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Mechanisms for C(sp²)–Si activation of aryltrimethylsilyl groups in palladium-catalysed couplings[†]

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Silyl-substituted aromatic compounds can participate as the electrophilic component in palladium-catalysed cross-couplings, and reactivity is enhanced by a neighbouring silyl-group. Products analogous to those obtained from C–H activation chemistry are accessible by this means with the additional benefit of regiochemistry defined by the site of silyl substitution. DFT studies described here show that the mechanism of C–Si cleavage is distinct from previously recognised mechanisms for C–H cleavage, with a cascade of silyl intermediates *en route* to a stable product. The amide directing-groups are involved only in the stabilisation of palladacyclic intermediates, and are never disposed to activate silicon directly. 5-Membered and 6-membered palladacycles are known to behave differently in coupling reactions and the calculations reveal underlying reasons in the cationic pathways studied here.

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Introduction

Despite the widespread use of silvl groups in organic synthesis,¹ their utilization in palladium-catalysed syntheses is relatively modest compared to boron or tin reagents. In contrast, there is much early mechanistic work on the electrophilic activation of arylsilicon bonds in aromatic substitution.² The catalytic activation of silicon-carbon bonds has a comparably early provenance, largely through publications from Vol'pin's laboratory.³ For example, the arylsilyl bond in PhSiMe₃ is readily cleaved by catalytic quantities of Li₂PdCl₄ in DMF at 100 °C. The synthetic application of arylsilanes in Pd coupling chemistry was pioneered through the early contributions of Hiyama using fluoride ion coordination to appropriately activated silvlarenes or vinylsilanes via pentacoordinated silicates,⁴ and by Denmark through the base-promoted activation of silanols.5 Intramolecular activation can be used to promote either the exocyclic (R = Ar) or endocyclic (R = Me) transfer of aryl groups, following the initial RLi attack at silicon.⁶ Direct Pd-catalysed oxidative coupling of arylsilanes is feasible.⁷ The scope of aryltrimethylsilanes in coupling catalysis was recently extended by Russell and Lloyd-Jones, employing gold(m) coup-



Scheme 1 Examples of silane reagents in catalytic couplings: (a) ref. 4a; (b) ref 5a; (c) ref. 6; and (d) ref. 8b.

ling of arylsilanes and arenes through C–H activation (Scheme 1).⁸

Many of the recent examples of catalytic C–H activation involve a directing group in the reactant, capable of ligating to the metal employed.⁹ The C–H bond cleavage step provides the electrophilic partner in a coupling process leading to further reaction with a nucleophile. In our own work, the original concern was to induce regiocontrol in the electrophilic activation step of catalysis, applied to the oxidative Heck reaction (Scheme 2). For *meta*-substituted acetanilides, it was known that a single product is formed where the new bond is formed at the less substituted *ortho*-position. This was confirmed for 3,4-difluoroacetanilide, but 2-SiMe₃ substitution reverses the



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Scheme 2 Oxidative Heck reaction with $Pd(OAc)_2$ as the catalyst by C-H activation or C-Si activation: (a) ref. 10; (b) ref. 16; and (c) ref. 11, Table 1; *cf.* ref. 12, Scheme 1 for the related case of *N*-methylbenzamide.

regiochemistry of the reaction (Scheme 2a).¹⁰ For benzanilides, the product formed *via* a 6-ring palladacycle is observed in an oxidative Heck reaction (Scheme 2b). After lithiation followed by silylation, the alternative pathway is followed since silyl substitution overrides the normal preference.¹¹ In the absence of added acid at higher temperatures however, the silyl displacement pathway may be accompanied by serious side-reactions that indicate the degradation of Si–CH₃ groups (Scheme 2c).^{12,13}

Results and discussion

Summary of objectives

The mechanism by which C–H activation occurs in palladium catalysis has been widely studied by computation and experiment, and a preferred pathway involves a coordinated acetate ion acting as the base with concurrent palladation (CMD; concerted metallation deprotonation) as a turnover-limiting step.¹⁴ For anilide as the directing group with added acid, and elsewhere, a general base pathway is energetically preferred.¹⁵ Neither route involves a palladium hydride at any stage. The mechanism of the desilylation pathway, which dominates in the examples described, has not previously been addressed by DFT, and a detailed study is described below.

