A kinetico-mechanistic study on the C–H bond activation of primary benzylamines; cooperative and solid-state cyclopalladation on dimeric complexes†

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The cyclometallation reactions of dinuclear μ-acetato complexes of the type [Pd(AcO)(μ-AcO)L]2 (L = 4-RC6H4CH2NH2, R = H, Cl, F, CF3), a process found to occur readily even in the solid state, have been studied from a kinetico-mechanistic perspective. Data indicate that the dinuclear acetato bridged derivatives are excellent starting materials to activate carbon–hydrogen bonds in a facile way. In all cases the established concerted ambiphilic proton abstraction by a coordinated acetato ligand has been proved. The metallation has also been found to occur in a cooperative manner, with the metallation of the first palladium unit of the dimeric complex being rate determining; no intermediate mono-metallated compounds are observed in any of the processes. The kinetically favoured bis-cyclopalladated compound obtained after complete C–H bond activation does not correspond to the final isolated XRD-characterized complexes. This species, bearing the classical open-book dimeric form, has a much more complex structure than the final isolated compound, with different types of acetato ligands.

Introduction

Palladium has proven to be a very versatile metal centre for C–H bond activation. Both oxidative additions to Pd0 complexes1–6 and formal electrophilic substitution reactions7,8 on PdII are thoroughly studied processes relevant to a number of high value-added industrial applications.9,10 In recent times, even the actuation of oxidative addition processes on PdII complexes has been proven to be extremely relevant,11–13 and an increasing amount of carefully designed PdIV complexes has been characterised.14–23 Most of the C–H bond activation reactions, nevertheless, occur via the formal electrophilic substitution process with the liberation of a proton.24–26 Furthermore, the majority of these reactions are related to intramolecular cyclometallation reactions, which are entropy favoured due to the existence of directing groups that anchor the organic molecule onto the PdII centre.7,8,27

In the latter processes, the starting material of the C–H bond activation reaction is an {PdII-E-CH} unit, where E represents the donor from the directing group.27,28 In this respect, we have been deeply involved in the study of these C–H bond activation reactions via cyclopalladation for a number of years. The studies carried out involve both the characterisation of cyclopalladated derivatives29–34 and the kinetico-mechanistic study of the reactions at variable temperature and pressure.35–41 The vast majority of the results collected are related to κN-Schiff-base directing groups included in an organic ligand. For all these reactions the PdII metal source is formally palladium acetate, although its nature in solution is far from being clear under the reaction conditions used.42–44 In all these reactions an important rate enhancement has been observed on increasing the acidity of the solvent used, typically from toluene to acetic acid, and the actuation of an ambiphilic mechanism has been proposed.45 In the mechanism, a coordinated acetato ligand serves as a proton depository for the reaction,46 which is accelerated when the ligand is already protonated, due to its better leaving characteristics.41,47 More recently these studies have been extended to the cyclometallation reaction of a variety of aminoacids48,49 in view of its relevance to the selective catalytic formation of lactames.50 In these reactions, the kineticomechanistic study on the cyclometallation reaction, which is a key-stone for the completion of the process, indicates a distinct behaviour from the equivalent reaction carried out on Schiff base derivatives.51,52

Reports about the relevance of the nature of palladium acetate in cyclometallation reactions, the key influence of the solvent, and the need for fairly weakly coordinated directing groups to facilitate C–H bond activation have recently appeared.53,54 Furthermore, for the synthesis of unnatural chiral aminoacids by a C(sp3) olefination process catalyzed by Pd(II) acetate, the addition of trifluoroacetic acid is required to generate a coordination vacant site for the reaction to proceed.55 Despite the fact that cyclopalladation of tertiary amines is a long known reaction,56 and a kinetico-mechanistic study has even been published,57 cyclometallation of primary amines has received much less attention, even though a general method for their ortho-palladation has been described.58 Besides this, the elegant isolation of a variety of dinuclear [Pd(AcO)(μ-AcO)L]2 complexes (L being a primary amine), potential starting materials for the cyclometallated compounds,59–63 is especially relevant.

With this background in mind, we present in this work a kinetico-mechanistic study of the cyclometallation reaction of a variety of precoordinated primary amines using the dinuclear [Pd(AcO)(μ-AcO)L]2 complexes ((1R)2, Scheme 1) as starting materials at varying temperatures and pressures, and using toluene and acetic acid as solvents. The data are compared with those from the classical one-pot preparative (palladium acetate plus amine) processes. In general, the reactions take place under relatively mild conditions, even in the solid state. While the one-pot processes are not accelerated when acetic acid is used as the solvent, the reaction on the precoordinated dimeric (1R)2 complexes undergoes a noticeable acceleration in acetic acid solution. The differences are especially evident on the thermal and pressure activation parameters determined. The competition between amine

protonation, acid assisted ambiphilic C–H bond activation, and formation of solvato species seems to be a determinant of the feasibility of the full process.

Results

Preparation of compounds

The mononuclear 0R compounds ([Pd(AcO)2L2]), as well as the dinuclear μ-acetato complexes (1R)2 ([Pd(AcO)(μ-AcO)L]2) shown in Scheme 1 (R = H, Cl and F), have been prepared according to the literature.59 The new 0CF3 and (1CF3)2 compounds (R = CF3) have also been prepared by the same procedure to assess the distinct electronic effects of the trifluoromethyl group. The cyclopalladated (2R)2 derivatives have been prepared and characterised in all cases as for the already described (2H)2 compounds.59 Compounds 0R are yellow solids, stable at room temperature for months; in contrast the dinuclear (1R)2 derivatives readily afford the abovementioned cyclopalladated (2R)2 derivatives. In this respect the 1H NMR spectra of the crude of reaction of 0R and palladium acetate shows, on addition of a few drops of d5-pyridine, the presence of mononuclear cyclopalladated compounds, 3R (Scheme 1), in 20%, 6%, 8% and 4% (for R = H, Cl, F and CF3 respectively). These appear via bridge splitting of the dinuclear cyclopalladated derivatives (2R)2 according to the fully described highly regiospecific process,60,64–67 which is a very useful spectroscopic handle for the general detection of cyclopalladated derivatives. The cis arrangement of the metallated carbon and the pyridine ligand in the mononuclear compound 3R formed produces an important high-field shift in the proton NMR spectra of the metallated ring proton signals.64,67,68

Formation of cyclometallated derivatives during the synthesis of (1R)2 is a very remarkable result, especially considering the mild reaction conditions used (dichloromethane, room temperature, 16 h.).59 Furthermore, the 1H NMR spectrum of the crude reaction mixture shows the presence of two minor distinct cyclometallated impurities (both producing compounds 3R in the presence of pyridine; see above). One of these minor cyclometallated compounds corresponds to the well characterized dinuclear dimer (2R)2 indicated in Scheme 1, while the other one (named {(2R2)} from here on), which is also a bis-metallated dinuclear derivative, has never been reported before. On treating these mixtures in acetic acid or toluene for several hours at 70–80 °C, depending on the amine, the formation of the well characterised cyclopalladated derivatives (2R)2 is observed, thus indicating that the initial (1R)2 dimers evolve initially to intermediate bis-metallated $(2R_2)$} compounds, and that these further evolve to the final (2R)2 characterised compounds. The complete process has distinct time-scales depending on the R substituent of the amine ligands (see the following sections for comprehensive details). 1H NMR spectra of both compounds show important highfield shifts, which suggest that they present the usual openbook structure of acetato bridged cyclopalladated derivatives. The fact that the dinuclear cyclometallated dimer (2R)2 shows a single acetato group signal in the 1H NMR spectrum agrees with the maintenance of the transoid structure already present in the dinuclear starting material (1R)2. This is a clear support for the study of the activation of C–H bonds on compounds (1R)2, the framework of the compounds having no associated structural changes on cyclometallation. In this respect, XRD analysis of the structure of [Pd(AcO)(μ-AcO)-(p-NO2C6H4CH2NH2)2] shows a distance of 2.429 Å between the dangling oxygen of the acetato ligand and the ortho hydrogen atom of the coordinated amine, which is a very suitable parameter for the compounds to undergo ortho C–H bond activation. 59 The XRD studies carried out on single crystals of (2F)2 and (2CF3)2, obtained by slow evaporation of deuterated chloroform solutions, fully agree with the spectroscopic data collected; Fig. 1a and 1b show the molecular drawing of these molecules.

