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The mechanism of the oxidative addition of aryl halides to Pd-catalysts: a DFT investigation†

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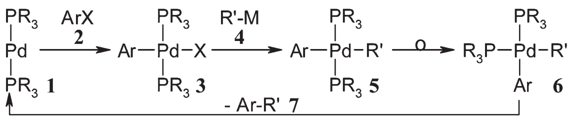
Based on DFT calculations, a new mechanism for the oxidative addition of aryl halides to Pd-catalysts is presented. The key intermediate is an anionic Pd-species in which the aryl halide coordinates to the palladium *via* the halide atom.

The oxidative addition of aryl halides to palladium(0) complexes under formation of aryl-palladium(II) species is the initiating step in numerous widely applied catalytic cross-coupling reactions, *e.g.* Suzuki reactions, Heck olefinations and Stille couplings.[1,2] Since it is of great importance to understand which factors determine the efficiency of this catalytic step, its mechanism has been investigated using experimental studies on model systems,[3] kinetic measurements[4,5] and quantum chemical calculations.[6–8]

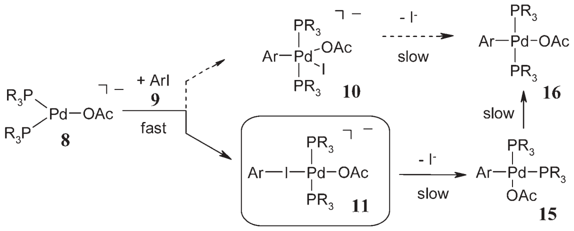
It has been proposed that under the reaction conditions, coordinatively unsaturated Pd(0)L_2 species **1** are formed from Pd(0)-phosphine complexes or, alternatively, from Pd(II) salts and phosphines.[1,2] These catalytically active species **1** should then react with aryl halides **2** under formation of the stable, isolable *trans*-configured complexes **3**, thus initiating the generic catalytic cycle for cross-coupling reactions depicted in Scheme 1. However, this "textbook mechanism" provides no explanation for the pronounced influence that counter-ions of the Pd(II) pre-catalysts and added metal salts have on catalytic activities.[5] Furthermore, isolated *trans*-complexes **3** have been found to couple so slowly with organometallic reagents that their intermediacy in catalytic reactions appears doubtful.[4,9]

In ground-breaking mechanistic studies, Amatore and Jutand recently revealed[5] that in the reaction of Pd(II) salts with phosphines, three-coordinate anionic Pd(0) complexes **8** are formed instead of Pd(0)L_2 **1** (Scheme 2). The counter-ion of the pre-catalyst remains bound to palladium and influences its reactivity. They also proved that on addition of iodobenzene (**9a**, Ar = Ph) to the three-coordinate complex **8b** (R = Ph), a new species forms quantitatively within seconds, while the solution remains free of iodide and acetate anions. It takes several minutes before the expected stable, four-coordinate *trans*-complex **16b** (R, Ar = Ph) can finally be detected.

For the initially formed intermediate, Amatore and Jutand propose the five-coordinate structure **10** and suggest that it serves as the starting point for competing, fast catalytic cycles *via* three- and five-coordinate Pd-species.[5] Although many experimental findings can be rationalized with this reaction mechanism, the dominating role of five-coordinate Pd-species in catalytic cycles seemed implausible[7] to us for the following reasons: only very few five-coordinate Pd-complexes are documented which are invariably forced by polydentate ligands[10]—there is rarely any example for a four-coordinate Pd-complex that adds an extra ligand.[11] Moreover, it is hard to see why the formation of **10**, which requires the cleavage of a strong C–I bond and the formation of two new bonds, should happen within seconds, while the release of an iodide ion to yield the stable *trans*-complex **16** should be so much slower.



Scheme 1 Textbook mechanism of cross-coupling reactions.



Scheme 2 Postulated intermediates of the oxidative addition.

