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Intramolecular benzylic C–H activation: palladium-catalyzed synthesis of hexahydromethanofluorenes†

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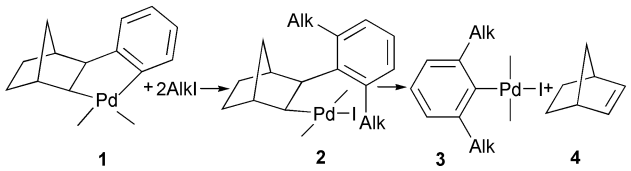
C–H activation of benzylic methyl groups has been realized catalytically under mild conditions through intramolecular reaction on a palladium complex.

Aromatic and aliphatic C–H activation catalyzed by transition metal complexes is an area of increasing interest in view of the elaboration of selective methodologies for the functionalisation of arenes and alkanes.[1] Cyclometallation and, in particular, cyclopalladation reactions are valuable tools to achieve intramolecular C–H bond cleavage.[1f–h]

We previously reported[2] a new methodology for selective aromatic substitution which implies C–H activation and *o*,*o*′-dialkylation of the hexahydropalladafluorene **1**. As shown in the simplified Scheme 1, the reaction proceeds through oxidative addition of alkyl halides, alkyl group migration on the aryl site of the palladacycle **1** and spontaneous expulsion of norbornene **4** to give the *o*,*o*′-dialkylated arylpalladium species **3**.

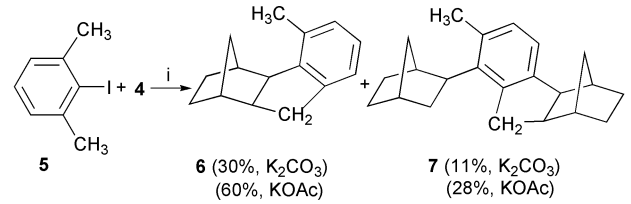
The reaction could be made catalytic by causing the final complex **3** to undergo further reaction so that palladium(0) could be formed.[3] An example is shown by the reaction of iodobenzene, *n*-propyl bromide, norbornene and phenylboronic acid to form 2,6-di-*n*-propyl-1,1′-biphenyl in 90% isolated yield.[3c]

We have now found that in the presence of a methyl group the reaction can take a completely different course, norbornene no longer being expelled as in Scheme 1, but instead undergoing ring closure on the methyl group.



Scheme 1

Compounds **6** and **7** (Scheme 2) are formed by heating an *N*,*N*-dimethylformamide (DMF, 5 mL) solution of norbornene (49 mg, 0.52 mmol) and *o*,*o*′-dimethyliodobenzene (103 mg, 0.44 mmol) at 105 °C for 18 h under nitrogen in the presence of $Pd(OAc)_2$ (10 mg, 0.044 mmol) as the catalyst and K_2CO_3 (61 mg, 0.44 mmol) as the base. *cis*,*exo*-Hexahydromethanofluorenes **6** (30%) and **7** (two diastereoisomers, 11%) correspond to palladium-catalyzed C–H activation of a benzylic methyl group. Yields of **6** and **7** could be raised to 60 and 28%, respectively, by using KOAc instead of K_2CO_3 as a base.



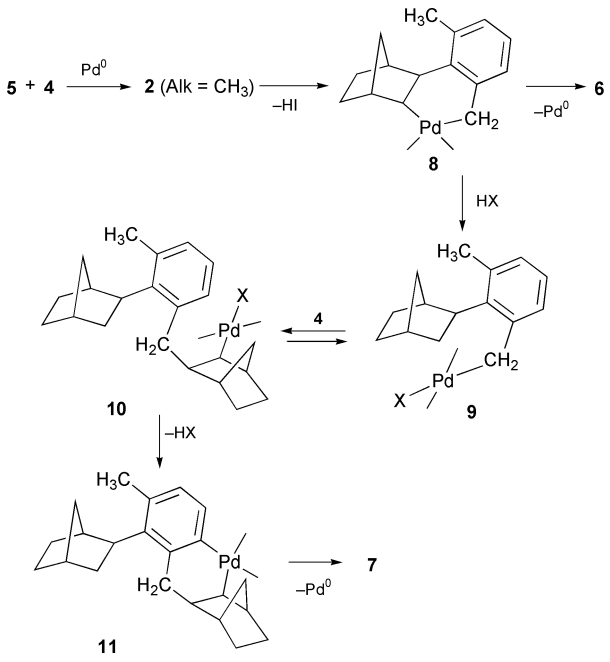
Scheme 2 *Reagents and conditions*: i, 10% mol $Pd(OAc)_2$, KOAc, DMF, N_2, 18 h, 105 °C, 91% conversion.

† Electronic supplementary information (ESI) available: selected spectroscopic data for compounds **6**, **7**, **15** and **16**. See http://www.rsc.org/suppdata/cc/b0/b005182i/

The positive influence of KOAc on the conversion of the disubstituted aryl iodide **5** could be ascribed to the favourable action exerted by the acetate anion on norbornene insertion,[4] this step being adversely affected by the steric hindrance of the two *ortho* methyl groups. The proposed course of the reaction leading to compounds **6** and **7** is shown in Scheme 3.

