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Switchable cyclopalladation of substrates containing two directing groups: on the way to non-symmetrical [2.2]-dipalladaparacyclophanes†

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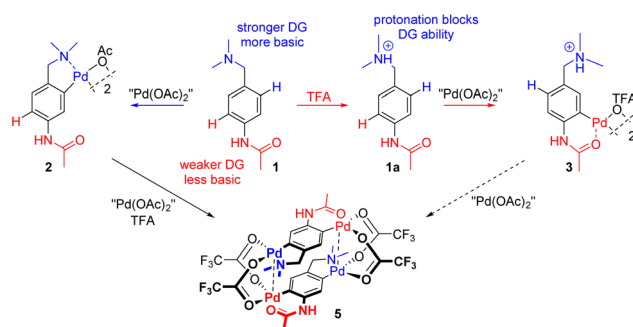
Simple switching of the site-selectivity of C–H activation reactions of substrates containing multiple directing groups is particularly important for the so-called late stage functionalization synthetic approach. In this work, we verified the possibility of achieving this by adding acids of different strengths. Using a substrate containing two differently strong (and basic) directing groups, the influence of the addition of acids on the regioselectivity of the C–H activation step of the reaction with palladium acetate was thoroughly studied. The addition of no or weak acids results in cyclopalladation being controlled by a stronger directing group. However, the addition of a strong acid causes protonation of this group and the reaction is then controlled by a weaker directing group. Finally, this approach enables double C–H activation leading to a unique class of compounds: “non-symmetrical” [2.2]-dipalladaparacyclophanes.

Introduction

Directing group (DG) assisted C–H activation is important not only in the synthesis of palladacycles¹ but also especially as a key step of the intensively studied C–H functionalization reactions.² During the past few decades, a number of DGs were introduced.³ Despite progress in this area, understanding and control of site-selectivity in complex substrates containing multiple DGs remains a challenge.⁴ The basic pillar for the prediction of regioselectivity is the determination of relative DG abilities. A few DG ability scales were introduced and their validity was verified on substrates containing two DGs.⁵ In simplicity, C–H activation is preferably assisted by a stronger DG. However, the possibility of controlling the reaction using a weaker DG can be very useful for purposes of organic synthesis, especially during the decoration of complex molecules in the late stages of their synthesis.⁶ Most probably the simplest and the most predictable way is based on changing the acid–base properties of the reaction mixture. This way, suggested *e.g.* by Sanford^{5b} or us⁷ and verified on one example

of C–H functionalization by Norrby *et al.*,^{5a} takes advantage of the fact that the stronger DG tends to be more basic.^{5b} Therefore, the addition of an acid to the reaction mixture causes its protonation and thus the loss of DG ability.⁸ This allows the weaker DG to direct the reaction (Scheme 1).

In addition, the occurrence of two different DGs offers an opportunity for gradual double C–H activation leading to unique “non-symmetrical” [2.2]-dipalladaparacyclophanes. Such doubly cyclopalladated compounds are known to be only “symmetrical”, *i.e.* containing two identical DGs, prepared by the reaction of substrates with two equivalents of palladium salts.⁹ In the case of substrates containing two different DGs, the reaction requires two steps (Scheme 1). The first stoichiometric C–H activation directed by a stronger DG is followed by



Scheme 1 General principle of site selectivity switch controlled by protonation of directing groups.

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the addition of a second equivalent of palladium acetate and a strong acid additive.

The aim of our study was to verify the viability of this approach for synthesizing (di)palladacycles and to examine the factors that influence the formation of individual regioisomers. By investigating these factors, we hope to enhance the understanding of DG-assisted C–H activation and contribute to the development of efficient synthetic strategies in organic chemistry.