The unambiguous full characterization of the {(2R2)} intermediate species has proved to be not an easy task. The kinetic analysis of the reactions (see below) indicates that the relative concentration of these species has a maximum value of 30–40%, with (1R)2 and (2R)2 being in the same percentage range in the reaction mixtures (see Fig. 3b as an example). The isolation of the species by column

chromatography or crystallization of the crude reaction mixture proved to be impossible, as expected from a dynamic reaction mixture.

Nevertheless, proton NMR experiments have allowed the proposal of a plausible tentative structure for these intermediate species. All their aromatic proton signals appear shifted to rather high fields (below 7.0 ppm), an unusual region for aromatic proton resonances, and at similar values than for the comprehensively characterized cyclopalladated derivatives, (2R)2. This high field shift of the aromatic signals of (2R)2 has been related to the magnetic influence of the aromatic ring of the other moiety of the dinuclear molecule in an open book arrangement. As a whole, the spectral 1H NMR data obtained confirm the open book structure of the intermediate derivatives {(2R2)} . In this respect, it is also to be noted that three acetato signals are observed in the proton NMR spectra of intermediate {(2R2)} compounds, two of them showing NOE exchange cross peaks, which lead us to propose a tentative structure for {(2R2)}. This structure (Scheme 2) contains two cyclopalladated palladium–amine fragments bonded by a bridging acetato ligand; the coordination positions are completed by a monodentate acetato and an acetic acid in fast exchange.

Although acetic acid is not a usual ligand, its existence in this type of complexes has been proposed in a number of occasions, and has also been supported by DFT calculations. 35,41,47,51,52 The tentative structure indicated in Scheme 2 explains also the fact that addition of pyridine to solution mixtures of (2R)2 and {(2R2)} produces exclusively the mononuclear cyclopalladated derivatives 3R. The fact that the same (2R)2 and {(2R2)} mixtures were obtained when compounds (1R)2 were heated in solid (see below) supports the validity of the above reasoning.

Solid-state cyclometallation

Reactions in the solid state, i.e. in the absence of solvent, result in reduced environmental pollution and can be relevant for industrial applications. In sharp contrast with the huge amount of information about cyclometallation reactions in solution, very few examples of solid state cyclometallation have been described. Some examples involve the treatment of solid samples of 1-alkyl-2,4′-bipyridinium palladium or platinum complexes at 130–190 °C, affording the corresponding cyclometallated derivatives via HCl elimination;69,70 of [PtCl2(Ph2CvNH)(RR′SO)] at 150–200 °C to produce benzophenone imine cycloplatination;71 of methylplatinum- or methyliridium(III)-tertiary phosphine complexes at 175–200 °C to produce methane elimination and internal metallation.72,73 Similarly, vacuum thermolysis (250 °C) of cis-[PtCl2(PCHO)2] (PCHO = ortho-diphenylphosphinobenzaldehyde) affords the corresponding metal–acyl derivative by activation of the carbon–hydrogen bond of the aldehyde fragment.74 In contrast, the cyclopalladation of benzylamines in solid state via acetic acid elimination takes place at lower temperatures (80 °C), when the dinuclear acetato bridged compounds are used as starting materials.59

In this respect the dinuclear acetato-bridged compounds described in this work, (1R)2, evolve in the solid state, even at room temperature, to the above-mentioned mixture {(2R2)} of and (1R)2 of cyclopalladated compounds. Thus, the 1H NMR spectrum of a solid sample of (1F)2, containing initially an 8% of cyclometallated derivatives (see previous section), shows an increase to a 25% of these compounds after one month at room temperature (evaluated as 3R). This is a very remarkable result that indicates that the activation of a strong carbon–hydrogen bond can occur even in the solid state at room temperature, once the right choice of the starting material is selected. The dinuclear acetato bridged derivatives (1R)2 seem thus to be excellent starting materials for the synthesis of cyclopalladated compounds, which prompted us to study the cyclometallation reaction in the solid state. For this purpose solid samples of (1R)2 ground for one minute, introduced in NMR tubes, and heated at 70 °C during different times, had their 1H NMR spectrum monitored immediately after solution and addition of d5-pyridine. The results obtained, shown in Table 1, are a clear indication of

important differences between the (1R)2 starting materials, even despite possible dependences on the degree of sample moulting.

The results described in Table 1 show only a definite correlation between the observed rate of cyclopalladation and the para-Hammet constants for (1R)2. It is clear that, for the processes studied, the effect of the R substituent is not related to an electrophilic substitution on the amine phenyl ring; a correlation with σm should be found under these circumstances, as observed recently in other systems.75 The correlation with para-Hammet constant indicates that the key-factor for the reactivity sequence observed lies in the exit process of the protonated acetato ligand after abstraction of the proton from the metalating C–H bond. The better donor the amine ligand is (lower σp Hammet parameter), the easier the exit of the leaving acetic acid from the metallated compound. A similar effect has also been observed in the metallation of α-aminoesters, where the donor ability of the amine group enables an easy metalation of the dangling phenyl groups, and agrees with the "false" electrophilic substitution nature of these cyclopalladation processes.51,52

Kinetico-mechanistic study in solution

With all the facts indicated in the previous sections in mind, we decided to undergo a kinetico-mechanistic study of the cyclometallation reaction of a variety of the dinuclear acetate bridge coordination compounds (1R)2 in solution. Given the previous experience of our group in the cyclometallation processes monitored on this type of complexes,41 the study of the (1R)2 → (2R)2 reaction has been carried out at varying temperatures and pressures, and in toluene and acetic acid as solvents. Time resolved UV-Vis spectra indicated the presence of more than a single step in the full process. In the more innocent medium toluene, the spectral monitoring features a fast set of small intensity changes followed by a much slower step; the latter showing the characteristic very large increase in absorbance associated with the C–H bond activation reaction (Fig. 2a). These two steps are followed by much slower changes that could not be time-resolved reproducibly under these conditions. Table 2 shows the relevant temperature and pressure trends of the data collected for the mentioned two timeresolved processes for (1R)2 compounds; for compounds (1F)2 and (1CF3)2 only the relevant C–H bond activation reaction has been monitored (see below). Fig. 2b presents some examples of the temperature and pressure dependence of the reactions observed.

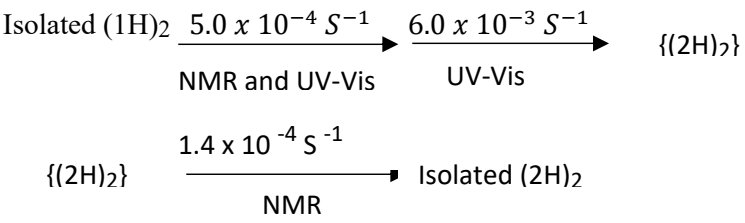
In order to ascertain the nature of the steps monitored via UV-Vis, a parallel monitoring of the 1H and 19F (where relevant) NMR spectra of a sample of compounds (1H)2, (1F)2 and (1CF3)2 in toluene at 70 °C was conducted (Fig. 3a). In all cases, the rate constant derived from the exponential decrease of the signals, corresponding to the coordination compounds (1R)2, is in excellent agreement with that extrapolated for the slow process (the one having the spectral characteristics of an C–H bond activation) quantified by UV-Vis spectroscopy.

