Selective aryl coupling *via* palladacycles: a new route to *m*-alkylbiphenyls or *m*-terphenyls

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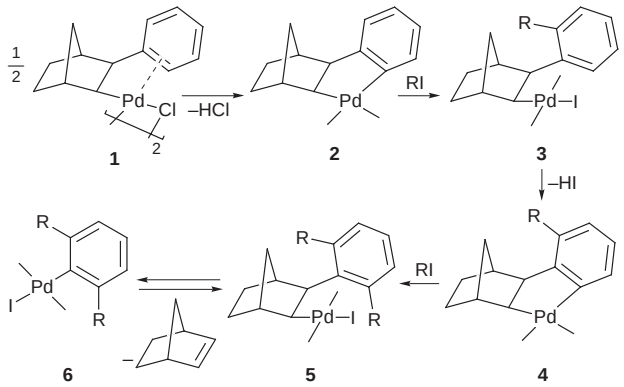
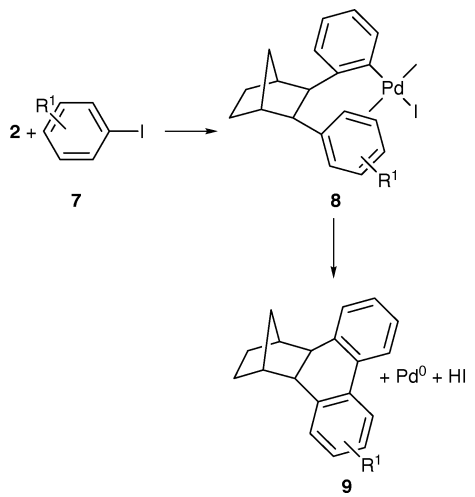
o-Alkyl- or *o*-aryl-substituted arylnorbornylpalladium chloride complexes react with aromatic iodides in dimethylformamide (DMF) *via* palladacycles to give after hydrogenolysis *m*-alkylbiphenyls or *m*-terphenyls.

Regioselectivity in aromatic substitution is a topic of fundamental interest in organic synthesis. Palladium chemistry has proved to be quite useful to this aim. In particular we recently succeeded in alkylating an aromatic ring of a palladacycle at the two *ortho* positions.[1] As shown in simplified Scheme 1 the reaction involves double alkylation with alkyl iodide RI of the *ortho* positions of the aromatic ring of complex **1** (*cis*,*exo*)[2] through metallacycles **2** and **4**,[3] followed by norbornene deinsertion with formation of an *o*,*o*′-dialkylated arylpalladium(II) species. The overall process thus implies selective formation of two sp^2–sp^3 carbon–carbon bonds.

When we tried to utilise the same procedure to obtain terphenyl complexes using aryl iodides in place of the alkyl ones