Results and discussion

Protonation of substrates

We synthesized *N*-(4-((dimethylamino)methyl)phenyl) acetamide **1** as the model substrate, *i.e.* a substrate containing two DGs differing in DG abilities and basicity. The *N,N*-dimethylamino group is a stronger and more basic DG ($pK_a \approx 9$).¹⁰ Therefore, it is expected to direct C–H activation under 'neutral' conditions (without or with the addition of a weak acid). On the other hand, this group was protonated to give **1a** after the addition of a stronger acid (*e.g.* trifluoroacetic acid (TFA)) or a higher amount of a weaker acid to the reaction mixture. The successful protonation was documented by changes in the chemical shifts especially of CH_2 and $N(CH_3)_2$ to higher values (Fig. 1a and b) and above that in the case of addition of strong TFA by the splitting of signals of the CH_2 and $N(CH_3)_2$ groups in proton NMR (Fig. 1c). Thus, in more acidic media the weaker acetamido group ($pK_a \approx -4$) should direct cyclopalladation.

Cyclopalladation in the media without additional acids

Initially, we examined the equimolar reaction of **1** with $Pd_3(OAc)_6$ (hereafter referred to as " $Pd(OAc)_2$ ") in dichloromethane (DCM) at room temperature. The reaction gave a satisfactory yield (68%) of yellow precipitate **2**. The 1H NMR spectrum (Fig. 1d) shows features analogous to the spectra of known C_2 -symmetric (clamshell) dinuclear palladacycles derived from *N,N*-dimethylbenzylamines,¹¹ specifically, the

diastereotopic CH_2 group appears as two AB doublets (CH_2 -a and CH_2 -b) and two different $N-CH_3$ groups are assigned to the axial and equatorial positions of the five-membered ring. Single-crystal X-ray diffraction confirmed the predicted structure palladated in the *ortho* position proximal to the stronger *N,N*-dimethylamino group (Fig. 2).

The structure of centrosymmetric dinuclear palladium complex **2** consists of two palladium centers bridged by two acetate ligands in an isobidentate-bridging fashion. The oxygen atoms of these ligands are mutually *cis* oriented at the base of square pyramidal coordination polyhedra of each palladium atom. Substituted phenyl with a pendant dimethylaminomethyl moiety chelates palladium atoms in the rest of the base positions, while a weak palladium–palladium bonding interaction¹² is responsible for the presence of the second palladium atom on the top of the pyramid. The mutual orientation of both chelating phenyl ligands is *anti-C*₂ symmetry. Such a coordination geometry is similar to *ca.* 30 examples of doubly carboxylate bridged dinuclear palladium complexes bearing adjacent monoanionic *C,N*-chelates with two five-membered palladacycles found within the Cambridge Crystal Structure Database.¹³ Most of the parameters characterizing the coordination polyhedra, interatomic distances and angles are similar, but significant differences are found in cases of Pd–Pd separations. While these distances are usually a weak bond of ~ 2.9 Å (also for **2**), the same type of parameter could be much longer for complexes with sterically demanding substituents on the amino groups (~ 3.2 Å),¹⁴ but also much shorter as, for example, for the dinuclear Pd^{III} complex (~ 2.5 Å).¹⁵

Cyclopalladation in the presence of weak acids

Very often, the C–H functionalization protocols involve the presence of additional acetic or other carboxylic acids. Therefore, we examined their influence on cyclopalladation

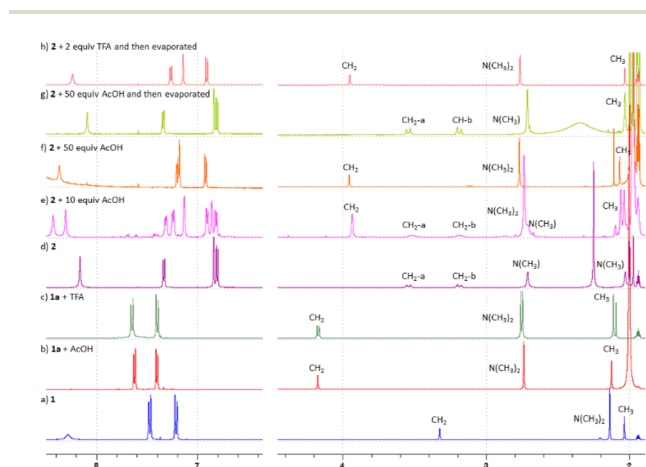


Fig. 1 Influence of additional acids (AcOH and TFA) on the 1H NMR spectra of compounds **1** and **2**.