Nevertheless, the NMR signals corresponding to the cyclometallated amine show a two-step trend, the first corresponding to the measured cyclometallation reaction indicated above (Fig. 3b), while the second has to be related to the very slow step that has not been quantified via UV-Vis spectroscopy. Although only the complex produced after this much slower process corresponds to the isolated final cyclopalladated species (2R)2, the product of the first step corresponds to the full metallation of the two amine ligands in (1R)2. This is supported by the reaction with pyridine of the reaction mixture obtained just after the completion of this step (formation of compounds 3R, see before and Scheme 1) where no evidences of non-cyclometallated coordination compounds are detected.51,52 Obviously, the first reaction step measured by NMR spectroscopy corresponds to the formation of the initial {(2R2)} cyclometallated compound (thus involving the proper C–H bond activation). A reorganization process of the isolated final (2R)2 complex is responsible for the second, slower, reaction observed by NMR and not quantified by UV-Vis. It seems clear that the cyclometallation process occurs neatly as

the quantified first slow step determined by UV-Vis spectral monitoring indicated in Table 2. As for the faster reaction occurring for all the complexes, and measured by UV-Vis for (1H)2 and (1Cl)2 (Table 2), it has to be related either to an isomerization reaction on the starting coordination complexes (highly improbable given the fact that it would occur after the long standing thermodynamic equilibration preparative procedures), or to a fast process following the quantified cyclopalladation reaction.

Finally, it is interesting to note that in all cases the thermal and pressure activation data measured for the metalation reaction of (1R)2 compounds are the same as those determined for the one-pot reaction of palladium acetate plus amine ligand under stoichiometric conditions (see data in Table 2 and Fig. S1†), despite the sluggishness of the latter reactions. It is thus clear that the rate determining process is the same for both starting materials. That is, the full preparative reaction leading to the cyclometallated complex can be associated with the sequence exemplified in eqn (1) for (1H)2, where {(2R2)} corresponds to a different form of the bis-cylometallated final compound (2H)2 isolated (see previous sections).

At 70 °C, toluene solution



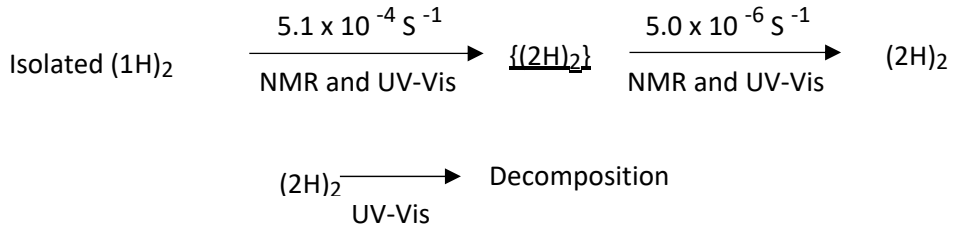
(1)

For the same (1R)2 cyclometallation reaction carried out using acetic acid as the solvent, UV-Vis monitoring also indicated the operation of a multistep process. The sequence can be readily separated into two distinct blocks; in Fig. 4 these are shown as an example for (1Cl)2. After a fast first step occurring in the 2 h time scale at room temperature, a set of two slower steps takes place in the same time scale at 65 °C. Only the first two steps of the full three-step sequence gave reproducible and reliable results on repeated monitoring; the slowest step being associated with the polymerisation reactions observed for these types of compounds in acetic acid medium.39 As can be seen in Fig. 4a, the first step of the sequence has the expected fairly large spectral changes associated with the C–H bond activation leading to cyclometallated compounds. This fact was, as for the toluene solution runs, confirmed via 1H NMR time-resolved monitoring in d4-acetic acid solution of the reaction mixture, followed by reaction with pyridine of the relevant reaction mixtures (see previous sections). Table 3 collects the relevant kinetic and thermal and pressure activation parameters data obtained in the usual way; again for complexes (1F)2 and (1CF3)2 only the above mentioned metallation step has been quantified.

Accordingly in this solution medium the cyclometallation process occurs readily as a fast (relative to the equivalent reactions in toluene solution) observed step on the coordination compounds of type (1R)2 dissolved in acetic acid. The existence of a faster consecutive step than that detected in toluene solutions cannot be discarded; the increased reactivity observed in this solvent (ca. 50–90 fold extrapolated from Table 2 data) should make the detection of a reaction not involving large spectral changes difficult. Similarly to the reactions carried out in toluene solution, the 1H NMR spectrum of an acetic acid solution of a true sample of the stable compound (2H)2 does not agree with that obtained after the first fast step characterised by the 5.1 × 10−4 s−1 rate constant at 27 °C; only the complex produced after the process characterised by the 5.0 × 10−6 s−1 rate constant (slow process, Table 3) corresponds to the isolated final cyclopalladated species (2H)2. That is the full preparative

reaction producing complex (2H)2 in acetic acid solution corresponds to the sequence indicated in eqn (2), fully equivalent to that occurring in toluene solution at a different time-scale.

At 27 °C, acetic acid solution



It is interesting to note that the metallation reaction kinetic and thermal and pressure activation data measured for the reaction of (1R)2 compounds are very different from those determined for the reactions occurring for the one-pot reaction of palladium acetate plus amine (R = H, Cl) ligand under stoichiometric conditions (see data in Table 3). Even the processes with the R = F and R = CF3 amines is not observed under the kinetic monitoring reaction conditions. Clearly the palladation reactions of compounds (1R)2 do not parallel those in the onepot preparative procedures.

Discussion

As a starting point, and in view of the kinetic results collected, as well as the non-detection in the characterisation procedures of any intermediate species having a single cyclometallated amine (i.e. (1R;2R), Scheme 3), important mechanistic implications have to be considered. From a kinetic perspective, although the operation of statistical kinetics[76,77] would produce a one-step reaction, as that observed, with kobs = 2 × kcyclometallation, the independent behaviour of the two palladium centres in complexes of type (1R)2 is somehow unexpected. Even so, if such an independence of the two metal centres exists, the complexes of type (1R;2R) indicated in Scheme 3 should be detected in the reaction medium during cyclopalladation. This is clearly not the case, as indicated in the preparative section and exemplified in Fig. 3 for R = H, where only bis-coordination and bis-metallated dimeric compounds, (1R)2, {$(2R)_2$}and (2R)2, are evident. The kinetic data, thus, demand the existence of a slow + fast reaction sequence producing compounds of type (1R;2R) as an undetectable intermediate due to its small build up. Under these conditions the fast reaction observed by UV-Vis monitoring of the metalation of compounds (1R)2 in toluene solution (see Table 2) might be tentatively attributed to such a (1R;2R) → {$(2R)_2$}relatively fast process. The behaviour in acetic acid solution can be anticipated to be parallel, nevertheless, the faster nature of the reactions observed should make the kinetic detection of the fast (1R;2R) → {$(2R)_2$} process even more difficult as indicated. Similar cooperative behaviours have already been observed by us in other organometallic reactions.[78,79] The fact that the cyclometallation reaction is also observed to occur readily in the solid state (see Table 1) seems to agree with this highly synergetic effect. The thermal and pressure activation parameters that have been tentatively measured for these initial reactions for R = H and Cl (see Table 2) fall within the range expected for this type of cyclopalladation processes.[41]

In this respect, comparison between one-pot and the (1R)2 → {$(2R)_2$} cyclometallation reactions in toluene indicates that the rate determining process is the same within error (see Table 2). The process thus follows the already well-established ambiphilic concerted metallation deprotonation mechanism, where a coordinated acetato ligand serves as the proton depository for the activated C–H bond once its agostic coordination to the PdII centre has occurred (Scheme 4, left). The thermal and pressure activation data agree with such a highly ordered compressed transition state.[45,52] From the data collected in Table 3 it is also clear that the acceleration observed for cyclopalladation reactions of some imine ligands in acetic acid[35,41] also applies in the present process involving compounds of type (1R)2. While the pressure activation parameters indicated in Table 3 clearly show a trend to less negative values than those indicated in Table 2, the values determined for ΔH‡ and ΔS‡ do not show any definite trend with respect to the data in toluene solution, except being in a relatively smaller margin. This effect has already been reported in similar reactions, where the use of acetic acid as solvents seemed to buffer the differences between substrates in innocent solvents. [80] The definite acceleration expected from the ambiphilic nature of the operating mechanism (i.e. the partial presence of acetic acid ligands in the coordination sphere of the PdII centre)[35,41,45] facilitates its exit after the abstraction of the proton from the activating C–H bond, thus accelerating the new Pd–C bond formation (Scheme 4, right).[35,41,47] In this respect, the trend of the values of k collected in Table 3 for the reactions in acetic acid as the solvent is fully paralleled by that seen in the solid-state (Table 1), thus indicating the similarity of the reaction medium, once a molecule of acetic acid is produced per C–H activated bond in the solid. Similar hydrogen bonded retention of leaving acetic acid molecules has already been reported in other solid state reactivity.[81]