For C-H activation from anilides,¹⁶ the palladacycle is a true reactive intermediate, as indicated by an entrainment experiment conducted for the Heck pathway.¹⁷ In approaching the mechanism of C-Si activation by DFT, a standard B3LYP functional together with Grimme's recently recommended dispersion corrections was implemented.¹⁸ For the low-energy pathway that was found to be predominant with anilides, the procedure was found to require an analysis of several distinct steps involving the activation of sp² Si-C bonds. Surprisingly



Scheme 3 DFT computed pathways for the cyclopalladation of *o*-trimethylsilylacetanilide **A**. Standard state free energies are relative to the intermediate **C**, in kcal mol⁻¹; all species are cationic. Here and for all subsequent calculations using Gaussian: (B3LYP, 6-31G(d,p), scrf = IEFPCM (AcOH), D3 dispersion corrected) see the ESI† for fuller details.²¹

low energy transition states were found, giving confidence to the likely involvement of the species postulated. The overall process is summarised for acetanilide in Scheme 3. The participation of benzamides in *ortho*-C–H activation chemistry is far less common than that of anilides. After efforts directed to optimization, C–Si activation was satisfactorily achieved albeit with much slower turnover (*cf.* Scheme 2c, alternatively the use of –SiMe₂Bu^{*t*}).¹¹ For these reasons, a parallel DFT analysis for the *N*-methylbenzamide case was conducted. Since the species are isomers, the energies of intermediates and transition states could be compared directly.

Computational results

Desilylation pathways for *o***-trimethylsilylacetanilide**. Initial computational work was carried out with the parent silylated acetanilide. In contrast to aromatic C–H activation in Pd catalysis, where there are many computational studies,¹⁹ only a few studies exist for aryl C–Si activation.²⁰ Since C–Si bond cleavage is formally an electrophilic substitution,² reaction *via* cationic palladium species is likely to prevail, in accord with the need for acid catalysis that is found experimentally. The intermediates and transition states involved in the procedure are shown in Scheme 3.

Using $[PdOAC]^+$ as the reactive entity generated in the presence of added acid,¹⁶ trapping of Pd by the basic carbonyl group of acetanilide is a likely first step giving the initial complex **B**, exergonic by >20 kcal mol⁻¹ (Scheme 3). This coordinatively unsaturated intermediate can be further stabilised by agostic interaction with a SiCH₂-H group forming **C** that lengthens both the Si-C and C-H bonds involved.^{22,23} As

observed in the computation of C-H activation with acetanilides,¹⁵ involvement of the arene ring in coordination to Pd provides a yet more stable Wheland-type intermediate D. A direct low energy pathway linking C and D was confirmed by a DFT scan of the relevant C-Si distance from C (3.4 Å) decreasing to <2.0 Å. The agostic CH-bond is maintained down to 2.6 Å with an overall energy barrier ≤ 3 kcal mol⁻¹ (see the ESI[†]). The structure of the C-Si complex D differs significantly from that of the C-H analogue. The computed Pd-C(aryl) bond length is close to that expected for a fully formed single bond at 2.05 Å; cf. 2.3 Å for the C-H analogue; and the bond is close to coplanar with the aromatic ring. The C-Si bond is considerably lengthened from 1.85 Å in the reactant to 2.07 Å in the intermediate D, and thus labilized. The tight geminal partial bonding of both Si and Pd in D leads to lengthening of the two adjacent C−C bonds to 1.43 Å, compared to ≤1.41 Å in B, C and E. Further DFT analysis reveals a low energy pathway for the 1,2 migration of the trimethylsilyl entity from carbon to palladium, via a well-defined transition state DE. The product E has a square-based pyramidal structure, the square plane defined by the palladacycle and acetate ligands with the Pd-Si bond orthogonal to that plane. Attempted minimization of alternative 5-coordinate geometries leads to reversion to E. The Pd-Si bond length in E is 2.45 Å, longer by ca. 0.1 Å than typical values for R₃Si-Pd bonds in the CSD database.^{24,25} The respective geometry of the intermediates is shown in Fig. 1.