Scheme 1

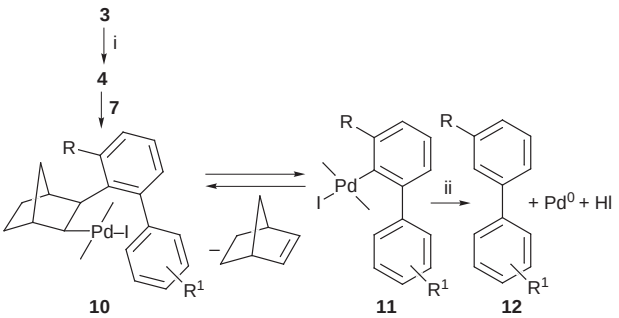


Scheme 2 Reagents and conditions: K_2CO_3, DMF, under N_2, room temperature, 6 h

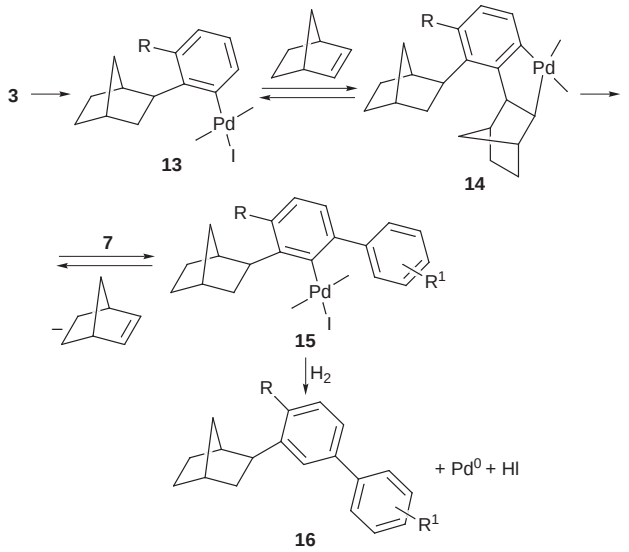
the system showed again a strong tendency to form an sp^2–sp^3 carbon–carbon bond, migration of the aryl group of the aromatic iodide this time occurring selectively onto the norbornyl site of the alkylaromatic palladacycle **2**. A clear example is offered by the reaction of **2** (formed *in situ* from **1**) with substituted aryl iodides **7**, which affords compound **9** through complex **8** and subsequent intramolecular aromatic substitution (R^1 = 4-CO_2Me, 68% yield) (Scheme 2). We have observed, however, that formation of an sp^2–sp^2 carbon–carbon bond leading to arylation at the aromatic site of metallacycle **2** can be achieved in the presence of an alkyl or aryl substituent R in the *ortho* position. Thus complexes **3** (R = alkyl or aryl) were prepared separately as dimers and caused to react *via* complexes **4** with aromatic iodides **7**[4] in DMF at room temperature in a one-pot reaction. The resulting intermediates **10** spontaneously liberate norbornene affording alkylbiphenyl- and terphenyl-palladium complexes **11** (R = alkyl or phenyl), from which biphenyl derivatives **12** (*m*-alkylbiphenyls or *m*-terphenyls) were obtained by hydrogenolysis according to Scheme 3. By contrast when *m*-alkyl or *p*-alkyl substituents were used in place of the *ortho* one in **3**, attack on the norbornyl site as in the unsubstituted compounds **8** invariably occurred, thus indicating that the effect of *ortho* substituents in directing arylation at the aryl site is essentially steric in origin.

While *o*-alkyl groups R in complexes **3** appear the most effective in promoting sp^2–sp^2 bond formation, aryl groups do not prevent the reaction at the norbornyl site from taking place to a limited extent (when R = Ph, R^1 = 4-CO_2Me 10% of a product characterized as *cis*,*exo*-3′-{3-(4-methoxycarbonylphenyl)-2-bicyclo[2.2.1]heptyl}-[1,1′:4′,1″-terphenyl]-4-carboxylic acid methyl ester was obtained).

For the success of the procedure it is important that the equilibrium corresponding to the deinsertion step (from **10** to **11**) is displaced to the right. Continuous removal of norbornene from the reaction mixture has a beneficial effect on



Scheme 3 Reagents and conditions: (i) K_2CO_3, DMF, under N_2, room temperature, 6 h; (ii) under H_2 at room temperature and atmospheric pressure



Scheme 4

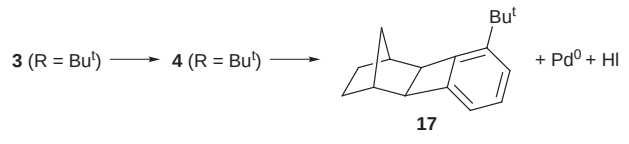
this aim; moreover it prevents further insertion of norbornene into C—Pd bonds of other species present in the reaction solution with formation of by-products such as **16**, as shown in Scheme 4.[5]

We were pleased to observe that removal of norbornene *in vacuo* results in satisfactory yields. Thus when the dimer of *o*-(*n*-butyl)phenylnorbornylpalladium chloride (analogous to iodide **3**, R = Bu^n), 4-methoxycarbonyliodobenzene (**7**, R^1 = 4-CO_2Me, in excess to minimise competitive reactions) and K_2CO_3 were reacted in DMF for 6 h at room temperature *in vacuo* (0.1 mm Hg) and subsequently treated with H_2 or $NaBH_4$ (in excess) compound **12** (R = Bu^n, R^1 = 4-CO_2Me) was obtained in almost quantitative yield according to Scheme 3 (entry 4). Working at atmospheric pressure without removing norbornene led to 71% only. Other representative examples are reported in Table 1.