Despite this fact, for the reactions carried out by one-pot procedures in acetic acid as the solvent the behaviour is not clear and/or evident (see Table 3). While the reactions of (1H)2 and (1Cl)2, despite taking place, show smaller reaction rates with respect to toluene solution, for the (1F)2 and (1CF3)2

the process is not even reproducible. A plausible explanation is that the presence of the amine in its protonated form (i.e. RBzNH3 +) in such a medium should prevent its precoordination, as observed in similar recently studied systems on aminoacid cylopalladation.51,52 The difference is remarkable in comparison with the reactions occurring on Schiff base derivatives where the acceleration in acidic medium is observed even in the one-pot processes;35,38,41,47 probably the basicity of the directing N-donor group is responsible for these changes.

In this respect the kinetic study of the one-pot cyclometallation reactions of the secondary, BzNMeH, and tertiary, BzNMe2, amines was carried out for comparison purposes. In toluene solution the C–H bond activation reaction occurs readily with kinetic and activation parameters within the range obtained for the primary BzNH2 parent amine.82 The greater the donor capability of the amine nitrogen, the faster the C–H bond activation reaction proceeds, as expected for the facilitated exit of the more weakly bound acetato proton abstractor (Scheme 4; left). This effect, also detected in the solid state reactivity indicated in Table 1 by a parallel trend between reaction times and σp Hammet constants, has been reported recently for the metalation of aminoacid derivatives.52 Surprisingly, though, in acetic acid solution metallation of the more basic tertiary amine is not observed,83–85 and the C–H bond activation for the secondary BzNMeH is only slightly accelerated from the parent BzNH2 (see Table 2).86 This is clearly indicative of the importance of the nitrogen basicity in the one-pot process where amine coordination must take place for C–H bond activation, and this process is hampered by possible protonation equilibria.

Conclusions

The cyclopalladation processes of the primary amine compounds shown in Scheme 1 have been studied from a kineticomechanistic perspective, via UV-Vis and NMR spectroscopies. In all cases the actuation of the established concerted ambiphilic proton abstraction by a coordinated acetato ligand has been proved. Even the acceleration of the reaction in acetic acid solution has been observed as a distinct proof of the mechanism. In all cases the donor character of the amine nitrogen represents the key factor for the process, as does the exit of the abstracting acetato ligand, in good agreement with the data collected in solid-state. In this respect the easy metalation of secondary and tertiary amines is thus explained.

The metallation of the dimeric starting complexes has been shown to occur in a cooperative manner, with the metalation of the first palladium unit being rate determining; no intermediate mono-metallated compounds are observed in any of the processes. The kinetically favoured compound obtained after complete C–H bond activation does not correspond to the final isolated complexes, and an intermediate bis-cyclopalladated complex is found for all the reactions. This species, bearing the classic open-book dimeric form, has a much more complex structure than the final isolated compound, with different types of acetato ligands.

Experimental

General

Microanalyses were performed at the Serveis Cientifico-Tècnics (Universitat de Barcelona). Electrospray mass spectra were performed at the Servei d'Espectrometria de Masses (Universitat de Barcelona) using a LC/MSD-TOF spectrometer using H2O–CH3CN 1 : 1 to introduce the sample. Routine spectra were recorded at the Unitat de RMN d'Alt Camp de la Universitat de Barcelona using a Mercury-400 spectrometer and referenced to SiMe4; two dimension NOE and HSQC NMR spectra were recorded at the same Unitat de RMN d'Alt Camp de la Universitat de Barcelona using a Bruker-500 spectrometer. δ values are given in ppm and J values in Hz. Abbreviations used: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad. For the in situ time resolved monitored NMR spectra in d8-toluene or d4-acetic acid a 600 MHz Bruker instrument was used at the ICIQ (Institut Català d'Investigació Química).

Compounds

Commercial chemicals were used throughout the processes without further purification. Compounds (1H)2, (1Cl)2 and (1F)2 were prepared according to literature methods;59 the corresponding cyclometallated derivatives (2H)2, (2Cl)2 and (2F)2 have also already been described.87 Characterization data agree with the published values. Chart 1 presents the numbering used for the 1H NMR characterisation data of all the compounds prepared.

(2H)2. 1H-NMR (400 MHz, CDCl3, δ/ppm): 2.09 (s, 3H, 7); 2.95 (br, 1H, 1); 3.17 (dt, 1H, J = 15 Hz, J = 6 Hz, 2); 3.55 (br, 1H, 1); 3.88 (dt, 1H, J = 15 Hz, J = 6 Hz, 2); 6.75 (d, 1H, J = 7.5 Hz, 3); 6.87 (d, 1H, J = 2.4 Hz, 6); 6.90–6.97 (m, 2H, 4–5). IR (KBr): ν¯sym (OCO): 1563 cm−1, ν¯asym (OCO): 1420 cm−1.

(2Cl)2: 1H-NMR (400 MHz, CDCl3, δ/ppm): 2.09 (s, 3H, 7); 2.95 (br, 1H, 1); 3.25 (dtd, 1H, J = 15 Hz, J = 6.5 Hz, J = 2 Hz, 2); 3.65 (br, 1H, 1); 3.90 (dtd, 1H, J = 15 Hz, J = 5.5 Hz, J = 2 Hz, 2); 6.69 (d, 1H, J = 8 Hz, 3); 6.80 (d, 1H, J = 2.4 Hz, 6); 6.96 (dd, 1H, J = 8 Hz, J = 2.4 Hz, 4). IR (KBr): ν¯sym (OCO): 1553 cm−1, ν¯asym (OCO): 1412 cm−1.

(2F)2: 1H-NMR (400 MHz, CDCl3, δ/ppm): 2.09 (s, 3H, 7); 2.95 (br, 1H, 1); 3.25 (m, 1H, 2); 3.52 (br, 1H, 1); 3.90 (m, 1H, 2); 6.69 (dd, 1H, J = 8 Hz, J = 2.4, 6); 6.80 (m, 2H, 3, 4). IR (KBr): ν¯sym (OCO): 1561 cm−1, ν¯asym (OCO): 1419 cm−1. The new R = CF3 amine derivatives (Scheme 1) were prepared by the following procedures:

0CF3: 692 mg (4 mmol) of amine p-CF3C6H4CH2NH2 were added to a suspension of palladium acetate (448 mg, 2 mmol) in 20 mL of acetone. The mixture was stirred at room temperature for 2 h, and the pale yellow solid obtained was filtered, washed with ether and air dried to afford the complex [Pd-(AcO)2(p-CF3C6H4CH2NH2)2] in 70% yield (800 mg). 1H-NMR (400 MHz, CDCl3, δ/ppm): 1.85 (s, 3H, 8); 3.78 (t, 2H J = 8 Hz, 1); 4.41 (br, 2H, 2); 7.52 (d, 2H, J = 8.1 Hz, 3); 7.63 (d, 2H, J = 8.1 Hz, 4). Elemental analysis for C20H22F6N2O4Pd: C: 41.7% (calc. 41.79); H: 3.9% (calc. 3.80); N: 5.0% (calc. 4.91). IR (KBr): ν¯sym (OCO): 1566 cm−1, ν¯asym (OCO): 1327 cm−1.