A further exergonic stage occurs from **E** through silyl transfer to oxygen of coordinated acetate, and separate transitionstates of very similar energy were located differing by the oxygen engaged in bond formation; transfer to the oxygen *trans*-C is incorporated, giving **F** via **EF**. The low computed activation free energies of the two silyl-transfer steps imply very rapid liberation of the palladacycle from the original adduct by a unimolecular process. Acetolysis of the Pd–Si group giving **G** could potentially compete with the steps between **D** and **F**, subject to energy costs for the correct organisation of the reagent and solvent in the bimolecular Si–O bond forming step. Throughout the process from **B** to **E**, the acetate ligand maintains η^3 -coordination with palladium, with a short Pd–O bond *trans*-O and longer *trans*-C. This is attenuated in the transition-state **EF**, lost in **F** and regained on the formation of palladacycle **G** by ligand exchange with OAc⁻ (or solvolysis of the O–Si group in **F**). The palladacycle **G** serves as the reactant for subsequent coupling with an alkene to form the Heck reaction product and regenerate the catalyst. This process has been the subject of several recent computational studies.²⁶

There are systematic changes during the course of the reaction. For the acetate ligand, the Pd–O (*trans*-O) bond length varies little (2.03–2.04 Å) until the transition-state **EF**, and then only lengthens to 2.07 Å. By contrast the Pd–O (*trans*-C) bond lengthens sequentially from 2.07 Å in **C** to 2.40 Å in **EF**. The Mulliken charges were compared for key atoms.²⁷ In the precursor **B**, Si is isolated from the arene, and on progressing to the Wheland intermediate **D** there is strong Pd–Si bonding. This results in charge transfer, making the Si atom more positive and the Pd much less so. Charge is redistributed within the aromatic ring making the reacting carbon more negative. After SiMe₃ migration giving **E**, both Pd and Si become less positive and the arene carbon loses the acquired negative charge (see the ESI†).

Comparison of the reaction pathway using alternative functionals. There has been substantial recent debate about the merits and demerits of the various functionals available for DFT computations.²⁸ B3LYP is widely used although the desirability of including dispersion correction is well recognised now. There are discussions about DFT replication of organometallic solid-state structures,²⁹ and in the goodness of fit to palladacycle X-ray geometries.³⁰ In order to have specific standards for comparison, the key reaction steps and transition states have been repeated with two alternative functionals using the same basis set with the SDD pseudopotential for Pd as before. Like B3LYP-D3, both the related hybrid functional B3PW91 and the newer long-range corrected hybrid functional ωB97x-D have been recently utilised in studies of palladiumcatalysed reactions.³¹ The free energies of ground and transition-states through the sequence C-F were obtained and results are recorded in Table 1.

Overall, these data provide similar outcomes; the highest energy barrier in each sequence is \mathbf{EF}^{\ddagger} , rather than \mathbf{DE}^{\ddagger} , and



Fig. 1 Structures of the reactant, transition-state and product in silylgroup transfer from Ar–C to Pd.

Table 1 Energies (kcal mol^{-1)^a} and TS frequencies (cm⁻¹) for the pathway of Scheme 3 with different functionals; same basis set

Stage	B3LYP-D3	B3PW91-D3	ωB97x-D
С	0.0	0.0	0.0
D	-15.5	-17.4	-15.3
DE^{\ddagger}	-11.1	-13.8	-9.4
ν	-116.0	-106.2	-77.1
Е	-18.5	-20.3	-15.0
EF [‡]	-10.3	-12.6	-9.1
ν	-163.0	-152.3	-144.6
F	-38.0	-37.4	-38.9

^{*a*} The baseline for each set of calculations is taken as the free energy of C.

