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Autocatalytic Intermolecular versus Intramolecular Deprotonation in C–H Bond Activation of Functionalized Arenes by Ruthenium(II) or Palladium(II) Complexes

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Abstract: The activation of the C–H bond of 1-phenylpyrazole (**2**) and 2-phenyl-2-oxazoline (**3**) by [Ru(OAc)$_2$(*p*-cymene)] is an autocatalytic process catalyzed by the co-product HOAc. The reactions are indeed faster in the presence of acetic acid and water but slower in the presence of a base K_2CO_3. A reactivity order is established in the absence of additives: 2-phenylpyridine > 2-phenyl-2-oxazoline > 1-phenylpyrazole (at RT). The accelerating effect of added acetate ions reveals an intermolecular deprotonation after C–H bond activation by a cationic Ru^{II} center (S_E3 mechanism). The reactions of 1-phenylpyrazole and 2-phenyl-2-oxazoline first lead to the neutral cyclometalated complexes $\mathbf{A_2}$ and $\mathbf{A_3}$ ligated by one acetate. The latter dissociate to the cationic complexes $\mathbf{B_2}^+$ and $\mathbf{B_3}^+$, respectively, and acetate. A slow incorporation of one or two D atoms into **2**, **3**, and 2-phenylpyridine (**1**) was observed in the presence of deuterated acetic acid. The "reversibility" of the C–H bond activation/deprotonation takes place from the cationic complexes $\mathbf{B}_n^+$ (n = 1–3). They are also involved in oxidative additions to PhI, which are rate-determining and lead to the mono- and bis-phenylated products at high temperatures. A general mechanism is proposed for the arylation of arenes **1–3** catalyzed by [Ru(OAc)$_2$(*p*-cymene)]. In contrast, the reaction of Pd(OAc)$_2$ with 2-phenylpyridine (**1**), is much faster: Pd(OAc)$_2$ > [Ru(OAc)$_2$(*p*-cymene)]. Since the kinetics is not affected by added acetates, the reaction proceeds through a CMD mechanism assisted by a ligated acetate (intramolecular process) and is irreversible. A bis-cyclometalated Pd^{II}^Pd^{II} dimer $\mathbf{D'_1}$ is formed whose bielectronic electrochemical oxidation leads to a [Pd^{III}^Pd^{III}]$^{2+}$ dimer, in agreement with the result of a reported chemical oxidation used in arene functionalizations catalyzed by Pd(OAc)$_2$.

Keywords: C–H bond activation · kinetics · palladium · reaction mechanisms · ruthenium

Introduction

The direct catalyzed functionalization of arene C–H bonds is more and more attracting for selective C–C cross-coupling reactions.[1–3] There is a general agreement for considering that the first step is a C–H bond activation by the catalysts, such as ruthenium(II)[1,2] or palladium(II) complexes.[1,3] The mechanism of such reactions has been widely investigated and discussed.[1,2k,4–6] A concerted metalation–deprotonation mechanism (CMD)[4c] is often proposed: C–H bond activation by the metal and deprotonation by a ligated base (carboxylate, hydrogencarbonate, or carbonate) in an intramolecular process.[4,5] DFT studies pointed out the formation of transient agostic M(C–H) bonds.[4] Intermolecular processes have also been proposed.[6] Indeed, the base strength (carboxylate, carbonate) is considerably reduced by coordination to the metal center. The C–H bond activated by the metal by an electrophilic process[6] is deprotonated by the more basic free base.[6a–c]

In contrast to DFT calculations, few kinetic data are available on C–H bond activation by transition metals. A pioneering work on the activation of benzylamines by Pd(OAc)$_2$ by Ryabov et al.[1a,5b,c] concluded an intramolecular process through electrophilic activation of the C–H bond leading to an arenium complex and deprotonation by the ligated acetate through a hydrogen bond with its carbonyl group. A work by Jones et al. also concluded an electrophilic activation of a C–H bond in PhN=CHPh by cationic complexes [Cp*M^{III}–OAc]$^+$ (M = Rh, Ir), followed by intramolecular deprotonation assisted by a ligated acetate.[7]

We recently reported kinetic data on the reaction of [Ru(OAc)$_2$(*p*-cymene)] (**I**) with 2-phenylpyridine (**1**) in acetoni-

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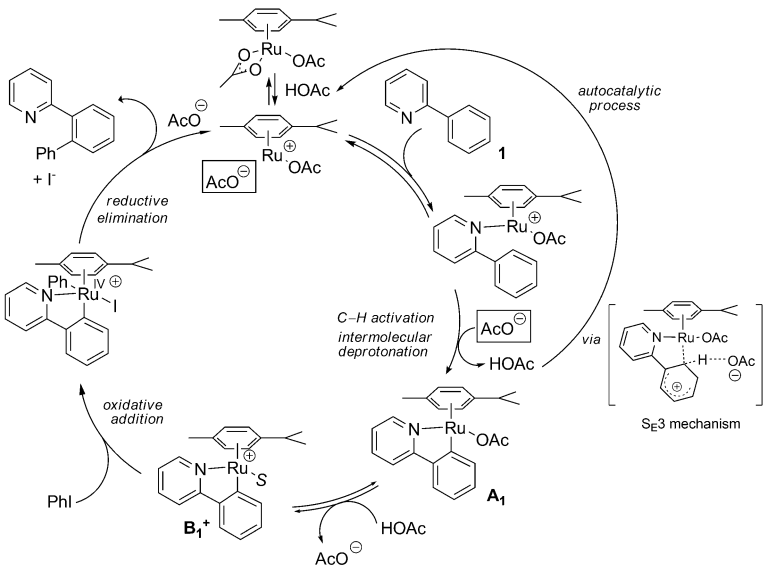


Scheme 1. Mechanism of the monophenylation of 2-phenylpyridine catalyzed by $[Ru(OAc)_2(p\text{-cymene})]$.[8]

trile that revealed a new C–H bond-activation/deprotonation mechanism: an autocatalytic process catalyzed by the acetic acid co-product (Scheme 1).[8] The overall reaction is indeed accelerated by acetic acid and water and retarded by a base. Acetic acid favors the dissociation of one acetate from $[Ru(OAc)_2(p\text{-cymene})]$[8] and consequently the ensuing complexation of **1**. The C–H bond activation initially delivers the neutral complex $\mathbf{A_1}$ ligated to one acetate (Scheme 1). The overall reaction is accelerated by added acetates, which means that the C–H bond activation proceeds through an intermolecular deprotonation of the activated C–H bond of the ligated 2-phenylpyridine by the acetate anion released from **I** (S_E3 mechanism).[8,1h] The 18e complex $\mathbf{A_1}$ easily dissociates to the cationic complex $\mathbf{B_1}^+$, which reacts with phenyl iodide (rate-determining oxidative addition) (Scheme 1), leading eventually to the mono- and bis-phenylated 2-phenylpyridine.[8]