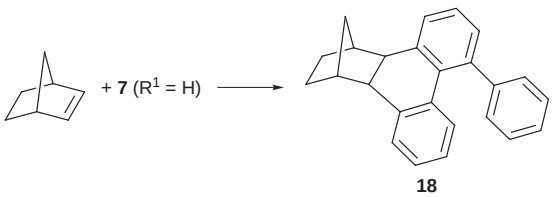
Table 1 Effect of R and R^1 on the yield of **12** in the reaction of complexes **3** with aromatic iodides **7** (Scheme 3) at room temperature in DMF[a]

Entry	R	R^1	Biphenyl **12** yield (%)[b]
1	Me	4-CO_2Me	61[c]
2	Me	3-Me	35[c], 68[d,e]
3	Me	4-Me	36[c], 67[d,e]
4	Bu^n	4-CO_2Me	71, 99[d]
5	Bu^t	4-CO_2Me	36[f]
6	Ph	4-CO_2Me	76[c,g]

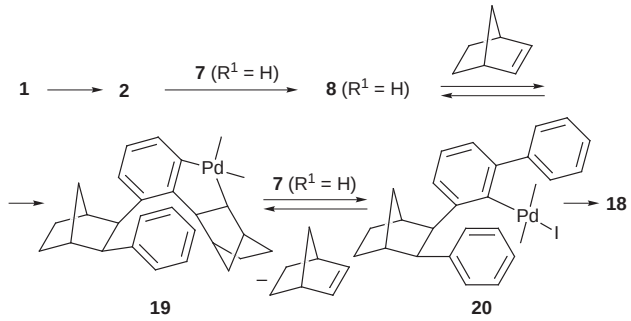
[a] Compound **3** as a dimer (0.05 mmol), K_2CO_3 (0.3 mmol) and aryl iodide (0.5 mmol). [b] GC yield based on **3**; conversions are higher than 95%. [c] The main by-product for runs 1, 2, 3, 6 is compound **16** with yields ranging from 11 to 15%. [d] Run under 0.1 mm Hg. [e] Ref. 6. [f] The only by-product is compound **17** (50% yield). [g] Run 6 also leads to *cis*, *exo*-3′-3-(4-methoxycarbonylphenyl)-2-bicyclo[2.2.1]heptyl-[1, 1′ : 4′,1″-terphenyl]-4-carboxylic acid methyl ester (10%) resulting from hydrogenolysis of the parent unsubstituted species **20** reported in Scheme 7.



Scheme 5



Scheme 6 Reagents and conditions: $Pd(OAc)_2$, K_2CO_3, Bu_4NBr, DMF, under N_2, 60–100 °C



Scheme 7 Proposed mechanism for the formation of compound **18**

While with R = Me and R^1 = 4-CO_2Me an acceptable yield was obtained even without working *in vacuo* (entry 1), with R^1 = 3- or 4-Me yields were low and almost doubled under vacuum (entries 2 and 3). With R = Bu^t (entry 5), however, the formation of **12** was accompanied by that of the benzocyclobutene derivative **17**, which is obtained from **4** by reductive elimination (Scheme 5). This anomalous behaviour may be attributed to excessive steric crowding generated by the *t*-butyl group, which makes complex **4** more susceptible to reductive elimination.[7]

In the case of R = Ph in complex **3**, when R^1 = 4-CO_2Me the yield of **12** (entry 6) was satisfactory (76%) even without norbornene removal, with compound **16** (Scheme 4) amounting to 11%. When R^1 was a *meta* or *para* alkyl group yields of **12** were lower (qualitative results not reported in the Table). This suggests that electronic effects are also involved in the aryl–aryl coupling.

Although at present the reaction is stoichiometric it adds to the existing organometallic methods[8] offering new perspectives in catalysis.[9] The above results also have a bearing as far as the interpretation of other palladium-catalysed arylations is concerned. In particular the reaction shown in Scheme 6 has been described.[10] Although a mechanism based on the formation of a coordinated aryne was proposed,[10] the reaction course can be explained straightforwardly by the same palladacycle mechanism already proved by us according to Scheme 7. In fact on comparing complex **4** with complex **19** we can observe that the situation is quite similar, this time the R substituent in the *ortho* positions being an arylnorbornyl group. Is has also been ascertained that the reaction shown in Scheme 7 does not occur in the absence of norbornene.