On the basis of DFT calculations (BP86/LANL2DZ),[12–15] we herein propose a different structure for the initially formed intermediate in which the aryl iodide linearly coordinates to palladium *via* the iodine atom.[16]

As a model system for our calculations, we chose the reaction of the three-coordinate anionic complex $[Pd(PMe_3)_2OAc]^-$ (**8a**, R = Me, Scheme 2)[17] with iodobenzene (**9a**). When approaching iodobenzene (**9a**) to the palladium centre of **8a**, minimization of the energy by means of DFT led to the four-coordinate Pd-species **11a** (Ar = Ph, R = Me) almost independently of the original orientation of the molecules; **11a** is clearly more stable than the reactants ($\Delta E_{tot} = -20.3$ kcal mol^{-1}, $\Delta G_{298} = -9.3$ kcal mol^{-1}). In sharp contrast, despite thorough, systematic searches, no energy minimum could be found for five-coordinated structures of type **10a** (Ar = Ph, R = Me) or **10b** (R, Ar = Ph).[7]

There is no significant energy barrier for the formation of the four-coordinate intermediate (**8a** + **9a** → **11a**), which is consistent with the experimental findings that within seconds after the addition of iodobenzene (**9a**) to $[Pd(PR_3)_2OAc]^-$ (**8b**, R = Ph), neither **8b** nor free iodide or acetate is detectable.[5] The formation of an analogous species from bromobenzene ($\Delta E_{tot} = -13.6$ kcal mol^{-1}, $\Delta G_{298} = -2.6$ kcal mol^{-1}) is also exothermic and exergonic, while coordination of chlorobenzene ($\Delta E_{tot} = -5.8$ kcal mol^{-1}, $\Delta G_{298} = +5.0$ kcal mol^{-1}) is still exothermic but endergonic. Experimentally, catalytic reactions of aryl chlorides require sterically highly demanding ligands, which presumably facilitate an alternative reaction pathway *via* coordinatively highly unsaturated Pd-species.[3] The addition of **9a** to a neutral species Pd(0)L_2 **1a** (R = Me) yielding a three-coordinate compound is energetically much less favorable ($\Delta E_{tot} = -8.5$ kcal mol^{-1}, $\Delta G_{298} = +3.0$ kcal mol^{-1}) than the addition to **8a**. This difference might serve to explain the profound influence of anions on Pd-catalyzed reactions.[18]

Starting from **11a**, we found an energetically favorable reaction pathway for the oxidative addition of iodobenzene (**9a**) *via* the intermediates **12a–14a** (Fig. 1).

It leads from **11a** *via* the transition state $[\mathbf{11a}–\mathbf{12a}]^{\ddagger}$ (Pd–I = 3.329 Å, Pd–OAc$^-$ = 4.627 Å) to the intermediate **12a** that shows an interaction of a phenyl C–H bond with palladium. The reaction continues *via* a low-lying transition state $[\mathbf{12a}–\mathbf{13a}]^{\ddagger}$

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† Electronic supplementary information (ESI) available: further computational data. See http://www.rsc.org/suppdata/cc/b4/b409144b/