We report herein kinetic data that reveals that the C–H bond activation/deprotonation of 1-phenylpyrazole (**2**) and 2-phenyl-2-oxazoline (**3**) by $[Ru(OAc)_2(p\text{-cymene})]$ also obeys an autocatalytic process in acetonitrile, accompanied by an intermolecular deprotonation by the acetate ion released from $[Ru(OAc)_2(p\text{-cymene})]$. In addition, evidence of the "reversibility" of the C–H bond activation highlights the multiple role of acetic acid. In contrast, new kinetic data revealed that the C–H bond activation of 2-phenylpyridine (**1**) by $Pd(OAc)_2$ is faster and obeys a CMD mechanism with an intramolecular deprotonation by a ligated acetate.

Results and Discussion

Mechanism of the C–H bond activation/deprotonation of 1-phenylpyrazole (2) by $[Ru(OAc)_2(p\text{-cymene})]$ (I): The kinetics of the reaction of $[Ru(OAc)_2(p\text{-cymene})]$ (**I**) (0.16 M) with a stoichiometric amount of 1-phenylpyrazole (**2**) (0.16 M) was followed by using ^{1}H NMR spectroscopy (Figure 1a and the Supporting Information, S7) in CD_3CN at 27 °C, as for 2-phenylpyridine (**1**).[8] The half-life of the reaction was estimated from the decay of **I** with time: $t_{1/2}=520$ min (Figure 1a) to be compared with $t_{1/2}=45$ min for the reaction of 2-phenylpyridine (**1**) performed under the same experimental conditions,[8] which is indubitably faster. As for **1**,[8] three cyclometalated ruthenium(II) complexes were formed: $\mathbf{A_2}$ first, and then $\mathbf{B_2}^+$ and $\mathbf{C_2}^+$ (Scheme 2), with $\mathbf{C_2}^+$ as the major complex at long reaction times (Figure 1a). They were identified in the ^{1}H NMR spectra performed with time by comparison with authentic samples; non-reported complexes that have been independently synthesized and fully characterized (the Sup-

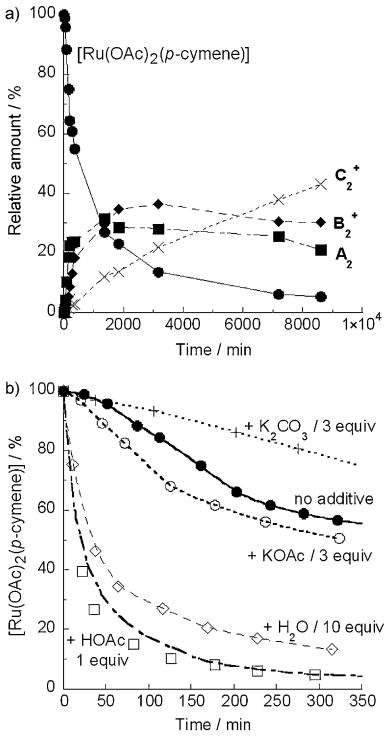
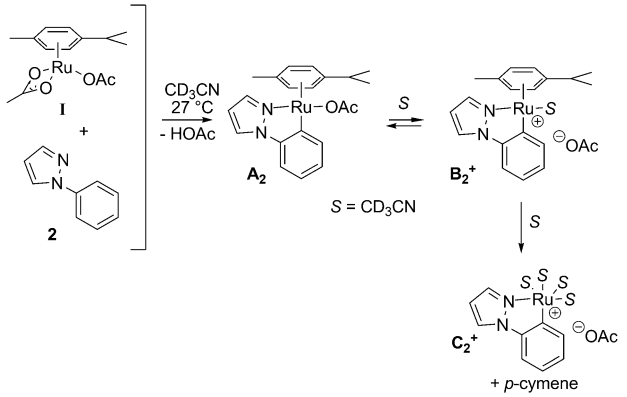
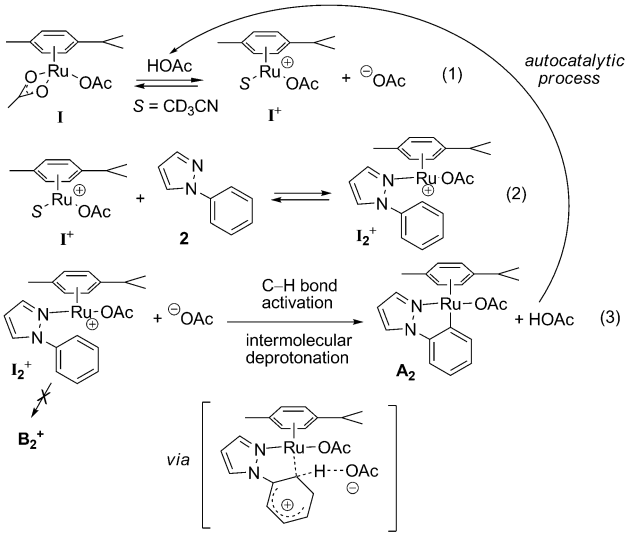


Figure 1. Kinetics of the C–H bond activation of 1-phenylpyrazole (**2**) (0.16 M) by $[Ru(OAc)_2(p\text{-cymene})]$ (**I**) (0.16 M) in CD_3CN at 27 °C, as monitored by ^{1}H NMR spectroscopy. a) (●) Decay of **I** with time and formation of complexes $\mathbf{A_2}$ (■), $\mathbf{B_2}^+$ (◆) and $\mathbf{C_2}^+$ (×). b) (●) Decay of **I** in the same conditions as in (a) but at a shorter time scale and then in the presence of additives: (+) K_2CO_3 (3 equiv), (○) KOAc (3 equiv), (◇) H_2O (10 equiv), (□) HOAc (1 equiv), added before the introduction of **2**.



Scheme 2. Cyclometalated ruthenium(II) complexes formed in the reaction of **I** and **2**, as observed by ^{1}H NMR spectroscopy.