(1CF3)2: 194 mg (0.86 mmol) of palladium acetate were added to a suspension of [Pd(AcO)2(p-CF3C6H4CH2NH2)2], 0CF3, (496 mg, 0.86 mmol) in 25 mL of dichloromethane. The mixture was stirred at room temperature for 24 h and filtered. The solvent was removed under vacuum, and the solid obtained was recrystallized in ether to afford (1CF3)2 in 80% yield (550 mg). 1H-NMR (400 MHz, CDCl3, δ/ppm): 1.87 (s, 3H, 7); 1.89 (s, 3H, 8); 3.63 (m, 1H, 2); 3.78 (m, 1H, 2); 4.21 (br, 1H,

1); 5.55 (br, 1H, 1); 7.68 (s, 4H, 3, 4). Elemental analysis for C24H28F6N2O8Pd2: C: 35.9% (calc. 36.06); H: 3.5% (calc. 3.53); N: 3.7% (calc. 3.50). IR (KBr): ν¯sym (OCO mono- and bidendate): 1580 cm−1, ν¯asym (OCO bidentate): 1422 cm−1, ν¯asym (OCO monodentate): 1326 cm−1.

(2CF3)2: A mixture of 173 mg (1 mmol) of p-trifluoromethylbenzylamine and 224 mg (1 mmol) of palladium acetate was stirred for 5 h at 85 °C in 10 mL of toluene. The yellow solid obtained was filtered, washed with ether and air dried to afford complex (2CF3)2 in 70% yield (240 mg). 1H-NMR (400 MHz, CDCl3, δ/ppm): 2.11 (s, 3H, 7); 2.87 (br, 1H, 1); 3.22 (br, 1H, 2); 3.57 (br, 1H, 1); 3.95 (br, 1H, 2); 6.87 (d, 1H, J = 8.1 Hz, 3); 7.13 (s, 1H, 6); 7.19 (d, 1H, J = 8.1 Hz, 4).

Intermediate {(2R)$_2$} bis-cyclometallated dinuclear complexes were characterised from the 1H NMR spectra of crude reaction mixtures of metallating (1R)2 complexes. 13C-{1H} and a HSQC characterisation has also been conducted for {(2Cl)2} as an example.

{(2H)$_2$}: 1H-NMR (400 MHz, CDCl3, δ/ppm): 1.88 (s, 3H, 7); 1.92 (s, 3H, 7); 2.10 (s, 3H, 7); 2.95 (br, 2H, 1); 3.40 (m, 2H, 2); 4.30 (m, 2H, 2); 6.60 (br, 2H, 1); 6.62 (d, 2H, J = 7.5 Hz, aromatic); 6.82 (t, 2H, J = 7.5 Hz, aromatic); 6.85 (m, 4H, aromatic).

{(2Cl)$_2$}: 1H-NMR (400 MHz, CDCl3, δ/ppm): 1.97 (s, 3H, 7); 2.05 (s, 3H, 7); 2.10 (s, 3H, 7); 2.95 (br, 2H, 1); 3.40 (m, 2H, 2); 4.30 (m, 2H, 2); 6.55 (d, 2H, J = 2.0 Hz, 6); 6.60 (br, 2H, 1); 6.87 (d, 2H, J = 7.5 Hz, 3); 6.95 (dd, 2H, J = 7.5 Hz, J = 2.0 Hz, 4). 13C-{1H}-NMR (101 MHz, CDCl3, δ/ppm): 20.3 (CH3COO), 23.4 (CH3COO), 23.8 (CH3COO), 47.6 (CH2N), 122.0 (C3), 124.7(C4), 130.1 (C6), 134.8 (C-quaternary), 150.7 (C-quaternary).

{(2F)$_2$}:: 1H-NMR (400 MHz, CDCl3, δ/ppm): 1.87 (s, 3H, 7); 1.92 (s, 3H, 7); 2.12 (s, 3H, 7); 2.95 (br, 2H, 1); 3.40 (m, 2H, 2); 4.30 (m, 2H, 2); 6.30 (dd, 2H, J = 8.9 Hz, J = 2.6 Hz, 6); 6.55 (br, 2H, 1); 6.70 (m, 2H, 4); 6.90 (dd, 2H, J = 8.9 Hz, J = 5.6 Hz, 3).

{(2CF$_3$)}: 1H-NMR (400 MHz, CDCl3, δ/ppm): 1.95 (s, 3H, 7); 2.05 (s, 3H, 7); 2.10 (s, 3H, 7); 2.95 (br, 2H, 1); 3.40 (m, 2H, 2); 4.40 (m, 2H, 2); 6.60 (br, 2H, 1); 6.85 (s, 2H, 6); 7.10 (d, 2H, J = 7.5 Hz, aromatic); 7.20 (partially overlapped with residual peak solvent, aromatic).

All the d5-pyridine derivatives, 3R, were prepared by the addition of few drops of d5-pyridine to dinuclear bis-cyclopalladated compounds.

(3H): 1H-NMR (400 MHz, CDCl3, δ/ppm): 1.93 (s, 3H, 7); 2.95 (br, 1H, 1); 4.25 (m, 1H, J = 15 Hz, J = 6 Hz, 2); 4.95 (br, 1H, 1); 6.25 (d, 1H, J = 7.5 Hz, 6); 6.75 (m, 1H, J = 7.5 Hz, 5); 6.96 (m, 2H, 4, 3).

(3Cl): 1H-NMR (400 MHz, CDCl3, δ/ppm): 1.93 (s, 3H, 7); 4.14 (t, 2H, J = 7.5, 2), 5.10 (br, 2H, 1); 6.20 (d, 1H, J = 2.6, 6); 6.65 (d, 1H, J = 7.5 Hz, 3); 6.95 (dd, 1H, J = 7.5 Hz, J = 2.5, 4). (3F): 1H-NMR (400 MHz, CDCl3, δ/ppm): 1.93 (s, 3H, 7); 4.14 (t, 2H, J = 7.5, 2), 5.00 (br, 2H, 1); 5.90 (dd, 1H, J = 9.2 Hz, J = 2.6, 6); 6.65 (td, 1H, J = 9.2 Hz, J = 2.6, 4); 6.95 (dd, 1H, J = 9.2 Hz, J = 6.3, 3).

(3CF3): 1H-NMR (400 MHz, CDCl3, δ/ppm): 1.95 (s, 3H, 7); 4.14 (t, 1H, J = 7.5, 2); 5.20 (br, 2H, 1); 6.47 (s, 1H, 6); 6.99 (d, 1H, J = 7.9 Hz, 4); 7.15 (d, 1H, J = 7.9 Hz, 3). IR (KBr): ν¯sym (OCO): 1552 cm−1, ν¯asym (OCO): 1422 cm−1.

X-Ray structure determination

Yellow prism-like specimens of C18H20F2N2O4Pd (ca. 0.088 × 0.117 × 0.258 mm) and of C20H20F6N2O4Pd2 were used for the XRD analysis. Intensity data were measured on a D8 Venture system equipped with a multilayer monochromator and a Mo microfocus (λ = 0.71073 Å). Frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. Data were

corrected for absorption effects using the multi-scan method (SADABS), and the structure was solved and refined using the Bruker SHELXTL Software Package. Table 4 collects the relevant XRD parameters for the structures.

Kinetics

The kinetic profiles for the reactions were followed by UV-Vis spectroscopy in the 700–300 nm range on HP8452A or Cary50 instruments equipped with thermostated multicell transports. Observed rate constants were derived from absorbance versus time traces at the wavelengths where a maximum increase and/or decrease of absorbance were observed. For the reactions carried out at varying pressure the previously described pillbox cell and pressurising system36,88–90 were used and final treatment of data was the same as described before. The calculation of the observed rate constants from the absorbance versus time monitoring of reactions, studied under second or first order concentration conditions, was carried out using the SPECFIT software.91 The monitored reaction solutions were made up directly by dissolving compounds (1R)2 in the desired solvent or by mixing the correct amounts of palladium acetate and the desired amine in a 0.8–1.2 stoichiometric ratio; the general kinetic technique is that previously described.47,92,93 The sluggishness of some of the reactions studied has obliged us to measure an increased number of repeats (3–5) in order to obtain a more reliable average of the value that has been used. Tables S1 and S2† collect all the obtained kobs values for the systems studied as a function of the starting complex, process studied, and temperature. All post-run fittings were carried out by the standard available commercial programs.