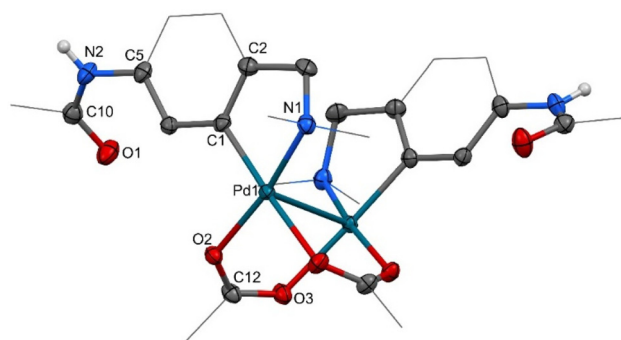


Fig. 2 The ORTEP structures of dinuclear complex **2**. Thermal ellipsoids are set at 50% probability and peripheral atoms are shown as wire-frames; most of the hydrogen atoms are omitted for clarity. Selected interatomic distances (Å) and angles (°): Pd1–C1 1.966(2), Pd1–O2 2.0603(17), Pd1–N1 2.065(2), Pd1–O3i 2.1500(17), Pd1–Pd1i 2.9304(4), O1–C10 1.226(3), N1–C9 1.486(3), C1–Pd1–O2 93.59(9), C1–Pd1–N1 82.40(9), O2–Pd1–N1 170.10(7), C1–Pd1–O3i 176.12(9), O2–Pd1–O3i 90.17(7), N1–Pd1–O3i 93.74(8), C1–Pd1–Pd1i 102.33(7), O2–Pd1–Pd1i 81.09(5), N1–Pd1–Pd1i 108.58(6), O3i–Pd1–Pd1i 79.18(5); symmetry code: (i) $-x + 1, y, -z + 3/2$.



using NMR spectroscopic (time-conversion) experiments. CD₃CN was selected as a solvent to avoid precipitation of the product **2**. While cyclopalladation without additional acid gave signals of dinuclear palladacycle **2** as an exclusive product, the addition of acetic acid (5 and 10 equivalents) to the reaction mixture caused the appearance of signals of a new compound **2a/b** (Fig. 1e), whose abundance increased with increasing amount of acetic acid present in the reaction mixture. The ¹H NMR spectrum showed signals of three aromatic protons with chemical shifts and coupling constants very close to the signals of **2**. On the other hand, signals in the aliphatic region resonated as singlets. After the addition of a high excess of AcOH (more than 50 equivalents) the signals of **2a/b** are solely present (Fig. 1f). To examine the nature of this behavior and the structure of **2a/b**, we took the resulting reaction mixture from the experiment without additional acid and containing only product **2** and added 10 equivalents of AcOH. The spectra recorded immediately after the addition were identical to the spectra recorded at the end of the kinetics in the presence of 10 equivalents of AcOH (Fig. S1†). This shows that **2a/b** is a different form of **1** and the ratio of the individual forms is dependent exclusively on the amount of added acetic acid. Evaporation of volatiles from the NMR tube, where exclusively signals of **2a/b** were recorded, to dryness and subsequent redissolution of the residue in CD₃CN or acetone-*d*₆ followed by immediate recording of the ¹H NMR spectrum gave rise to a sole set of signals attributable to **2** (Fig. 1g). This indicates that **2a/b** exists only in the solution containing AcOH and that the evaporation of solvents leads to the release of AcOH and the restoration of dinuclear palladacyclic complex **2**.