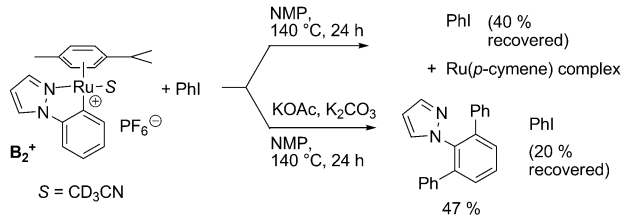
Scheme 3. Mechanism of the C–H bond activation/deprotonation of **2**.

porting Information, Figures S1–S6). Complex $\mathbf{A_2}$ was synthesized by treating the related reported complex containing a Ru–Cl bond ($\mathbf{D_2}$)[5l] by AgOAc in CH_2Cl_2 (see the Supporting Information). Complexes $\mathbf{B_2}^+$ and $\mathbf{C_2}^+$ were synthesized with PF_6^- as the counteranion, by using the same procedure as for the 2-phenylpyridine derivatives[8] $\mathbf{B_1}^+$ and $\mathbf{C_1}^+$ (see the Supporting Information). The equilibrium $\mathbf{A_2} \rightleftharpoons \mathbf{B_2}^+ + AcO^-$ was evidenced upon addition of *n*-Bu_4NOAc to $\mathbf{B_2}^+$ PF_6^- (see the Supporting Information).

The decay of [Ru(OAc)$_2$(*p*-cymene)] at short times was not hyperbolic from the beginning as it should be for a reaction performed under stoichiometric conditions (Figure 1b). Instead, the reaction became faster and faster as the reaction proceeded, revealing an autocatalytic process (i.e., catalyzed by one product of the reaction). The reaction was faster in the presence of acetic acid (Figure 1b, the Supporting Information, S8), establishing that HOAc, the co-product formed together with $\mathbf{A_2}$ after C–H bond activation/deprotonation of the 1-phenylpyrazole, was responsible for the autocatalytic process by favoring the dissociation of **I** to $\mathbf{I}^+$ ([Eq. (1)] in Scheme 3).[8] In agreement with this mechanism, the reaction was faster in the presence of H_2O (Figure 1b), which made the acetic acid more acidic than in pure acetonitrile, and retarded in the presence of K_2CO_3 (Figure 1b), a base that inhibited the autocatalytic process by neutralizing HOAc. The reaction was also accelerated in the presence of added acetate ions (Figure 1b), which means that external acetates are involved in the rate-determining deprotonation step. One has to face two competitive kinetic effects in the presence of acetates. The first one is a shift of the equilibrium ([Eq. (1)] in Scheme 3) towards complex **I**, which would induce a slower overall reaction. The second one is an acceleration of the deprotonation step ([Eq. (3)] in Scheme 3). For the acetate concentrations considered in this work, the competition was in favor of the acceleration of the reaction, which means that free acetates are involved in an intermolecular deprotonation step ([Eq. (3)] in Scheme 3), which is rate-determining.

From those experiments, one concludes that the mechanism of the C–H bond cleavage in the 1-phenylpyrazole by [Ru(OAc)$_2$(*p*-cymene)] is similar to that of 2-phenylpyridine, that is, an autocatalytic process due to the co-product HOAc that favors the dissociation of complex **I** to $\mathbf{I}^+$. The formation of $\mathbf{A_2}$ as the first product of the reaction (and not $\mathbf{B_2}^+$) associated with an accelerating effect of added acetates indicated that the C–H bond was cleaved in an intermolecular process (S_E3 mechanism, Scheme 3).

Once the mechanism of the C–H bond activation established with the characterization of the three products $\mathbf{A_2}$, $\mathbf{B_2}^+$, and $\mathbf{C_2}^+$ formed successively (Scheme 2), it was of interest to find out which one could react with PhI to generate the mono- or bis-phenylated 1-phenylpyrazole, as it was observed in catalytic reactions.[2v] The 18e complex $\mathbf{A_2}$ is intrinsically unreactive but was found to be in equilibrium with $\mathbf{B_2}^+$, which was transformed to $\mathbf{C_2}^+$ at long reaction times (Scheme 2). The formation of $\mathbf{B_2}^+$ was even enhanced in the presence of HOAc that favored the dissociation of $\mathbf{A_2}$ to $\mathbf{B_2}^+$. Indeed, the reaction of **I** with **2** performed in the presence of HOAc (1 equiv) after 250 min led to the major $\mathbf{B_2}^+$ (the Supporting Information, Figure S8). Whereas the complex $\mathbf{C_2}^+PF_6^-$ (0.15 mmol) did not react with PhI (0.375 mmol) in *N*-methyl-2-pyrrolidone (NMP; at 140 °C after 24 h), the complex $\mathbf{B_2}^+PF_6^-$ reacted with PhI under the same experimental conditions since only 40% of PhI was recovered after work-up but no phenylated product was formed (Scheme 4). A dark complex was formed that could not be characterized due to its low solubility even in DMSO; however, it was still ligated by *p*-cymene since free *p*-cymene was not present in the ^{1}H NMR spectrum of the crude mixture after work-up. It is only in the presence of additives KOAc (0.3 mmol) and K_2CO_3 (0.3 mmol) as in catalytic reactions[2v] that the 1-(2,6-phenyl)phenylpyrazole was formed in 47% yield (non-optimized reaction with 20% recovered PhI) (Scheme 4).



Scheme 4. Products formed from the reaction of cyclometalated species $\mathbf{B_2}^+$ and phenyl iodide in NMP at high temperature in the presence and in the absence of $KOAc/K_2CO_3$.

This indicates that the oxidative addition of PhI to complex $\mathbf{B_2}^+$ took place in the absence of additives but one of the following reactions stopped, either the reductive elimination from an intermediate Ru^{IV} complex, or if the latter took place, the 1-(2-phenyl)phenylpyrazole (not detected in the NMR spectrum) must stick onto the cationic Ru^{II} center without any further C–H bond activation. It is only in the presence of KOAc and K_2CO_3 (conditions of the catalytic reactions)[2v] that the second C–H bond activation took place to deliver the bis-phenylated product after a second oxidative addition to PhI (the Supporting Information, Figure S9). In both cases, the oxidative addition of $\mathbf{B_2}^+$ to PhI was slower than the C–H bond activation that proceeded at room temperature (see above).

Mechanism of the C–H bond activation/deprotonation of 2-phenyl-2-oxazoline (3) by [Ru(OAc)$_2$(*p*-cymene)] (I): The kinetics of the C–H bond activation/deprotonation of 2-phenyl-2-oxazoline (**3**) (0.16 M) by $Ru(OAc)_2$(*p*-cymene) (**I**) (0.16 M) was similarly investigated by ^{1}H NMR spectroscopy in CD_3CN (Figure 2a and the Supporting Information, S18). The half-reaction time was $t_{1/2}=157$ min (Figure 2a) leading to the following reactivity order for the C–H bond activation by [$Ru(OAc)_2$(*p*-cymene)] (**I**) in the absence of additives:[9] 2-phenylpyridine > 2-phenyl-2-oxazoline > 1-phenylpyrazole.