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Fig. 2 Comparison of transition state geometries from the three functionals; following the least-squares overlay of the arenes and Pd atom in each individual set: (i), (ii) DE^{\dagger} ; and (iii) EF^{\dagger} ; see text below.

transition-state energies for the individual steps are within 1.5 kcal mol⁻¹ for DE^{\ddagger} , and 0.7 kcal mol⁻¹ for EF^{\ddagger} . Relative to the Wheland intermediates D, the B3PW91 calculation indicates a lower energy (3.6 kcal mol^{-1}) than B3LYP (4.4 kcal mol^{-1}) for the first barrier, whilst $\omega B97$ is higher (5.9 kcal mol⁻¹). The most striking difference lies in the energies of the silvlpalladium complex E. For both B3LYP and B3PW91, this is more stable than the precursor **D** by 3 kcal mol^{-1} , whilst for ω B97 it is less stable by 0.3 kcal mol⁻¹. Both transition-states were analysed in more detail for structural variation in Fig. 2: for the silyl migration step DE[‡], B3LYP and B3PW91 show only small differences in Fig. 2(i), with the latter more compact, with the Pd-Si bond 0.06 Å and C-Si bond 0.04 Å shorter. A similar comparison of B3LYP-D3 and wB97x-D in (ii) shows that the Si atom is visibly skewed in the latter; an 0.07 Å shorter Pd-Si bond together with an 0.04 Å longer C-Si bond; the C-Pd bond is shortened from C to ca. 2.00 Å in all cases. For the second transition state \mathbf{EF}^{\ddagger} , there are small systematic differences in (iii) without distinctiveness. Reassuringly, the same mechanistic conclusions on the preferred reaction pathway would have been reached with any of these functionals.

Desilylation pathway for *o***-trimethylsilyl-N-methylbenzamide.** The aromatic ring in a benzamide is electron-poor relative to acetanilide. This will be expected to make the silyl derivatives less prone to electrophilic displacement in Pd catalysis. A further difference lies in the geometry of the ensuing 5-membered ring palladacycle. The stability of this class of palladacycles is demonstrated by examples of crystal structures in the CSD structural database, albeit fewer in number than anilide palladacycles.²⁴

The sequence of reactions shown in Scheme 3 for acetanilide may be recreated for *N*-methylbenzamide in Scheme 4. There are strong parallels between the two, with an exergonic initial complexation step giving **B1**, further stabilized by formation of the agostic bond in **C1**. The geometry of the ensuing Wheland intermediate **D1** differs from the acetanilide sequence, since the Pd–C bond is longer at 2.11 Å and the Pd–



Scheme 4 DFT computed pathways for cyclopalladation of (o-trimethylsilyl)-*N*-methylbenzamide A1. Details are as those in Scheme 3.

Si bond is shorter at 2.03 Å. The palladacyclic structure is less developed, with the Pd atom 1.41 Å out of the mean arene ring plane compared to 0.95 Å in the acetanilde case. The remainder of the reaction pathway follows the earlier sequence with silyl transfer transition states **DE1** and **EF1** and is shown in Scheme 4.

Full DFT characterization of the intermediates for the two reactants in **A** and **A1** allows direct comparison of the energies of all the intermediates and transition states, as shown in Fig. 3. Acetanilide has a lower energy than *N*-methylbenzamide by $3.1 \text{ kcal mol}^{-1}$ and this is reflected throughout. The agostic-bonded reactants C and C1 that constitute the benchmark state are only 0.46 kcal mol⁻¹ separated, however. On this



Fig. 3 Comparison of the relative free energies of cationic intermediates and transition states in the A series and A1 series. Free energies in kcal mol^{-1} relative to C or C1.

basis the highest distinction in ground-state free energies lies in the Wheland intermediates, where the 6-membered ring palladacycle precursor **D** is *ca.* 7 kcal mol^{-1} lower in energy than D1, reflecting additional steric strain en route to the 5-membered ring palladacycle. The difference in energy may be reflected in the greater tendency of the amide A1 to side reactions in palladium catalysis.¹³ The transition state energies leading to **DE**[‡] and **DE1**[‡] are remarkably low in both cases; even when the mitigating effects of specific solvent reorganization on ΔG^{\ddagger} are considered, the Wheland intermediates are transient relative to E and E1. In turn, these intermediates are very easily transformed to the end-products of the cycle F and F1, stabilised by the energy gain in formation of the strong Si-O bond. Solvolysis of this bond leads to the neutral model palladacycles F and F1.32 Overall, the formation of palladacycles by aromatic desilylation occurs far more readily than by aromatic deprotonation and involves a distinct mechanism.