Complex **2** (Alk = CH_3) instead of undergoing norbornene deinsertion as previously observed (see Scheme 1), prefers to activate the methyl group to give the palladacyclohexene complex **8**. This means that the tendency of palladium to react with a suitably positioned methyl group, possibly through agostic interaction,[1h,5] is strong enough relative to C–C bond cleavage so preventing norbornene deinsertion. Complex **8** can either undergo $C(sp^3)$–$C(sp^3)$ coupling to give compound **6** or ring opening catalyzed by protonic species HX in the manner previously described[6] and thoroughly investigated by Carmona's group in a recent study.[7] Norbornene then inserts into the new alkylpalladium complex **9** to form **10**; the latter gives the new disubstituted *cis*,*exo*-hexahydromethanofluorene **7** through the intermediacy of a six-membered palladacycle of type **11**.

Since compound **7** must originate from a benzylpalladium complex of type **9**, which in turn requires the palladacyclohex-



Scheme 3 Proposed mechanism for the palladium-catalyzed synthesis of **6** and **7**. Solvent or reagent molecules as ligands are omitted for simplicity.

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ene **8** as precursor, its presence unequivocally confirms the proposed mechanism.

The reaction shows some analogy with those of *o*-*tert*-butyliodobenzene and *o*-iodoanisole described by Dyker[8] which, however, imply palladium-catalyzed C–H activation at a *tert*-butyl group and at a methoxy group, respectively, and end up with a $C(sp^3)$–$C(sp^2)$ ring closure.

To further support these results we carried out the stoichiometric reaction of the dimeric *o*-tolylnorbornylpalladium chloride complex **2** (one Alk = CH_3, the other being H)[9] (52 mg, 0.08 mmol) with methyl iodide (23 mg, 0.16 mmol) in the presence of K_2CO_3 (33 mg, 0.24 mmol) in DMF (5 mL) at room temperature for 5 h under nitrogen. The cyclopentene derivative **6** was obtained in 73% yield.

At this point we wondered whether a catalytic reaction involving benzylic activation could be possible also using *o*-iodotoluene in place of *o*,*o*′-dimethyliodobenzene. Poor results were obtained with KOAc while using K_2CO_3 led to the formation of four products. Thus compounds **15**–**18** (Scheme 4) were obtained by heating a DMF (25 mL) solution of norbornene (57 mg, 0.6 mmol) and *o*-iodotoluene (109 mg, 0.5 mmol) in the presence of $Pd(OAc)_2$ (11 mg, 0.05 mmol) as catalyst and K_2CO_3 (70 mg, 0.5 mmol) as the base under the conditions previously reported. The formation of products **15** (63%) and **16** (two diastereoisomers, 5%) implies the same type of C–H activation of a benzylic methyl group as observed for **6** and **7**.

The reaction pathway involves the intermediacy of palladacycle **13** and its further reaction with a second molecule of *o*-iodotoluene to form eventually **14**.[9c] Once the *o*,*o*′-disubstituted aromatic is formed the reaction proceeds as shown in Scheme 3 for *o*,*o*′-dimethyliodobenzene.

Although the cyclisation reaction leading to **15** could be expected to occur between one molecule of iodotoluene and one of norbornene, it surprisingly takes place only after a second tolyl unit has been introduced into the free *ortho* position. This fact can be explained considering that, as long as one *ortho* methyl group only is present, coordination with the aromatic ring is preferred. This point has been recently highlighted by Crabtree and coworkers.[1g,10]

The formation of **17** (10%)[11] and **18** (two diastereoisomers, 4%) does not involve benzylic C–H activation. However, since it can readily be explained according to a pathway previously described,[11] it will not be examined further. Yields are strongly influenced by reaction conditions (such as temperature, concentration, solvent) as well as by the base used and the addition of ligands and salts. For example by adding tetrabutylammonium bromide to the reaction mixture, compound **16** becomes the main product, being obtained in 37% yield together with compounds **15**, **17** and **18** in 23, 6 and 14% yield, respectively.

Compounds **6**, **7**, **15** and **16** were fully characterised by spectroscopic methods and by elemental analysis (ESI).†

In conclusion we have shown that C–H bonds of benzylic methyl groups can be activated catalytically with formation of cyclopentene rings. The use of the appropriate organometallic precursors allows the reaction to occur stoichiometrically even at room temperature. The generality of the reaction is being investigated.

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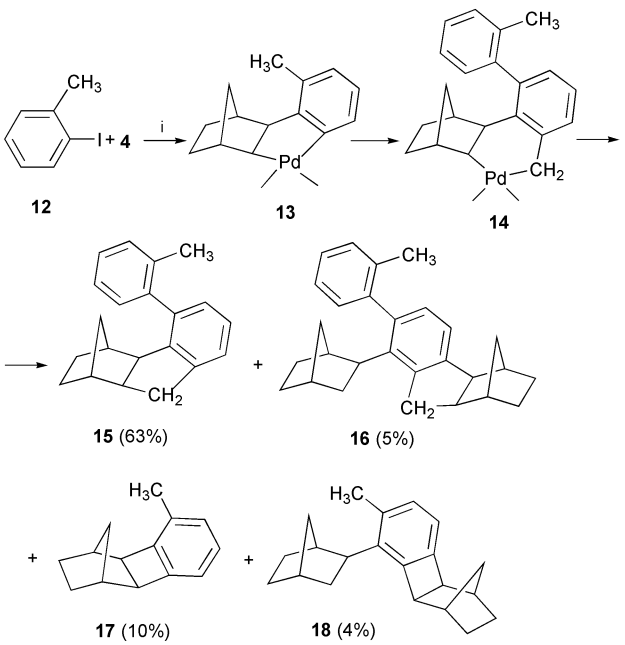

Scheme 4 *Reagents and conditions*: i, 10% mol $Pd(OAc)_2$, K_2CO_3, DMF, N_2, 18 h, 105 °C, 93% conversion.

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