Two possible structures of compound **2a/b** can be proposed (Scheme 2). First, the clamshell dinuclear complex **2** is fragmented by adjacent acid to unprotonated monopalladium species **2b**. In this case it can be expected that aliphatic signals are not split (or only very little) analogously to the 'open-shell' shaped chloride bridged dinuclear complexes.¹¹ Second, confirmed by other evidence, there is a possibility of protonation of the basic *N,N*-dimethylamino group giving acyclic palladium species **2a**, as is known *e.g.* from the chemistry of organostannanes.¹⁶ The validity of the protonation is confirmed not only by the chemical shift of the CH₂ and N-(CH₃)₂ groups (Fig. 1f vs. Fig. 1a) but also by the observation that the amount of additional acid necessary for full conversion of **2** to **2a** decreases with its strength or concentration (Fig. 1f and Fig. S2†). Thus, full conversion requires the addition of more than 50 equivalents of AcOH but less than 2 equivalents of much stronger TFA. Furthermore, the evapor-

ation of **2a**-TFA formed in the presence of stronger trifluoroacetic acid does not lead to the restoration of dinuclear complex **2** (Fig. 1h).

From the NMR and FTIR data it is not possible to distinguish the exact structure of **2a** and whether it is mononuclear or dinuclear. The NMR analysis of **2a**-TFA reveals the presence of a signal set corresponding to one trifluoroacetate anion. However, the exact stoichiometry of the "substrate vs. OTFA" cannot be determined. Furthermore, FTIR analysis of the powder does not show a band typical of nitriles in the region 2200–2300 cm⁻¹ (Fig. S23†).

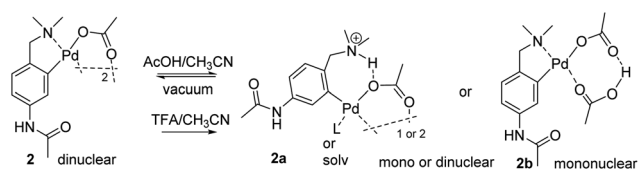
In any case, the occurrence of such an acyclic species **2a** in acidic media may be interesting especially from a mechanistic point of view in studies of C–H functionalization, where its occurrence has not yet been considered and at the same time it can be an important reactive intermediate or catalyst resting state.

Finally, the time-conversion experiments (Fig. S3†) show that the addition of acetic acid (5 equiv.) causes a decrease in the reaction rate. However, further increasing the amount of acid has no longer such a significant effect. The addition of stronger acids (methoxyacetic or dichloroacetic) leads to a further reaction rate slowdown and full cyclopalladation is achieved in a few days.

Cyclopalladation in the presence of strong acids

This part of our work examines the influence of additional strong acid (TFA) on the regioselectivity and cyclopalladation outcome. First, the treatment of substrate **1** with 5 equivalents of TFA in DCM for 15 minutes (giving **1a**) was followed by the addition of 1 equivalent of "Pd(OAc)₂". In this case, it can be assumed that the reactive palladium containing species are [Pd₃(OAc)_{6-x}(OTFA)_x] (*x* = 1–6) formed by a sequential ligand exchange from [Pd₃(OAc)₆] prior to the reaction with **1a**.¹⁷ The resulting (rapidly formed) oil solidified after trituration in hexane, giving yellow powder **4**. After its dissolution in CD₃CN the ¹H NMR spectrum contains signals of three aromatic protons (two doublets and one singlet) indicating successful cyclopalladation. The palladation directed by the acetamido group is confirmed by *e.g.* the ¹H and ¹³C-HMBC NMR spectra showing the correlation of the benzylic carbon atom with two aromatic protons (Fig. S20†). Furthermore, chemical shifts of N-CH₃ and CH₂ protons are almost identical to those of the protonated substrate **1a**, whereas the signals of acetamido CH₃ groups are downfield-shifted (Fig. S4†). However, the spectrum slowly changed in time (Fig. 3). Within a few hours signals of a new compound **3** appeared. These are signals of two aromatic protons accompanied by signals of the CH₂ and N-(CH₃)₂ groups. After three days the change was complete reaching a ratio of prime to new signals of 1 : 0.7. The analogous behavior results in a ¹⁹F NMR spectrum containing one broad signal whose intensity increased in time and four narrow signals in the region 74.5–75.5 ppm that slowly disappeared.

The probable explanation (Scheme 3) is that the original yellow complex formed in DCM is trinuclear palladacyclic complex **4**,¹⁸ which is also indicated by elemental analysis. Its dissolution in CD₃CN led to the rapid expulsion of "Pd



Scheme 2 Possible structures of compounds **2a/b**.