In conclusion we have found a new type of aromatic arylation *via* palladacycles which is promoted by the presence of *ortho* alkyl or aryl substitutents. Further study is in progress to ascertain the scope of the method here described.

Experimental

General procedure for compounds 12

The desired compound **3** prepared as a dimer (0.05 mmol) according to the literature procedure reported for the parent complex,[2a] and K_2CO_3 (0.3 mmol) were introduced under nitrogen into a Schlenk-type flask and dissolved in DMF (4 ml). The appropriate aryl iodide **7** (0.5 mmol) in DMF (2 ml) was then added and the reaction mixture was stirred at room temperature for 6 h. The decomposition of the arylpalladium species **11** and of the unconverted starting compound was carried out either by adding $NaBH_4$ in excess or by placing

the solution under hydrogen for 2 h at room temperature and atmospheric pressure. After conventional work up the crude product was separated by flash chromatography using hexane or mixtures of hexane–ethyl acetate as eluents. Reactions under vacuum (0.1 mm Hg) were carried out analogously.

Compound **9** was prepared under the same conditions.

NMR data of selected compounds ($CDCl_3$, 20 °C; COSY, NOESY, C—H correlation experiments; *: interchangeable assignments). 1,2,3,4,4a,12b-Hexahydro-7-methoxycarbonyl-1,4-methanotriphenylene (**9**, R^1 = 4-CO_2CH_3). ^{1}H NMR: δ 8.49 (1H, d, J = 1.8 Hz, H8), 7.91 (1H, m, H9), 7.83 (1H, dd, J = 8.0, 1.8 Hz, H6), 7.29 (1H, d, J = 8.0 Hz, H5), 7.26–7.20 (3H, m, H10, H11, H12), 4.03 (3H, s, CO_2CH_3), 3.35 (2H, AB system, H4a, H12b), 2.53 (2H, m, H1, H4), 1.98–1.78 (4H, m, $H2_{exo}$, $H3_{exo}$, $H2_{endo}$, $H3_{endo}$), 1.53 (1H, d quintets, J = 10.0, 1.6 Hz, $H13_{syn}$), 1.23 (1H, d quintets, J = 10.0, 1.5 Hz, $H13_{anti}$); ^{13}C NMR: δ 167.2, 143.0, 137.5, 131.7, 130.4, 130.3, (C5), 130.2 (C10*), 128.3 (C6), 128.2 (C11*), 128.1 (C7), 126.4 (C12*), 123.6 (C8), 122.4 (C9), 52.05 (CO_2CH_3), 49.7 (C1**), 49.5 (C4**), 46.1 (C4a***), 45.8 (C12b***), 33.2 (C13), 30.3 (C2****), 30.2 (C3****).

3′-(*n*-Butyl)-(1,1′-biphenyl)-4-carboxylic acid methyl ester (**12**, R = Bu^n, R^1 = 4-CO_2CH_3): ^{1}H NMR: δ 8.10 (2H, H3, H5), 7.66 (2H, H2, H6), 7.47–7.41 (2H, m, H2′, H6′), 7.37 (1H, dd, J = 8.2, 7.4 Hz, H5′), 7.22 (1H, dt, J = 7.4, 1.5 Hz, H4′), 3.94 (3H, s, CO_2CH_3), 2.69 (2H, ABX system, CH_2Ar), 1.65 (2H, m, CH_2CH_2Ar), 1.39 (2H, sxt, J = 7.3 Hz, CH_2CH_3), 0.95 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR: δ 167.0, 145.9, 143.6, 139.9, 130.0 (C3, C5), 128.8 (C5′), 128.7 (Cl), 128.3 (C4′), 127.4 (C2′), 127.1 (C2, C6), 124.6 (C6′), 52.1 (CO_2CH_3), 35.7 (CH_2Ar), 33.7 (CH_2CH_2Ar), 22.4 (CH_2CH_3), 13.9 (CH_3).