The non-reported complexes $\mathbf{A_3}$ and $\mathbf{B_3}^+$ formed in the reaction (Scheme 5 and the Supporting Information, Figure S18) have been characterized by comparison to independently synthesized authentic samples (the Supporting Information, Figures S10–S17).

An autocatalytic process catalyzed by acetic acid took place, as evidenced by the accelerating effect of added HOAc, water and the retarding effect of carbonate (Figure 2b). The reaction was faster in the presence of added acetates (3 equiv, Figure 2b), which means that the acetates are involved in a rate-determining intermolecular deprotonation step ([Eq. (6)] in Scheme 6). This was also confirmed by the fact that complex $\mathbf{A_3}$ (still ligated by one acetate detected at $\delta=1.6$ ppm) was formed as the first product of the reaction through a S_E3 mechanism, as was observed for the arenes **1**[8] and **2** (see above).

The complex $\mathbf{B_3}^+PF_6^-$ reacted with PhI (30% recovered) leading to an intermediate complex that could not be characterized. The expected phenylated products were not formed. It was only in the presence of KOAc and K_2CO_3 that the mono- and bis-phenylated products were formed but in poor yields (Scheme 7, the Supporting Information, Figure S19). Nevertheless such experiments show that the oxidative addition of PhI to the cationic $\mathbf{B_3}^+$ complex took place in a slow reaction.

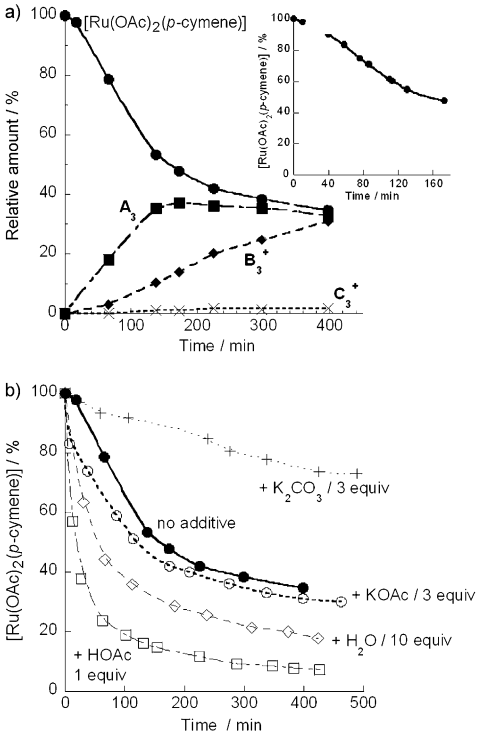
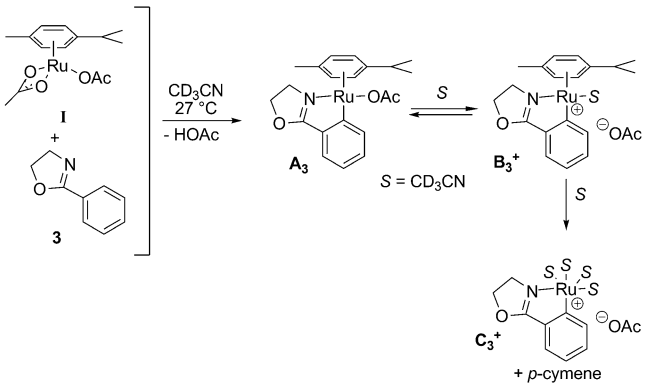
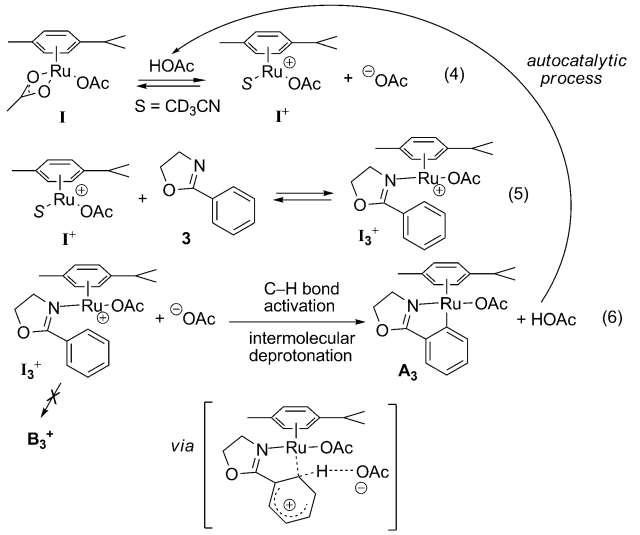


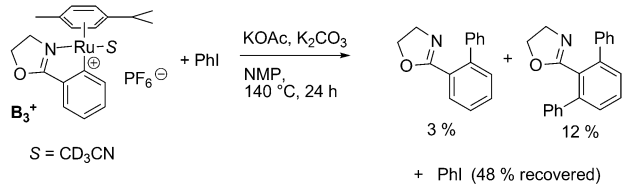
Figure 2. Kinetics of the C–H bond activation of 2-phenyl-2-oxazoline (**3**) (0.16 M) by [$Ru(OAc)_2$(*p*-cymene)] **I** (0.16 M) in CD_3CN at 27 °C, as monitored by ^{1}H NMR spectroscopy. a) (●) Decay of **I** with time and formation of complexes $\mathbf{A_3}$ (■), $\mathbf{B_3}^+$ (◆) and $\mathbf{C_3}^+$ (×); inset: (●) decay of **I** with time at a shorter time scale. See Figure S18 (in the Supporting Information) for the reaction at long time scales (4280 min). b) (●) Decay of **I** alone and in the presence of additives: (+) K_2CO_3 (3 equiv), (○) KOAc (3 equiv), (◇) H_2O (10 equiv), (□) HOAc (1 equiv), added before the introduction of **3**.