Thermodynamics of palladacycle formation. This work was conducted to support earlier studies on oxidative Heck chemistry. For the directing groups involved, the pathway may be divided into two stages, formation and consummation of a palladacycle, each with several individual steps. For each stage, the thermodynamics may be calculated, and the results are shown in Scheme 5. For this purpose, the SMD solvation was employed here following indications for its superior treatment of solvation thermodynamics.³³ For comparison, the data were acquired with both B3LYP-D3 and wB97x-D under otherwise identical conditions.

For standard directed C–H activations, the palladacycle forming step is mildly exergonic for the **A** series but slightly less so for the **A1** series. In the case of C–Si activation however, this stage is much more exergonic, due to transfer of the silyl group from carbon to oxygen. In the coupling stage, the overall energy benefit to the catalytic cycle is reinforced, in large part due to the reduction of benzoquinone to hydroquinone with concomitant gain from aromaticity. This emphasises the importance of the correct choice of oxidising agent in Pd(u)coupling catalysis. The energy balances are not very dependent on the functional used here or on the reactant; for the C–H activation step shown with the difluorinated electron-deficient



Scheme 5 Free energy changes for the stages of the oxidative Heck reaction. DFT calculations as before with the scrf = SMD solvation model.

substrate of Scheme 2a, $\Delta G^{\circ} = -6.4 \text{ kcal mol}^{-1}$. The wide range of reactivity observed experimentally is driven more by kinetics than by thermodynamics.

C-H vs. C-Si activation in benzanilide. Lithiation of benzanilide *ortho*- to C=O followed by silylation with Me₃SiCl affords a reactant for directed Heck coupling. Under the conditions tried, the desilylation pathway dominated over C-H activation, thus activating the ring that is the less reactive one in the parent benzanilide.¹¹ It was of interest to compare the structures involved through DFT analysis. For activation of the C-Si bond towards palladacycle formation, the full reaction sequence should follow that of *N*-methylbenzanilide in Scheme 4. *C*-Silyl activation formally competes with C-H activation, and it was of interest to compute the relative energies of the respective intermediates. Scheme 6 demonstrates these possibilities.

The equivalent to the agostic C–H–Pd stabilised initial complex here is **BA1** (Scheme 6). This may bond to either arene, giving three alternative more stable species. The geminally bonded Si–C–Pd species **BA2** that is a precursor to the observed product is very slightly higher in energy than the 6-membered ring palladacycle precursor **BA4**; both are preferred over the 5-ring palladacycle precursor **BA3** by more than 7 kcal mol⁻¹. The crucial difference lies in the low barrier to the pathway accessible to **BA2** by silyl migration giving **BA5**. In principle, a related proton migration could occur from **BA3** giving the Pd–H complex **BA6**.³⁴ This Pd hydride forming step is strongly endergonic, and serves as further evidence of the need for cooperative mechanisms in coupling catalysis requiring the formal activation of a C–H bond.



Scheme 6 Free energies (in red) of different isomeric TMS-benzanilide complexes, relative to the agostic precursor BA1; C-Pd bond lengths are in blue.

Summary and conclusions

In the course of studies on silane activation for the oxidative Heck reaction,³⁵ a low energy pathway has been found that does not require direct involvement of a neighbouring carbonyl group. There are contrary claims for intramolecular activation of electropositive elements, particularly Si and Sn, by a Lewis base. Examples include nitrogen bases for tin,³⁶ and oxygen bases for silicon that may involve an alkoxide.³⁷ At this stage it is not feasible to claim complete generality for the mechanism suggested here. Future work will seek to extend the observations, in particular by further analysis of the activation of silylmethyl groups by neighbouring amides and ureas in Heck reactions that lead to alkene methylation.¹²

Conflicts of interest

There are no conflicts to declare.

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