3′-(1,1′-Dimethylethyl) (1,1′-biphenyl)-4-carboxylic acid methyl ester (**12**, R = Bu^t, R^1 = 4-CO_2CH_3). ^{1}H NMR: δ 8.10 (2H, H3, H5), 7.66 (2H, H2, H6), 7.62 (1H, br s, H2′), 7.48–7.40 (3H, m, H4′, H5′, H6′), 3.94 (3H, s, CO_2CH_3), 1.38 (9H, s, $3CH_3$); ^{13}C NMR: δ 167.0, 151.8, 146.3, 139.8, 130.0 (C3, C5), 128.7 (C1), 128.6 (C4′*), 127.2 (C2, C6), 125.2 (C5′*), 124.5 (C6′*), 124.3 (C2′), 52.1 (CO_2CH_3), 34.8 [$C(CH_3)_3$], 31.4 ($3CH_3$). (1,1′ : 3′,1″-Terphenyl)-4-carboxylic acid methyl ester, **12** (R = Ph, R^1 = 4-CO_2CH_3). ^{1}H NMR: δ 8.13 (2H, H3, H5), 7.83 (1H, t, J = 1.8 Hz, H2′), 7.72 (2H, H2, H6), 7.65 (2H, H2″, H6″), 7.63–7.59 (2H, m, H4′, H6′), 7.54 (1H, t, J = 7.5 Hz, H5′), 7.48 (2H, H3″, H5″), 7.39 (1H, tt, J = 7.3, 1.3 Hz, H4″), 3.95 (3H, s, CO_2CH_3); ^{13}C NMR: δ 167.0, 145.6, 142.0, 140.9, 140.5, 130.1 (C3, C5), 129.3 (C5′), 129.0 (C4), 128.8 (C5″, C3″), 127.5 (C4″), 127.2 (C2″, C6″), 127.1 (C2, C6), 127.0 (C4′*), 126.2 (C2′), 126.1 (C6′*), 52.1 (CO_2CH_3).

3′-(2-Bicyclo[2.2.1]heptyl)-(1,1′ : 4′,1″-terphenyl)-4-carboxylic acid methyl ester (**16**, R = Ph, R^1 = 4-CO_2CH_3). ^{1}H NMR: δ 8.12 (2H, H3, H5), 7.70 (2H, H2, H6), 7.62 (1H, d, J = 1.9 Hz, H2′), 7.47 (1H, dd, J = 7.8, 1.9 Hz, H6′), 7.43 (2H, H3″, H5″), 7.39 (1H, H4″), 7.32 (2H, H2″, H6″), 7.28 (1H, d, J = 7.8 Hz, H5′), 3.95 (3H, s, CO_2CH_3), 2.82 (1H, dd, J = 9.0, 6.0 Hz, H2‴), 2.37 (1H, m, H1‴), 2.33 (1H, m, H4‴), 1.76 (1H, d quintets, J = 9.8, 1.8 Hz, $H7'''_{syn}$), 1.62 (1H, m, $H3'''_{exo}$), 1.53–1.43 (3H, m, $H3'''_{endo}$, $H5'''_{exo}$, $H6'''_{exo}$), 1.26 (1H, d further split, J = 9.8 Hz, $H7'''_{anti}$), 1.10 (2H, m, $H5'''_{endo}$, $H6'''_{endo}$).

5-(1,1′-Dimethylethyl)-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene (**17**). ^{1}H NMR: δ 7.16 (2H, H6, H7), 6.82 (1H, H8), 3.28 (1H, br d, J = 3.9 Hz, H4a), 3.10 (1H, br d, J = 3.9 Hz, H8b), 2.41 (1H, m, H4), 2.26 (1H, m, H1), 1.65–1.54 (2H, m, $H2_{exo}$, $H3_{exo}$), 1.32 (9H, s, CH_3), 1.24–1.16 (2H, m, $H2_{endo}$, $H3_{endo}$), 0.97, 0.92 (2H, AB system further split, 2H9); ^{13}C NMR: δ 146.8, 146.2, 143.0, 127.5 (C6), 123.9 (C7), 119.0 (C8), 52.6 (C4a), 49.6 (C8b), 37.4 (C4), 36.7 (C1), 34.7 [$C(CH_3)_3$], 31.7 (C9), 31.0 ($3CH_3$), 27.9 (C2, C3).

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