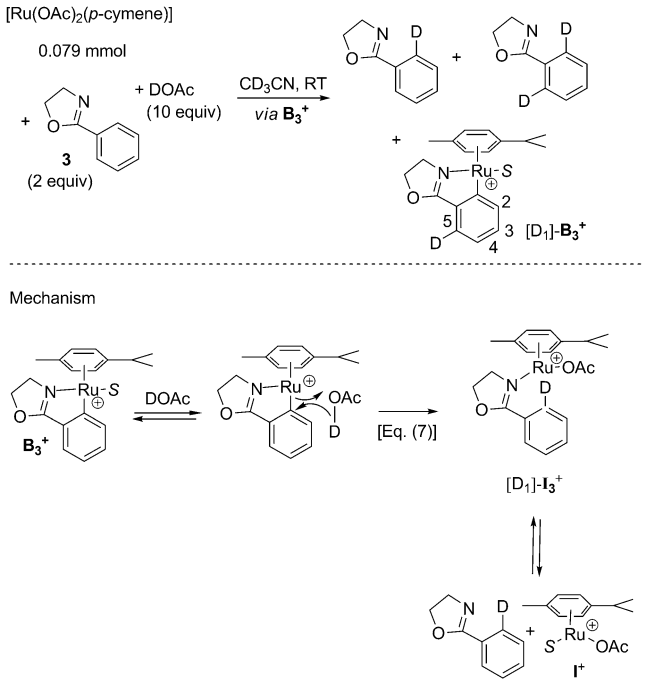
Scheme 5. Cyclometalated ruthenium(II) complexes formed in the reaction of **I** and **3**, as observed by ^{1}H NMR spectroscopy.



Scheme 6. Mechanism of the C–H bond activation/deprotonation of **3**.



Scheme 7. Products formed from the reaction of cyclometalated species $\mathbf{B_3}^+$ and phenyl iodide in NMP at high temperature in the presence of $KOAc/K_2CO_3$.



Scheme 8. Products and mechanism of the deuteration of **3** in the presence of $[Ru(OAc)_2(p\text{-cymene})]$ and $[D_4]$acetic acid.

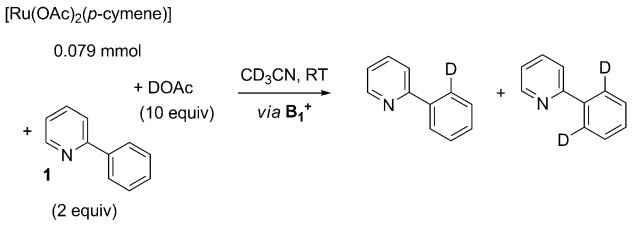
Comparison of the reactivity of $\mathbf{B}^+$ complexes with PhI to form the phenylated products led to an overall decreasing reactivity order according to the sequence: $\mathbf{B_1}^+ > \mathbf{B_2}^+ > \mathbf{B_3}^+$, for reactions performed under similar experimental conditions.

"Reversibility" of the C–H bond activation of arenes 1–3: The reaction of 2-phenyl-2-oxazoline (**3**) with **I** was found to be reversible. Indeed, incorporation of D atoms was observed when $[Ru(OAc)_2(p\text{-cymene})]$ **I** (0.16 M) was treated with 2-phenyl-2-oxazoline (2 equiv) in the presence of $[D_4]$acetic acid (10 equiv) in acetonitrile (Scheme 8). This slow reaction was followed by ^{1}H NMR spectroscopy (the Supporting Information, Figure S20). The first recorded spectrum (after 10 min) did not exhibit the signals of complex $\mathbf{A_3}$ but those of complex $\mathbf{B_3}^+$ in agreement with the promoted dissociation of $\mathbf{A_3}$ to $\mathbf{B_3}^+$ by acetic acid. Extra signals were observed for the 2-phenyl-2-oxazoline in excess (1 equiv vs. the $\mathbf{B_3}^+$ complex) but with incorporation of D atoms. Indeed, the integration of the doublet of the H in *ortho,ortho′* of the phenyl group were deficient compared with those of the *meta,meta′* and *para*-H due to the formation of 2-(2[D])phenyl-2-oxazoline and 2-(2,6[D])phenyl-2-oxazoline (Scheme 8), structures which were confirmed by mass spectroscopy after work-up (see the Supporting Information). This indicates that the deuterated acetic acid DOAc reacted with the complex $\mathbf{B_3}^+$ to give a cleavage of the Ru–C bond by D^+ leading to the formation of 2-(2[D])phenyl-2-pyrazole and $\mathbf{I}^+$ (see the mechanism in Scheme 8).

Interestingly, the ^{1}H NMR spectrum of $\mathbf{B_3}^+$ was affected during the reaction due to the formation of [D1]-$\mathbf{B_3}^+$ (Scheme 8). Indeed, the structure of the triplet of the proton H_4 was strongly modified whereas the integration of H_5 became lower and lower as the D incorporation proceeded (the Supporting Information, Figure S20 a–c). This indicates that the complex $\mathbf{I}^+$ released after the first incorporation of one D has activated the *ortho*-C–H bond of 2-(2[D])phenyl-2-oxazoline, leading to [D1]-$\mathbf{B_3}^+$ and then to a second incorporation of a D atom after reaction of [D1]-$\mathbf{B_3}^+$ with DOAc. The mechanism of the D incorporation given in Scheme 8 is similar to that reported by Jones et al. for cationic cyclometalated iridium(III) or rhodium(III) complexes involving phenylimines (e.g., PhN=CHPh).[7] Interestingly, the overall reaction of **I** with 2-phenyl-2-oxazoline is "reversible" but it includes two irreversible reactions: 1) [Eq. (6)] in Scheme 6 that leads to $\mathbf{A_3}$ but the latter was rapidly converted to $\mathbf{B_3}^+$ in the presence of acetic acid and 2) [Eq. (7)] in Scheme 8, since the complex $\mathbf{I_3}^+$ did not lead directly to $\mathbf{B_3}^+$ but to $\mathbf{A_3}$ as the first complex formed in the presence of acetate (Scheme 6).

As reported in our previous work,[8] no incorporation of D atoms was observed when the reaction of **I** (0.16 M) with 2-phenylpyridine (**1**) (2 equiv) was performed in the presence of excess D_2O (10 equiv) leading to the conclusion that the C–H bond activation/deprotonation was irreversible.[8]

Indeed, the ^{1}H NMR spectroscopy revealed the formation of complex $\mathbf{A_1}$ together with a stoichiometric amount of non-deuterated 2-phenylpyridine. This reaction has been revisited. A similar experiment was performed in the presence of [D_4]acetic acid (10 equiv) instead of D_2O. The first recorded spectrum revealed the exclusive formation of $\mathbf{B_1}^+$ together with one equivalent of 2-phenylpyridine. After two weeks, the isolated 2-phenylpyridine revealed the incorporation of D atoms in the *ortho* position (Scheme 9 and the Supporting Information, Figure S21), as evidenced by mass spectroscopy. This confirms that the reaction of acetic acid did proceed from the cationic complex $\mathbf{B_1}^+$ and not from $\mathbf{A_1}$. If $\mathbf{B_1}^+$ is not formed, as when D_2O was used instead of acetic acid (as in our previous work),[8] no deuteration takes place.