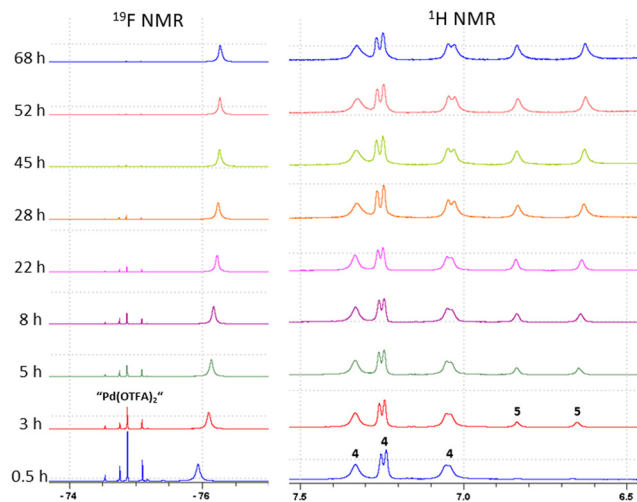
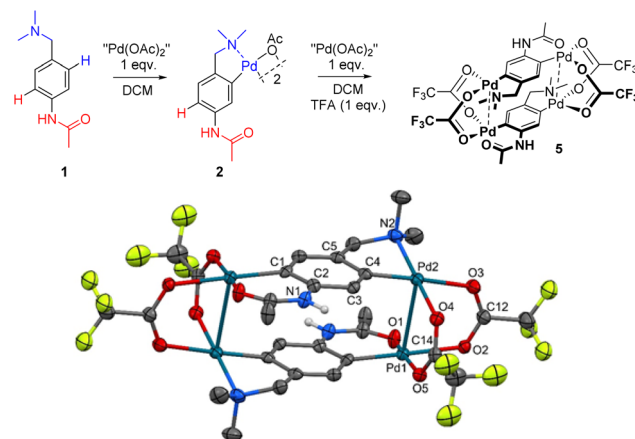


Fig. 3 Changes with time of the important areas of the ^{19}F and ^1H NMR spectra of the solution of complex 4 in CD_3CN .

(OTFA) $_2$ ”, giving a dinuclear palladacyclic complex 3 (major signals in NMR). Such an instability of the trinuclear species in coordinating solvents and in the presence of nucleophiles was observed in our previous work.¹⁷ The formed palladacycle 3 slowly underwent a second C–H activation with liberated “Pd(OTFA) $_2$ (AN) $_2$ ” (narrow signals in ^{19}F NMR) directed by the *N,N*-dimethylamino group (there was no additional free acid present in this case), giving doubly activated compound 5. The structure of the complex 5 was determined using single-crystal X-ray diffraction (Scheme 4.). The results show its existence in the [2,2]-dipalladaparacyclophane form containing two doubly activated C–H units connected by four bridging acetate ligands. The addition of a higher amount of TFA to the reaction mixture caused a slowdown of the reaction rate.

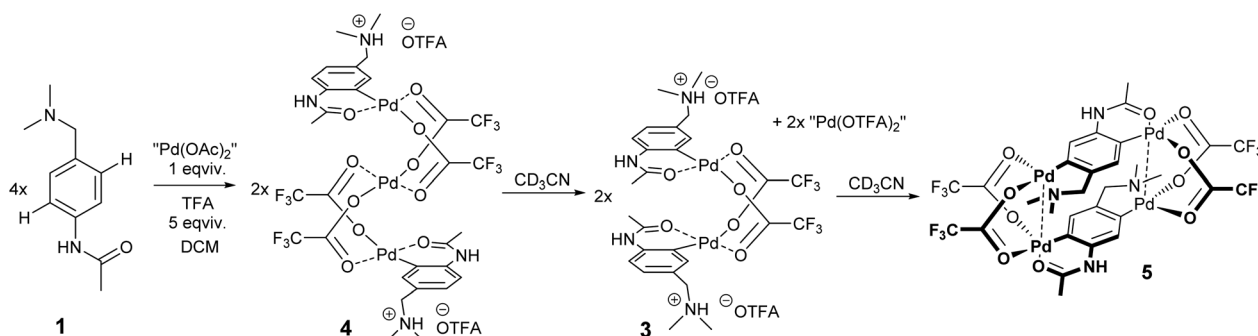
Interestingly, the change of the solvent from DCM to acetonitrile caused a dramatic effect on the reaction course. First, the reaction slowed down significantly. At the beginning, only ^1H NMR signals of protonated substrate 1a-TFA were present (Fig. S5†). Surprisingly, within a few days, signals of the complex 2a-TFA began to appear. Thus, in acetonitrile the C–H activation is directed solely by the *N,N*-dimethylamino group



