144.2 (C(6)); 130.9 (C(9a)); 121.5 (C(9)); 111.0 (C(7)); 91.8 (C(4a)); 55.9 (OMe); 51.3 (C(9b)); 42.4 (C(1)); 42.0 (C(4)); 32.0 (C(10)); 27.7 (C(2)); 23.3 (C(3)). MS, m/z (I_{rel} (%)): 244 $[M]^+$ (100), 216 (68), 189 (33), 175 (29), 165 (33), 79 (36), 44 (45). IR, ν/cm^{-1}: 1680 (s).

1,4-Ethano-1,2,3,4,4a,9b-hexahydrodibenzofuran (4). Found (%): C, 73.89; H, 6.67. $C_{15}H_{16}O_3$. Calculated (%): C, 73.75; H, 6.60; O, 19.65. ^1H NMR, δ: 7.12 (t, 1 H, H(7), J = 7.3 Hz); 7.09 (d, 1 H, H(9), J = 7.4 Hz); 6.84 (td, 1 H, H(8), J = 7.4 and 1.0 Hz); 6.78 (d, 1 H, H(6), J = 7.9 Hz); 4.88 (ddd, 1 H, H(4a), J = 10.3, 4.1, and 1.3 Hz); 3.44 (dd, 1 H, H(9b), J = 10.3 and 3.3 Hz); 1.98 (m, 1 H, H(1)); 1.87 (sext, 1 H, H(4), J = 3.0 Hz); 1.80—1.66 (m, 3 H, $H(2)_{exo}$, $H(3)_{exo}$, $H(11)_{syn}$); 1.66—1.51 (m, 2 H, $H(2)_{endo}$, $H(3)_{endo}$); 1.39—1.20 (m, 3 H, $H(10)_{anti}$, $H(10)_{syn}$, $H(11)_{anti}$). ^{13}C NMR, δ: 160.5 (C(5a)); 129.7 (C(9a)); 128.0 (C(7)); 124.9 (C(9)); 120.0 (C(8)); 108.7 (C(6)); 84.3 (C(4a)); 44.8 (C(9b)); 28.5 (C(4)); 28.0 (C(1)); 24.8 (C(2)); 22.2 (C(3)); 21.0 (C(10)); 18.4 (C(11)). MS, m/z (I_{rel} (%)): 200 $[M]^+$ (100), 172 (26), 157 (31), 133 (64), 118 (40), 107 (39).

8,11-Methano-7a,8,9,10,11,11a-hexahydro[*b*]naphtho[1,2-*d*]furan (5). Found (%): C, 84.39; H, 8.22; N, 7.53. $C_{13}H_{15}N$. Calculated (%): C, 84.28; H, 8.16; N, 7.56. ^1H NMR, δ: 7.79 (d, 1 H, H(4), J = 8.2 Hz); 7.72 (d, 1 H, H(1), J = 8.2 Hz); 7.64 (d, 1 H, H(5), J = 8.7 Hz); 7.46 (t, 1 H, H(2)); 7.29 (t, 1 H, H(3)); 7.06 (d, 1 H, H(6), J = 8.7 Hz); 4.88 (d, 1 H, H(7a), J = 7.4 Hz); 3.65 (d, 1 H, H(11a), J = 7.4 Hz); 2.65 (m, 2 H, H(8), H(11)); 1.70—1.59 (m, 2 H, H(9), $H(10)_{exo}$); 1.54 (d.quint, 1 H, $H(12)_{syn}$, J = 10.5 and 1.7 Hz); 1.51—1.40 (m, 1 H, $H(10)_{endo}$); 1.30—1.22 (m, 1 H, $H(9)_{endo}$); 1.18 (d.quint, 1 H, $H(12)_{anti}$, J = 10.5 and 1.7 Hz). MS, m/z (I_{rel} (%)): 236 $[M]^+$ (78), 207 (35), 168 (100).

1,4-Methano-1,2,3,4,4a,9b-hexahydrocarbazole (6). Found (%): C, 86.40; H, 6.83. $C_{17}H_{16}O$. Calculated (%): C, 86.40; H, 6.83; O, 6.77. ^1H NMR, δ: 7.02 (br.d, 1 H, H(5), J = 7.2 Hz); 6.96 (t, 1 H, H(7), J = 7.6 Hz); 6.64 (td, 1 H, H(6), J = 7.3 and 0.9 Hz); 6.50 (br.d, 1 H, H(8), J = 7.7 Hz); 3.79 (br.d, 1 H, H(9a), J = 8.1 Hz); 3.50 (br.s, 1 H, NH); 3.27 (br.d, 1 H, H(4a), J = 8.1 Hz); 2.29 (m, 1 H, H(4)); 2.19 (m, 1 H, H(1)); 1.62—1.47 (m, 3 H, $H(2)_{exo}$, $H(3)_{exo}$, $H(7)_{syn}$); 1.35 (m, 1 H, $H(3)_{endo}$); 1.25—1.18 (m, 1 H, $H(2)_{endo}$); 1.14 (d.quint, 1 H, $H(10)_{anti}$, J = 10.1 and 1.5 Hz). ^{13}C NMR, δ: 152.5 (C(8a)); 132.0 (C(4b)); 127.4 (C(7)); 124.6 (C(5)); 118.0 (C(6)); 108.3 (C(8)); 65.3 (C(9a)); 52.4 (C(4a)); 44.3 (C(1)); 43.2 (C(4)); 32.3 (C(10)); 28.6 (C(3)); 25.3 (C(2)). MS, m/z (I_{rel} (%)): 185 $[M]^+$ (50), 156 (34), 144 (100), 118 (61). IR (film), ν/cm^{-1}: 3216 (br).

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* Centered at 1.16 ppm.

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