Scheme 9. Products of the deuteration of **1** in the presence of [Ru(OAc)$_2$-(*p*-cymene)] and [D_4]acetic acid.

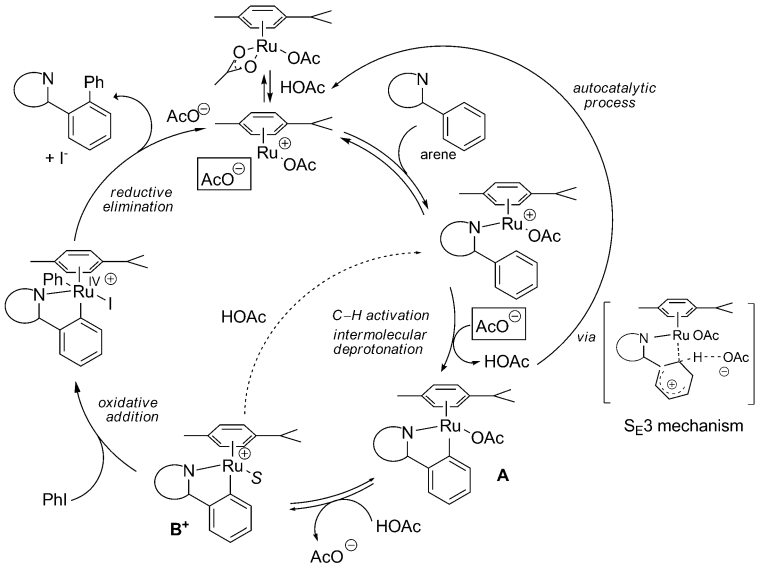
Incorporation of deuterium atoms into the 1-phenylpyrazole (**2**) was also observed when the reaction of **I** (0.16 M) and **2** (2 equiv) was performed in the presence of [D_4]acetic acid. Once again the complex $\mathbf{A_2}$ was not formed but $\mathbf{B_2}^+$ and incorporation of D into **2** (the Supporting Information, Figure S22) took place from $\mathbf{B_2}^+$ (Figure S23). Therefore, the "reversibility" of the C–H bond activation of functional arenes seems to be general.[10] However, this reaction is quite slow and cannot not interfere significantly into the kinetics of the C–H bond activation.

Mechanism for the monoarylation of arenes 1–3: A general catalytic cycle for the monophenylation of the arenes **1–3** catalyzed by [Ru(OAc)$_2$(*p*-cymene)] is now proposed in Scheme 10.

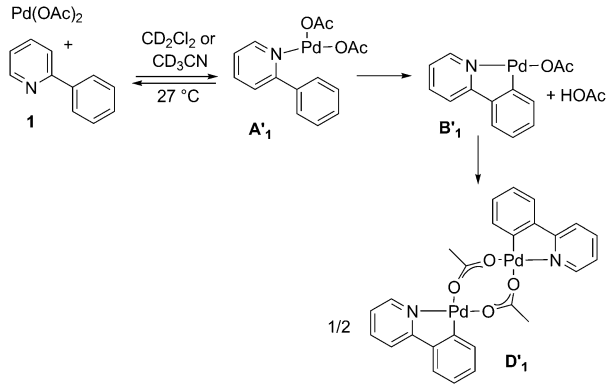
It reveals the key role of acetic acid that is responsible for: 1) the autocatalytic process in the C–H bond activation, 2) the dissociation of **A** to the cationic $\mathbf{B}^+$ involved in the oxidative addition to PhI, 3) the reincorporation of protons leading to a kind of loop that slowly recycles the starting arene (dashed arrow in Scheme 10). In all cases, an intermolecular deprotonation by acetates is observed (S_E3 mechanism). The role of carbonates required as a base in the catalytic reactions is explained by their decelerating effect in the C–H bond activation that makes the rate of this fast reaction closer to the rate of the slow oxidative addition, thus increasing the efficiency of the catalytic cycle.[11] There may also be a second role: by neutralizing the acetic acid, the carbonates interrupt the loop that leads to the regeneration of the starting arene from $\mathbf{B}^+$ (dashed arrow in Scheme 10).

Scheme 10 exhibits the first catalytic cycle of the monophenylation of an arene. Since it is difficult to stop at the level of the first phenylation (as was observed in the catalytic reactions), this suggests that the complex $\mathbf{I}^+$ is not recycled in the first catalytic cycle as written in Scheme 10, but a new cationic complex is formed in which the cationic Ru center is ligated to the monophenylated arene from which a second C–H bond activation/deprotonation could easily occur in the presence of acetate ions, leading to the bisphenylated arene.

Mechanism of the C–H bond activation/deprotonation of 2-phenylpyridine (1) by Pd(OAc)$_2$: Due to the ability of Pd(OAc)$_2$ to catalyze the functionalization of C–H bonds,[3] it was of interest to compare the kinetics and mechanism of the reaction of 2-phenylpyridine (**1**) with Pd(OAc)$_2$ with that performed from [Ru(OAc)$_2$(*p*-cymene)].[8] Moreover, no kinetic data on the reaction of Pd(OAc)$_2$ with **1** are available in literature. The kinetics of the reaction of **1** (0.16 M) with Pd(OAc)$_2$ (0.16 M) were followed by ^{1}H NMR spectroscopy in CD_3CN at 27 °C. A fast reaction took place (within less than 10 min) with precipitation of a bright-yellow solid in the NMR tube. This yellow complex has been isolated (46 % yield) and characterized. Its X-ray structure (the Sup-



Scheme 10. Catalytic cycle of the phenylation of arenes.



Scheme 11. Successive Pd^{II} complexes formed in the C–H activation of **1** by $Pd(OAc)_2$. The solvent on the Pd center is omitted for clarity.

porting Information, Figure S24) revealed the structure of the dimer $\mathbf{D'_1}$ (Scheme 11),[12] already reported.[12b]

The reaction of **1** with $Pd(OAc)_2$ was then followed by ^1H NMR spectroscopy at lower concentrations (0.08 M each) in CD_2Cl_2 in which $\mathbf{D'_1}$ was more soluble (Figure 3a). A fast decay of **1** was observed ($t_{1/2}$ = ca. 6 min, Figure 3a). The dimer $\mathbf{D'_1}$ was formed through two intermediate complexes $\mathbf{A'_1}$ and $\mathbf{B'_1}$ (Scheme 11 and the Supporting Information, Figure S25). They could not be isolated but were characterized by the chemical shift of the Me protons in their ligated