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Legends to figures

Figure 1. Molecular drawing of the new: (a) (2F)2 compound; selected bond distances (Å) and angles (°): Pd(1)–C(1) = 1.951(3), Pd(1)–N(1) = 2.034(3), Pd(1)–O(1) = 2.148(2), Pd(1)–O(2) = 2.0459(19), N(1)–C(7) = 1.484(5), C(1)–Pd(1)–N(1) = 81.80(12), C(1)–Pd(1)–O(2) = 92.75(10), N(1)–Pd(1)–O(1) = 92.73(11), O(2)–Pd(1)–O(1) = 92.45(9). (b) (2CF3)2 compound; selected bond distances (Å) and angles (°): Pd(1)–C(3) = 1.957(6), Pd(1)–N(1) = 2.053(5), Pd(1)–O(4) = 2.162(4), Pd(1)–O(2) = 2.053(4), N(1)–C(7) = 1.473(8), C(3)–Pd(1)–N(1) = 82.8(2), C(3)–Pd(1)–O(2) = 92.3(2), N(1)–Pd(1)–O(4) = 93.74(18), O(2)–Pd(1)–O(1) = 91.10(16).

Figure 2. (a) Time monitoring of the changes observed in the UV-Vis spectrum of a 4 × 10−4 M toluene solution of (1Cl)2 at 80 °C (inset corresponds to the changes at 310 nm). (b) Eyring and ln k versus P plots for the two processes observed on spontaneous reaction of a 4 × 10−4 M toluene solution of (1H)2.

Figure 3. (a) Changes with time of the NMR proton spectrum for the spontaneous reaction of (1H)2 to produce (2H)2 in toluene solution at 70 °C. Signals in the 7.29–7.39 ppm zone correspond to coordinated BzNH2, while those shifted to higher fields correspond to cyclometallated compounds. (b) Changes with time of the intensity of the signals corresponding to the coordinated (o, 7.33 ppm) or cyclometallated (Δ, 6.63 ppm) BzNH2 amine in the spontaneous (1H)2 to (2H)2 reaction in toluene at 70 °C.

Figure 4. (a) Time monitoring of the changes observed in the UV-Vis spectrum of a 4 × 10−4 M acetic acid solution of (1Cl)2 at 35 °C (inset corresponds to the changes at 310 nm). (b) Slow step block for the same process at 65 °C (inset corresponds to the changes at 395 nm).

692 **Table 1** Yield of C–H bond activated compounds (evaluated as 3R) obtained from (1R)2 at 70 °C in
693 solid state, para and meta Hammet parameters are also included for the R substituents on the
694 metalating amines

Reaction time→			2 h	4 h	6 h
R amine substituent	σ_p	σ_m	Cyclopalladated species (measured as **3R**)/%		
H	0	0	70	85	90
F	0.15	0.34	40	50	65
Cl	0.25	0.27	20	30	45
CF_3	0.54	0.43	10	12	15

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698 **Table 2** Kinetic and thermal and pressure activation parameters for the two quantified processes
699 observed on spontaneous reaction of compound of type (1R)2 in toluene solution. The values
700 determined directly from a mixture of palladium acetate and the corresponding amines are also
701 included for comparison purposes

Compound	Reaction	$10^4 \times {}^{323}k_{calc}/s^{-1}$	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	$\Delta V^{\ddagger}$(T)/cm^3 mol^{-1}(K)
$(\mathbf{1H})_2$	k_{fast}	8.9	86 ± 4	−40 ± 12	−27 ± 2 (315)
	k_{slow}	1.2	67 ± 3	−116 ± 9	−16 ± 2 (343)
$Pd(AcO)_2 + BzNH_2$	Single process[a]	1.4	73	−91	−16
$(\mathbf{1Cl})_2$	k_{fast}	13	67 ± 3	−96 ± 8	Not measured[b]
	k_{slow}	0.58	95 ± 8	−35 ± 24	−20 ± 4 (338)
$Pd(AcO)_2 + ClBzNH_2$	Single process	0.21	97 ± 2	−36 ± 6	−11 ± 2 (338)
$(\mathbf{1F})_2$	$k_{slow\ (metallation)}$	0.13	83 ± 5	−79 ± 16	Not measured[c]
$Pd(AcO)_2 + FBzNH_2$	Single process	0.25	91 ± 12	−60 ± 32	−9 ± 1 (348)
$(\mathbf{1CF_3})_2$	$k_{slow\ (metallation)}$	0.20	86 ± 14	−72 ± 42	Not measured[c]
$Pd(AcO)_2 + CF_3BzNH_2$	Single process	0.15	111 ± 12	3 ± 34	−16 ± 1 (348)

[a] From ref. 39. [b] UV-Vis spectral changes too small for reliable determination. [c] Data equivalent to that of the mixture of palladium acetate and amine (see text).

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705 **Table 3** Kinetic and thermal and pressure activation parameters for the two quantified processes
706 observed on spontaneous reaction of compound of type (1R)2 in acetic acid solution. The values
707 determined directly from a mixture of palladium acetate and the corresponding amines are also
708 included for comparison purposes

Compound	Reaction	$10^4 \times {}^{300}k_{calc}/s^{-1}$	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	$\Delta V^{\ddagger}$(T)/cm^3 mol^{-1} (K)
$(\mathbf{1H})_2$	k_{fast}	5.1	79 ± 3	−47 ± 10	−9 ± 2 (298)
	k_{slow}	0.050	109 ± 6	14 ± 17	14 ± 2 (328)
$Pd(AcO)_2 + BzNH_2$	Single process[a]	0.50	100	3	−11
$(\mathbf{1Cl})_2$	k_{fast}	1.5	83 ± 8	−44 ± 25	−6 ± 3 (338)
	k_{slow}	0.070	109 ± 4	17 ± 11	Not measured[b]
$Pd(AcO)_2 + ClBzNH_2$	Single process	0.02	99 ± 7	−26 ± 20	−15 ± 1 (338)
$(\mathbf{1F})_2$	$k_{fast\ (metallation)}$	3.2	55 ± 3	−131 ± 11	−5 ± 1 (308)
$Pd(AcO)_2 + FBzNH_2$			Sluggish reaction		
$(\mathbf{1CF_3})_2$	$k_{fast\ (metallation)}$	0.75	91 ± 5	−23 ± 15	~0 (308)
$Pd(AcO)_2 + CF_3BzNH_2$			Sluggish reaction		

709 [a] From ref. 39. [b] UV-Vis spectral changes too small for reliable determination.

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712 **Table 4** Crystal data and structure refinement for complexes (2F)2 and (2CF3)2

Empirical formula	$C_{18}H_{20}F_2N_2O_4Pd_2$; $(2F)_2$	$C_{20}H_{20}F_6N_2O_4Pd_2$; $(2CF_3)_2$
Formula weight	579.1	679.18
Temperature	100(2) K	100(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Orthorhombic
Space group	*C*2/*c*	*P*212121
Unit cell dimensions	a = 19.3777(18) Å α = 90°	a = 9.8749(10) Å α = 90°
	b = 8.1701(9) Å β = 116.645(3)°	b = 11.7989(11) Å β = 90°
	c = 13.6078(12) Å γ = 90°	c = 19.907(2) Å γ = 90°
Volume	1925.6(3) $Å^3$	2319.5(4) $Å^3$
Z	4	4
Density (calculated)	1.998 mg m^{-3}	1.945 mg m^{-3}
Absorption coefficient	1.914 mm^{-1}	1.628 mm^{-1}
F(000)	1136	1328
Crystal size	0.088H0.117H0.258 mm	0.067H0.097H0.207 mm
θ range for data collection	2.352–30.564°.	2.302–28.321°.
Index ranges	$-27 \le h \le 27, -11 \le k \le 11, -19 \le l \le 19$	$13 \le h \le 12, -14 \le k \le 15, -26 \le l \le 26$
Reflections collected	25 530	21 207
Independent reflections	2950 [*R*(int) = 0.0587]	5747 [*R*(int) = 0.0508]
Completeness to θ = 25.242 °	99.9%	99.7%
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.7461 and 0.6591	0.7457 and 0.6356
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2950/0/134	5747/0/309
Goodness-of-fit on F^2	1.069	1.071
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0336, wR_2 = 0.0561	R_1 = 0.0354, wR_2 = 0.0549
R indices (all data)	R_1 = 0.0620, wR_2 = 0.0624	R_1 = 0.0511, wR_2 = 0.0588
Extinction coefficient	n/a	n/a
Largest diff. peak and hole	0.976 and −0.667 e $Å^{-3}$	0.635 and −1.034 e $Å^{-3}$
CCDC code	993787	993639