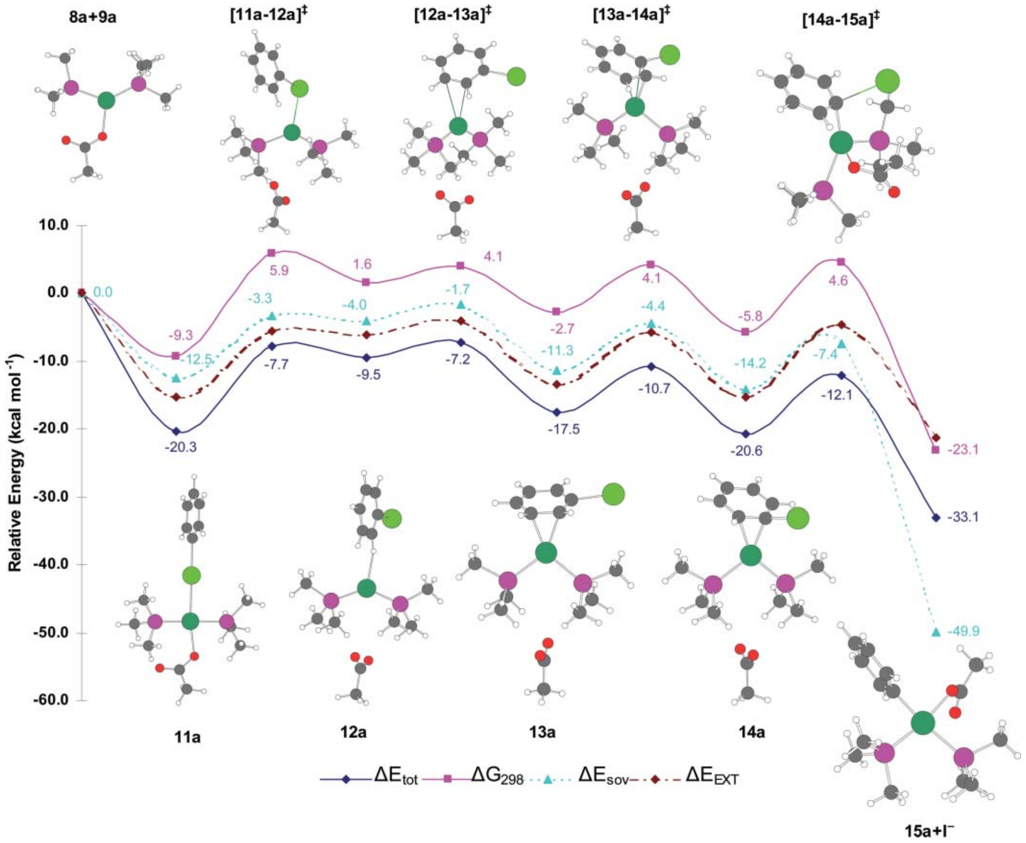


Fig. 1 Calculated reaction path for the oxidative addition of iodobenzene (**9a**) to $[Pd(PMe_3)_2OAc]^-$ (**8a**).

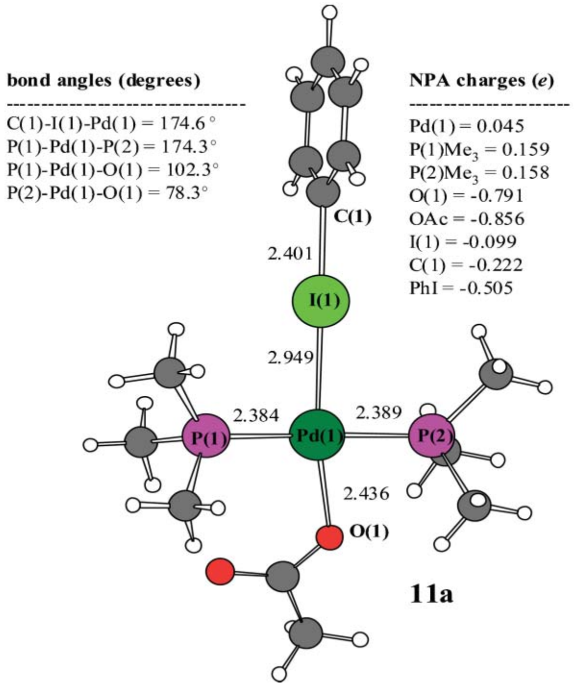
(Pd–C2 = 2.756 Å, Pd–C3 = 3.075 Å), affording the π-complex **13a** (Pd–C2 = 2.220 Å, Pd–C3 = 2.191 Å), in which the palladium coordinates to the C2–C3 bond of the aromatic ring. The shift of the π-interaction from the C2–C3 bond to the C1–C2 bond *via* the transition state [**13a–14a**]‡ requires only little energy (<7 kcal mol^{-1}). The resulting π-complex **14a** (Pd–C1 = 2.089 Å, Pd–C2 = 2.245 Å) has great similarity with previously postulated intermediates,[6–8] and the actual oxidative addition *via* the transition state [**14a–15a**]‡ proceeds smoothly. Notably, the release of iodide does not directly lead to **16a** but to the *cis*-configured Pd(II) complex **15a** (Pd–OAc$^-$ = 2.110 Å).‡

During the reaction, the acetate is close to the metal in **11a** (Pd–O = 2.436 Å), [**14a–15a**]‡ (Pd–O = 2.645 Å), and **15a** (Pd–O = 2.110 Å). In all other species, it is a remote ligand which remains in proximity to the hydrogen atoms of a PMe_3 group. In solution, one may expect that these weak gas-phase interactions will not survive and that acetate will be solvated.

Single-point energies for the structures optimized in the gas phase were also calculated by using the "conductor-like polarizable continuum model" for THF (ΔE_{sov}, Fig. 1).[19] The formation of the intermediate **11a** in THF is still exothermic (ΔE_{sov} = -12.5 kcal mol^{-1}) and the solvent effects on the energies of most structures are relatively small (Fig. 1). Only the formation of **15a** is much more exothermic than in the gas phase, as the iodide released will be stabilized in a polar solvent (Fig. 1).