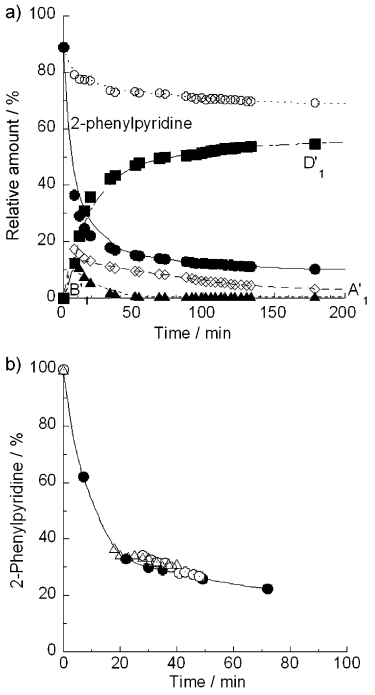
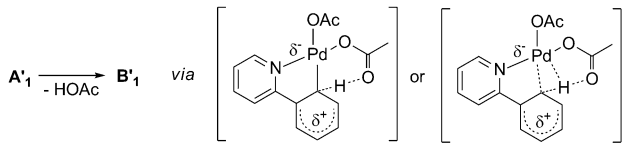


Figure 3. a) Kinetics of the C–H bond activation of 2-phenylpyrydine (**1**) (0.08 M) by $Pd(OAc)_2$ (0.08 M) in CD_2Cl_2 at 27 °C, as monitored by ^1H NMR spectroscopy at 27 °C. (●) Decay of 2-phenylpyridine (**1**) with time and formation of Pd^{II} complexes: $\mathbf{D'_1}$ (■); $\mathbf{A'_1}$ (◇); $\mathbf{B'_1}$ (▲); sum (○). b) Same reaction in CD_3CN. (●) Decay of 2-phenylpyridine (**1**) with time. In the presence of: (○) HOAc (10 equiv); (△) KOAc (3 equiv) added to $Pd(OAc)_2$ before **1**.

OAc. $\mathbf{A'_1}$ was characterized by a singlet at $\delta = 1.87$ ppm (close to the singlet of $Pd(OAc)_2$ at $\delta = 1.99$ ppm). In addition, the N-ligated 2-phenylpyridine in $\mathbf{A'_1}$ was characterized by two broad signals at $\delta = 8.95$ (1H) and 8.30 ppm (2H), shifted downfield when compared with those of the free 2-phenylpyridine at $\delta = 8.72$ (d, 1H), 8.07 ppm (d, 2H), respectively. $\mathbf{B'_1}$ was characterized by a singlet at $\delta = 1.41$ ppm, typical of a σ-bonded OAc in contrast to bridging acetates located at $\delta = 2.27$ ppm as in the dimer $\mathbf{D'_1}$. The σ-ligated 2-phenylpyridine in $\mathbf{B'_1}$ was characterized by two broad singlets at $\delta = 8.8$ and 8.6 ppm integrating for 1H each when compared with the integration of the Me of its ligated OAc. HOAc generated in the C–H bond activation/deprotonation was also detected at $\delta = 2.12$ ppm and formed in the same amount as complex $\mathbf{D'_1}$ (the Supporting Information, Figure S25c).

To allow a comparison of the kinetics and mechanism of the C–H bond activation of **1** by $Pd(OAc)_2$ or $[Ru(OAc)_2(p\text{-cymene})]$ in acetonitrile,[8] the kinetics of the reaction of **1** (0.08 M) with $Pd(OAc)_2$ (0.08 M) were followed by ^1H NMR spectroscopy in CD_3CN at 27 °C. The same intermediate complexes $\mathbf{A'_1}$ and $\mathbf{B'_1}$ were formed. The reaction was too fast ($t_{1/2}$ = ca. 11 min) to allow accurate NMR data at very short times (Figure 3b), but the decay of **1** with time appeared to be classical (hyperbolic for a stoichiometric reaction).

No significant effect of additives (HOAc, KOAc) on the rate of the reaction was evidenced (Figure 3b). In contrast to $[Ru(OAc)_2(p\text{-cymene})]$, no accelerating effect of KOAc was observed (zero-order reaction for the deprotonation step) in the case of $Pd(OAc)_2$, which indicates a CMD mechanism assisted by a ligated acetate (Scheme 12).



Scheme 12. Proposed intermediates for the acetate-assisted C–H bond activation and deprotonation of **1**; equivalent intermediates were proposed in the literature for the case of dimethylbenzylamine.

Whereas the saturated 18e $[Ru(OAc)_2(p\text{-cymene})]$ should dissociate to allow coordination of **1**, the unsaturated $Pd(OAc)_2$ can easily coordinate **1** giving complex $\mathbf{A'_1}$, which is then engaged into a CMD mechanism to deliver complex $\mathbf{B'_1}$ and eventually the dimer $\mathbf{D'_1}$ (Scheme 11). However, our kinetic data cannot discriminate between the mechanisms usually proposed for related reagents such as dimethylbenzylamine, either an electrophilic substitution through a Wheland intermediate (Scheme 12) with subsequent intramolecular deprotonation by the ligated acetate after hydrogen bonding of its carbonyl group, as was proposed by Ryabov[5b] or an agostic C–H complex in which the agostic interaction, even if weak, is sufficient to polarize the C–H bond to form an intramolecular hydrogen-bond with the ligated

acetate, as was proposed by Davies and Macgregor through DFT calculations[4a,5e] for dimethylbenzylamine (Scheme 12).

The activation of the C–H bond of 2-phenylpyridine in the absence of any additives followed the reactivity order: $Pd(OAc)_2 > [Ru(OAc)_2(p\text{-cymene})]$.

No D incorporation was observed when $[D_4]$acetic (10 equiv) was added to the dimer $\mathbf{D'_1}$ in CD_2Cl_2 after 20 h. The NMR spectrum was not modified. Only the two bridging OAc of $\mathbf{D'_1}$, which exchanged by those of the deuterated acetic acid and the Me protons of the released OAc, appeared at $\delta = 2.12$ ppm. No deuterated 2-phenylpyridine was detected and the C–H bond activation/deprotonation was thus irreversible. No D incorporation into **1** was observed when acetic acid$[D_4]$ (10 equiv) was added to a solution of $Pd(OAc)_2$ (0.08 M) and **1** (2 equiv) in acetonitrile.

Electrochemical properties of the dimer $\mathbf{D'_1}$: The dimer $\mathbf{D'_1}$, a Pd^{II}^Pd^{II} complex (Scheme 11), is oxidized by the chemical oxidant $PhI(OAc)_2$ to give a neutral dimeric Pd^{III}^Pd^{III} complex (σ-ligated by two extra acetates) that has been isolated and well characterized, as reported by Ritter et al.[3k,13] It was thus of interest to investigate the electrochemical properties of $\mathbf{D'_1}$.