Scheme 4 Scheme of one pot double functionalization (top). The ORTEP structures of double activated complex 5. Thermal ellipsoids are set at 40% probability; most of the hydrogen atoms and minor disordered parts of CF_3 groups are omitted for clarity. Selected interatomic distances (Å) and angles ($^\circ$): Pd1–C1 1.956(5), Pd1–O1 1.986(4), Pd1–O5 i 2.073(3), Pd1–O2 2.169(3), Pd1–Pd2 i 3.0074(5), Pd2–C4 1.960(5), Pd2–O4 2.058(4), Pd2–N2 2.064(5), Pd2–O3 i 2.197(4), C1–Pd1–O1 91.91(18), C1–Pd1–O5 i 95.46(18), O1–Pd1–O5 i 170.47(14), C1–Pd1–O2 178.55(18), O1–Pd1–O2 86.68(14), O5 i –Pd1–O2 85.98(13), C1–Pd1–Pd2 i 99.53(14), O1–Pd1–Pd2 i 106.01(12), O5 i –Pd1–Pd2 i 78.75(10), O2–Pd1–Pd2 i 80.56(9), C4–Pd2–O4 95.00(18), C4–Pd2–N2 81.6(2), O4–Pd2–N2 174.40(16), C4–Pd2–O3 i 176.60(18), O4–Pd2–O3 i 86.09(15), N2–Pd2–O3 i 97.54(17), C4–Pd2–Pd1 i 97.62(14), O4–Pd2–Pd1 i 79.89(10), N2–Pd2–Pd1 i 104.92(14), O3 i –Pd2–Pd1 i 79.38(10); Symmetry code: (i) $-x + 1, -y + 1, -z + 1$.

even in acidic media. Over time (weeks), the signals of 2a-TFA were accompanied by signals from substance 5.

We currently have no clear explanation for this. The result of the NMR titration speaks against the possibility of a fundamentally different basicity of the individual DGs of both solvents (Fig. S6†); however, it cannot be fully excluded. Titration of substrate 1 with TFA in both solvents leads to similar changes in the chemical shifts of individual NMR signals. Another possible explanation is the different structure (nuclearity) and thus the reactivity of palladium trifluoroacetate in dichloromethane and acetonitrile. While we have confirmed¹⁶ the retention of the trinuclear cyclic structure in dichloro-



Scheme 3 Probable structure of complex 4 and its transformation in CD_3CN .

methane, this may not be the case in acetonitrile. However, a detailed explanation will require further work.

The double C–H activation giving complex **5** can be achieved by an alternative way (Scheme 4). First, an equimolar amount of **1** was reacted with “Pd(OAc)₂” in DCM. After 30 minutes the second equivalent of “Pd(OAc)₂” dissolved in DCM containing 5 equivalents of TFA was added. The ¹H NMR spectrum of the formed yellow precipitate **5** (70% yield) shows signals of only two aromatic protons and the chemical shifts are analogous/identical to the chemical shifts shown in Fig. 3. Furthermore, a small number of broad signals appear in the ¹H NMR spectra, probably belonging to the polymer structure of the doubly activated species.