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717 **Scheme 1**

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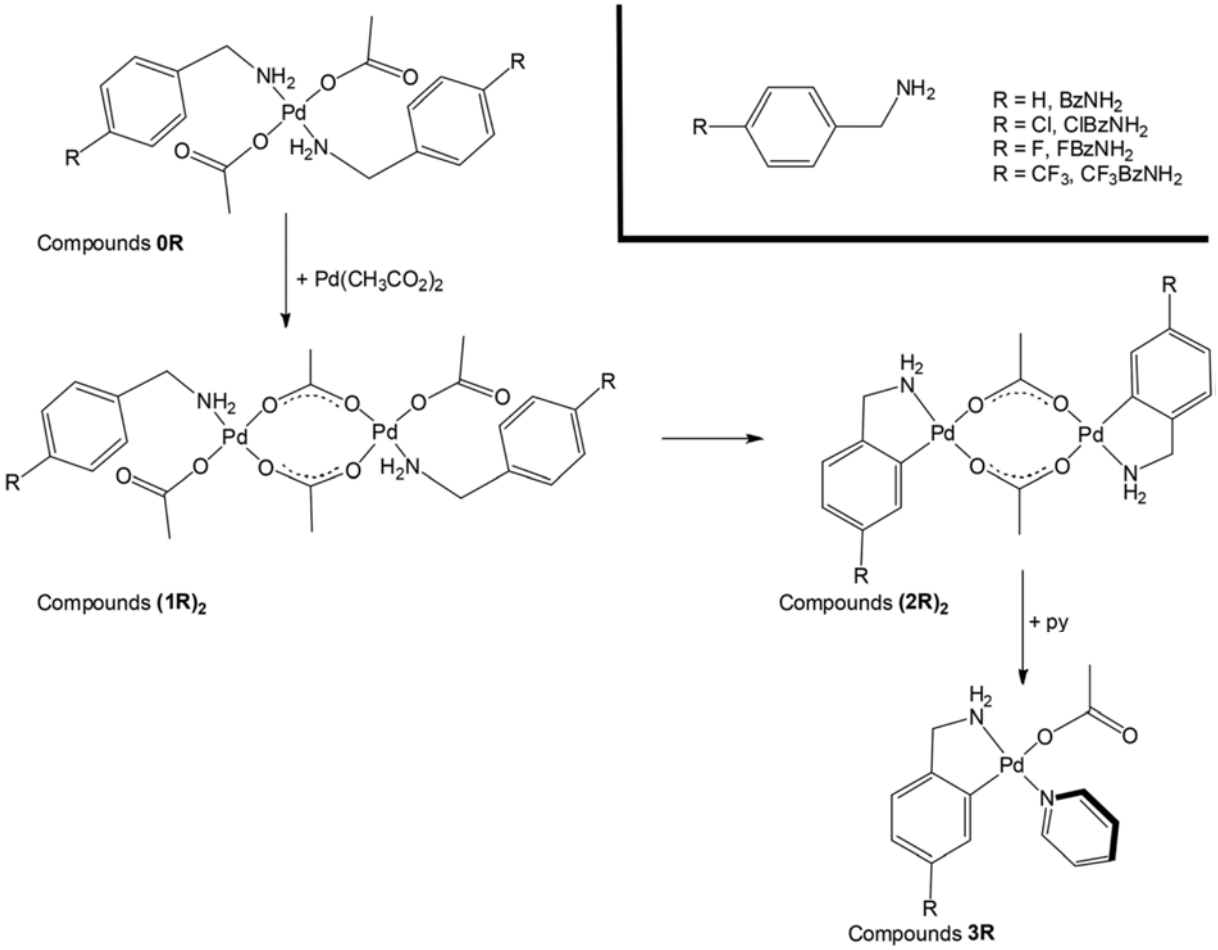

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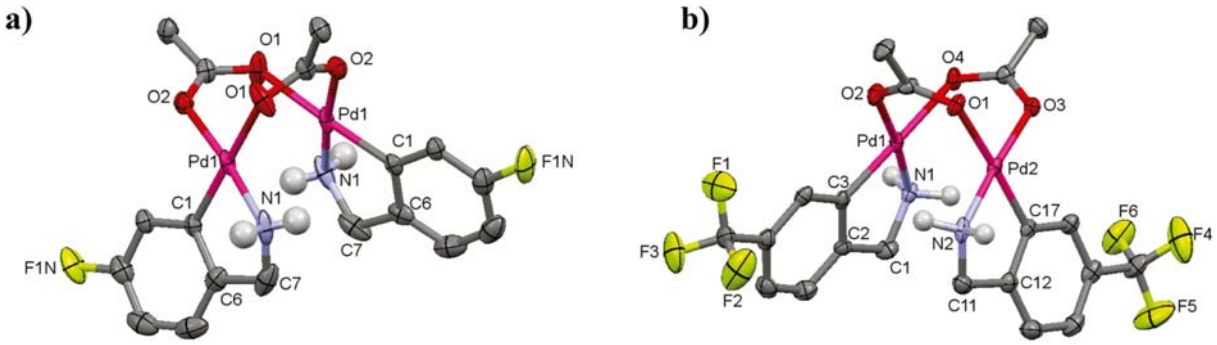
Figure 1


a)
O1
O2
O2
O1
Pd1
C1
F1N
Pd1
N1
N1
C1
C6
C7
F1N
C6
C7
b)
O4
O2
O1
O3
Pd1
F1
C3
N1
Pd2
C17
F6
F4
F3
C2
N2
C1
F2
C12
C11
F5

733 **Scheme 2**

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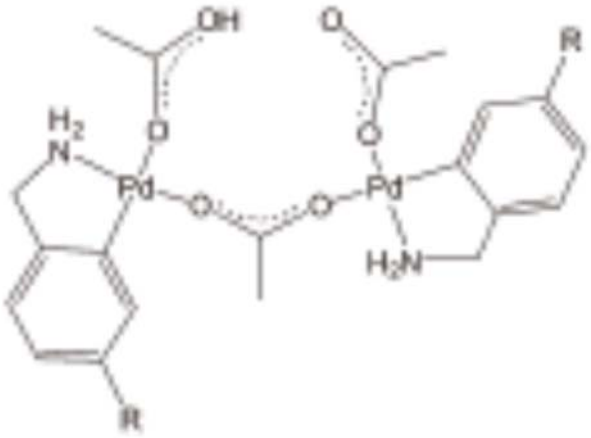