The four-coordinate complex **11a** is the crucial intermediate in the proposed mechanism. Its geometrical parameters and NPA[20] charges are depicted in Fig. 2. Both the acetate and iodine ligands are bound to the metal center (Pd–I = 2.949 Å, Pd–OAc$^-$ = 2.436 Å). Upon complexation to **8a**, PhI gains 0.505 *e* (0.249 *e* at I), mainly due to a charge transfer into the antibonding σ*(C–I) orbital, and iodine may be considered as hypervalent in **11a**. Geometry optimization (BP86/LANL2DZ) in THF using COSMO methodology as implemented in the TURBOMOLE package[21] confirms that the four-coordinate intermediate **11a** exists in THF solution as a distinct minimum. By contrast, the four-coordinate species $[(THF)Pd(PMe_3)_2OAc]^-$ loses THF upon such optimization, indicating that the three-coordinate anion **8a** is favored in THF solution.

The fact that it is the *cis*-Pd(II)-complex **15a** that results from the oxidative addition rather than the more stable *trans*-Pd(II)-complex **16a** ($\Delta E_{tot} = -11.2$ kcal mol^{-1}, $\Delta G_{298} = -11.4$ kcal mol^{-1}) may rationalize why catalytic reactions of aryl halides with organometallic reagents sometimes proceed more rapidly than the analogous stoichiometric transformations of *trans*-Pd(L_2)(Ar)I complexes:[9] If



bond angles (degrees)

C(1)-I(1)-Pd(1) = 174.6°
P(1)-Pd(1)-P(2) = 174.3°
P(1)-Pd(1)-O(1) = 102.3°
P(2)-Pd(1)-O(1) = 78.3°

NPA charges (*e*)

Pd(1) = 0.045
P(1)Me_3 = 0.159
P(2)Me_3 = 0.158
O(1) = -0.791
OAc = -0.856
I(1) = -0.099
C(1) = -0.222
PhI = -0.505

Fig. 2 Calculated geometrical parameters (bond distances in Å and angles in degrees) and NPA charges (in *e*) for **11a**.

the *cis–trans*-isomerization from **15** to **16** is slower than the transmetallation of **15**, the latter reaction will be favored and directly yield a complex ready for reductive elimination, without requiring another slow isomerization (*cf.* Scheme 1).

In summary, DFT calculations predict an energetically favorable mechanism for the oxidative addition of aryl halides to Pd-catalysts *via* a stable four-coordinate anionic intermediate. This simple mechanism offers an alternative explanation for the complex experimental observations in cross-coupling reactions, without involving five-coordinate Pd-intermediates.

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Notes and references

‡ *Computational details*: All calculations were performed with the Gaussian98 and 03 program packages[12] and the BP86 density functional.[13] The atoms H, C and O were described by the D95V basis,[14] while LANL2DZ pseudopotentials and valence basis sets were used to represent P, I and Pd.[15] All geometries of minima and transition states were fully optimized. Harmonic force constants were calculated for the optimized geometries to characterize the stationary points either as minima or transition states. Transition states were located from a linear transit scan in which the reaction coordinate was kept fixed at different distances while all other degrees of freedom were optimized. The nature of transition states **[12a–13a]**‡, **[13a–14a]**‡ and **[14a–15a]**‡ was verified by following the intrinsic reaction coordinates. Single-point energy calculations at the gas-phase structures were performed within the "conductor-like polarizable continuum model" to account for solvent effects (THF, $\varepsilon = 7.58$) using the "United Atom Topological" model with PBE0/6-31G(d) optimized atom radii (Gaussian03).[19]For further validation, single-point calculations were performed at the optimized BP86/LANL2DZ geometries employing larger basis sets. Using quasirelativistic pseudopotentials,[22,23] Pd and I were described by (8s7p5d)/[6s5p3d][22] and SDB-cc-pVTZ[24] valence basis sets, respectively; the aug-cc-pVTZ basis[25] was employed for O, P and C, and the cc-pVDZ[26] basis for all H atoms. The relative energies derived from these BP86/EXT single-point calculations (E_{ext}) are included in the corresponding reaction profile (Fig. 1), together with the corresponding BP86/LANL2DZ results. The reaction profile remains qualitatively unchanged upon basis set extension. Moreover, we have optimized the three-coordinate complex **8a** and the four-coordinate intermediate **11a** at the BP86/EXT level of theory using the TURBOMOLE code. Both species are minima. The complexation energy for the reaction **8a** + **9a** → **11a** is -14.5 kcal mol^{-1} (exothermic), with **8a, 9a** and **11a** fully optimized at the BP86/EXT level.

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