With respect to the structure of **2**, **5** is also centrosymmetric but tetranuclear with the doubly deprotonated (palladated) ligands in *para* positions. These two ligands with an opposite orientation of the *N,N*-dimethylamino and acetamido groups bridge the dinuclear units. The major difference from the published structures of a similar kind is the fact the *C,N*- and *C,O*-chelates have the same orientation of donors within the dinuclear moiety, while the donors in the rest of forty-five dinuclear species containing two carboxylates and *C,N*- or *C,O*-chelating ligands are in opposite positions. Nevertheless, the most interesting fact is that the ligands form a doubly bridged structure, which resembles the structural motif of [2.2]paracyclophane. Such a prototype of a unique tetrametalla [2.2]paracyclophane structure was described only for one tetragermanium compound¹⁹ and a very few⁹ analogues of palladium species containing *e.g.* the 1,4-bis-(benzothiazol-2-yl)phenylene ligand,^{9e} whereas all of these are based on symmetric ligands. There is a direct comparison between **5** and the former, where the Pd–Pd separation is shorter by ~0.2 Å, and the π – π stacking interaction between ligands of 3.613 Å in **5** is a bit longer than the 3.418 Å in the published structure as a result of flexible donor parts *versus* completely flat ones, which allow the planes to get closer.

DFT calculations

DFT calculations were employed to gain further insights into the observed trends. Therefore, we calculated²⁰ and compared simplified energy profiles for C–H activation directed by both directing groups (Fig. 4). For simplicity, the reaction profiles contain only pre-complexes (**pre**), intermediates (**int**) and transition states (**TS**).²¹ Furthermore, it can be assumed that a relative comparison of profiles is not strongly affected by the nuclearity of the reaction species;²² therefore, only mono-nuclear species are involved in the calculations.

The comparison of relative energies of pre-complexes (**pre**) shows a strong preference for the formation of the *N,N*-dimethylamino coordinated one. On the other hand, the energy differences between pre-complexes (**pre**) and transition states (**TS**) in both profiles are almost identical (15.2 vs. 14.6 kcal mol^{–1}). It follows that preferential coordination of palladium by the DG and not C–H-activation itself is responsible for the different directing group abilities.⁵ This offers a complement to the work of Norrby *et al.*,^{5a} who used relative stabilities of

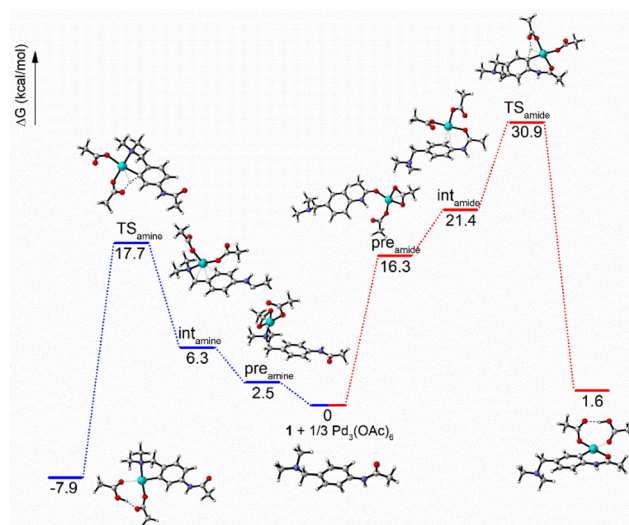


Fig. 4 Comparison of simplified reaction profiles (relative Gibbs energies in DCM at 298 K in kcal mol^{–1}) of the C–H activation of **1** directed by *N,N*-dimethylamino (blue) and acetamido (red) groups.

formed palladacycles for the determination of DG abilities, or to the work of Lapkin.²³

Conclusions

This work demonstrates that it is possible to switch the site-selectivity of the cyclopalladation reaction of substrates containing two different directing groups using the acidity of the environment. However, it depends on factors such as solvent or nuclearity. Furthermore, the work proves the existence of a protonated palladacyclic compound **2a** and its possible application as a reaction intermediate in C–H functionalization reactions. Last but not least, directed stepwise double cyclopalladation enables the synthesis of “non-symmetrical” [2.2]-dipalladaparacyclophanes.

Author contributions

T. K., J. B. and L. M.: investigation; A. R.: crystallography and writing – review & editing; J. H.: writing – review & editing; and J. V.: conceptualization, investigation and writing – original draft.

Conflicts of interest

There are no conflicts to declare.

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