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742 **Figure 2**

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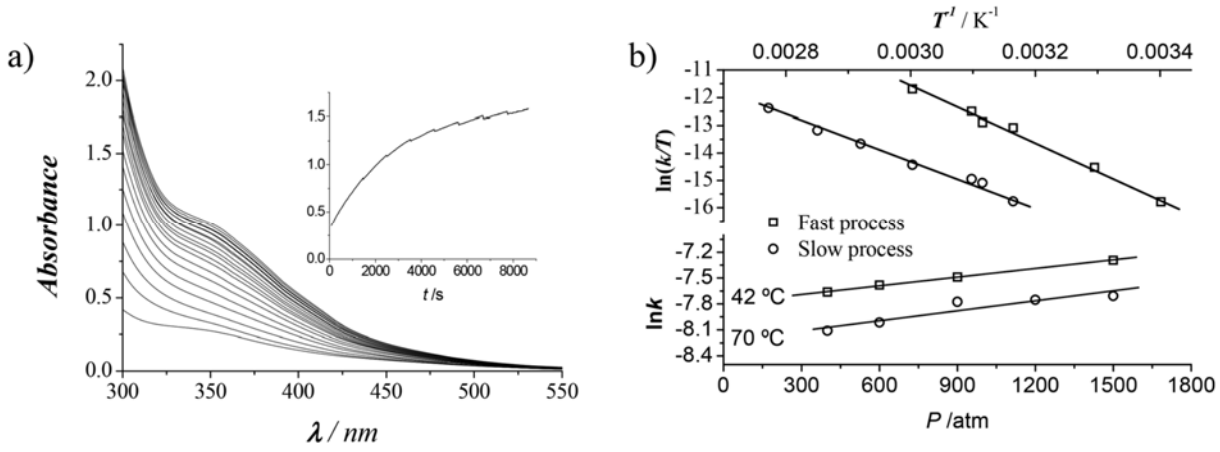

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750 **Figure 3**

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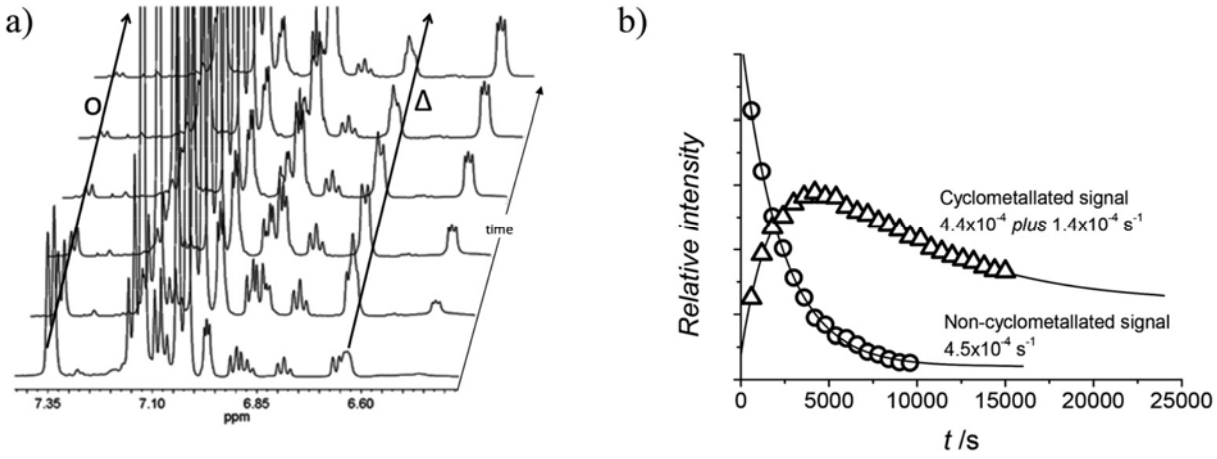

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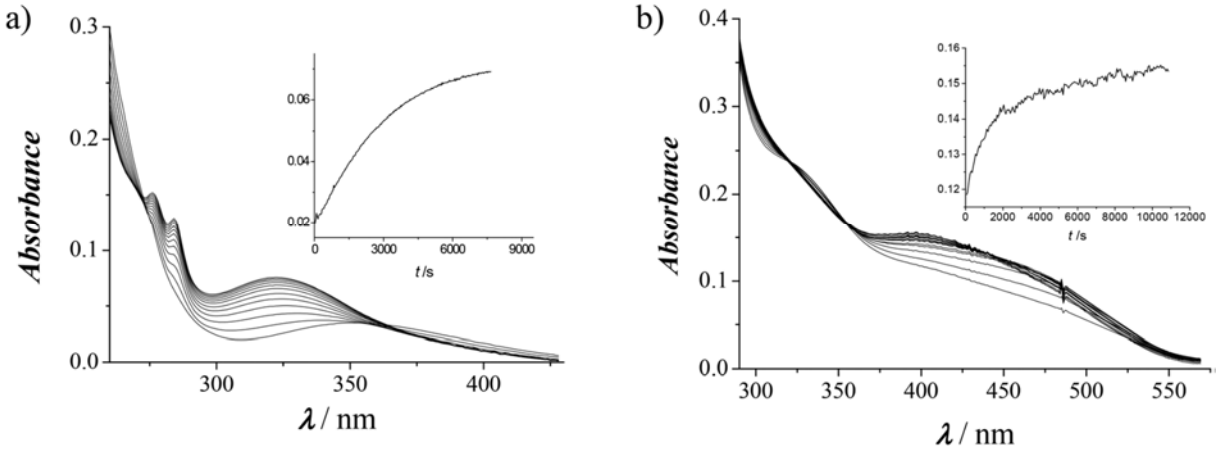
Figure 4



764 **Scheme 3**

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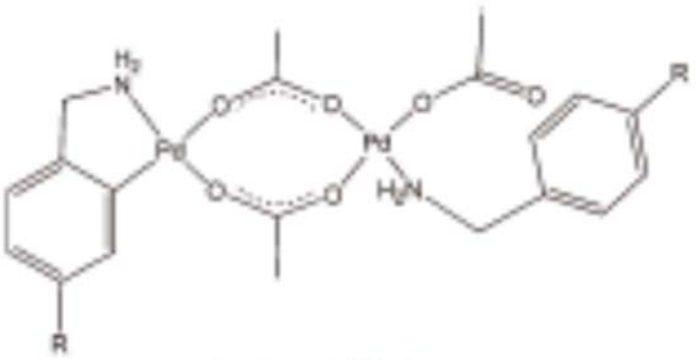

767 Compounds (1R:2R)

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772 **Scheme 4**

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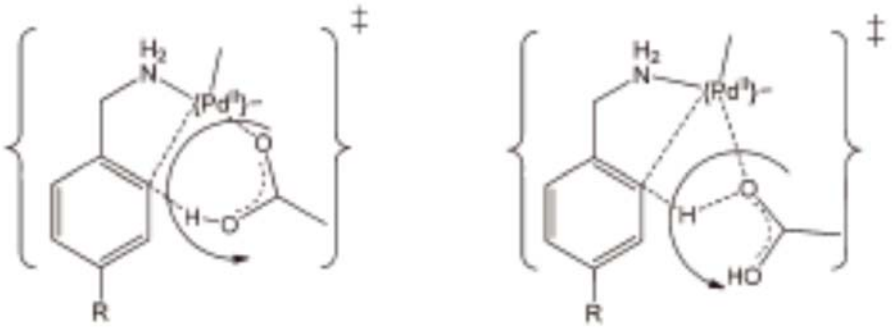

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779 **Chart 1**

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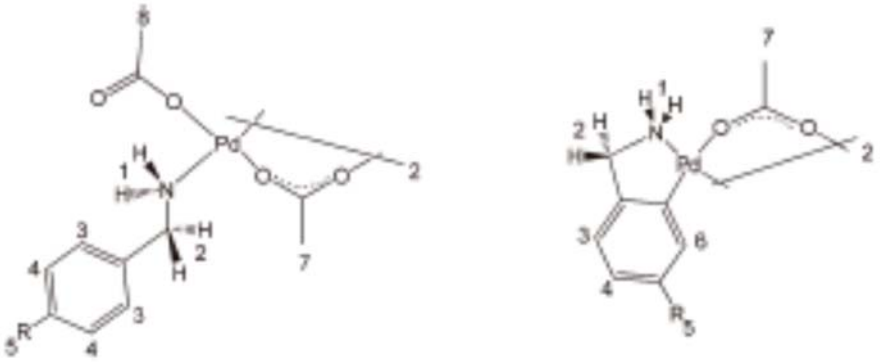

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