The cyclic voltammogram of $\mathbf{D'_1}$ (3 mM) in dichloromethane containing n-Bu_4NBF_4 (0.3 M) as supporting electrolyte exhibited a chemically reversible oxidation peak at $E^p_{O1} = +1.07$ V versus SCE at a gold-disk electrode (Figure 4).[14] The absolute number of electron(s), n, involved in the oxidation process was determined according to a reported procedure: $n = 2.3 \pm 0.1$.[15] It means that the oxidation of the dimeric Pd^{II}^Pd^{II} complex delivers a dimeric Pd^{III}^Pd^{III} complex. The two electrons were transferred at the same potential, indicating that the two Pd^{II} centers in $\mathbf{D'_1}$ did not communicate and behaved as two independent Pd^{II} moieties oxidized at the same potential without any cleavage of the bridging acetates (chemically reversible process). This suggests that the Pd–Pd bond evidenced in the X-ray structure (the Supporting Information, Figure S24) and induced by π-stacking in the solid state,[14] disappeared in solution, as was evidenced in the ^{1}H NMR spectrum of complex $\mathbf{D'_1}$ that exhibited well-resolved aromatic protons (the Supporting Information, Figure S25c). In the absence of additives (e.g., acetate ions present in the chemical oxidation of $\mathbf{D'_1}$ by $PdI(OAc)_2$), a bis cationic Pd^{III}^Pd^{III} complex was formed and was stable at the time scale of the cyclic voltammetry [Eq. (8)].

$$Pd^{II}\text{^}Pd^{II} \rightleftharpoons [Pd^{III}\text{^}Pd^{III}]^{2+} + 2e^- \quad (8)$$

The results of the electrochemical oxidation are thus in agreement with those of the chemical oxidation of the same Pd^{II}^Pd^{II} dimer $\mathbf{D'_1}$ by $PhI(OAc)_2$,[3k,13] supporting the involvement of Pd^{III} species in functionalization of arenes catalyzed by $Pd(OAc)_2$ when a chemical oxidant is required.[13,16]

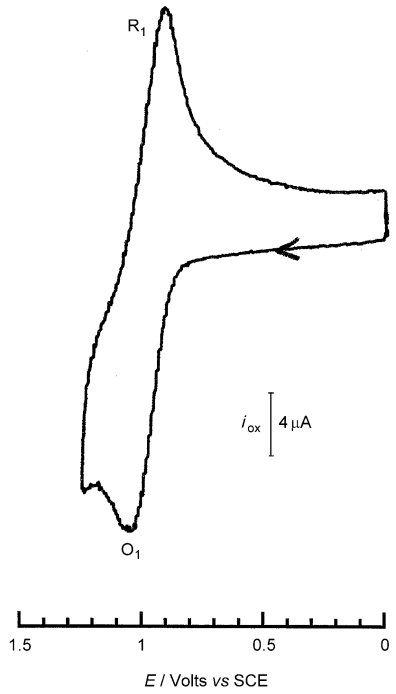


Figure 4. Cyclic voltammetry: oxidation of $\mathbf{D'_1}$ (3 mM) at O_1 in dichloromethane containing n-Bu_4NBF_4 (0.3 M) at a gold-disk electrode (d = 2 mm) at a scan rate of 0.5 V s^{-1} at 22 °C.

Conclusion

The activation of the C–H bond of 1-phenylpyrazole (**2**) and 2-phenyl-2-oxazoline (**3**) by $[Ru(OAc)_2(p\text{-cymene})]$ is an autocatalytic process catalyzed by HOAc, analogous to that of 2-phenylpyridine (**1**). All reactions are accelerated by acetic acid and water and decelerated by a base K_2CO_3. A decreasing reactivity order is established in the absence of additives: 2-phenylpyridine > 2-phenyl-2-oxazoline > 1-phenylpyrazole. The accelerating effect of added acetate ions reveals an intermolecular deprotonation after C–H bond activation by a cationic Ru^{II} center. The activation of 1-phenylpyrazole and 2-phenyl-2-oxazoline led to neutral cyclometalated complexes $\mathbf{A_2}$ and $\mathbf{A_3}$, respectively, ligated by one acetate. They easily dissociate to the cationic complexes $\mathbf{B_2}^+$ and $\mathbf{B_3}^+$, respectively, and the acetate ion. A slow incorporation of one or two D atoms into 1-phenylpyrazole (**2**), 2-phenyl-2-oxazoline (**3**) and 2-phenylpyridine (**1**) was observed in the presence of deuterated acetic acid. The "reversibility" of the C–H bond activation/deprotonation takes place from the cationic $\mathbf{B_2}^+$, $\mathbf{B_3}^+$, and $\mathbf{B_1}^+$, respectively. Cations $\mathbf{B_2}^+$ and $\mathbf{B_3}^+$ are involved in an oxidative addition to PhI, leading to bis-phenylated products at high temperatures. The reaction of $Pd(OAc)_2$ with 2-phenylpyridine (**1**) is much faster than that of $[Ru(OAc)_2(p\text{-cymene})]$. In contrast, the activation by $Pd(OAc)_2$ proceeds through a CMD mechanism assisted by the ligated acetate through an intramolecular and irreversible process. A dimeric Pd^{II}^Pd^{II} ($\mathbf{D'_1}$) is formed whose bielectronic electrochemical oxidation leads to a dimeric $[Pd^{III}\text{^}Pd^{III}]^{2+}$ complex, in agreement with

the results of the chemical oxidation of $\mathbf{D'_1}$ by $PhI(OAc)_2$ involved in catalytic reactions.

Experimental Section

General procedure for the kinetics of the *ortho*-C−H bond activation of arenes 2 and 3 by [Ru(OAc)$_2$(*p*-cymene)]: An oven-dried NMR tube was charged with [Ru(OAc)$_2$(*p*-cymene)] (28 mg, 0.079 mmol) in CD_3CN (500 μL). After complete dissolution of the complex, 1-phenylpyrazole (**2**) (10.1 μL, 0.079 mmol) or 2-phenyl-2-oxazoline (**3**) (10.6 μL, 0.079 mmol) was then added and the NMR tube was vigorously shaken. ^{1}H NMR (300 MHz) was performed at 27 °C immediately after and then from time to time.

General procedure for the kinetics of the *ortho*-C−H bond activation of 2-phenylpyridine (1) by Pd(OAc)$_2$: An oven-dried NMR tube was charged with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol) in CD_2Cl_2 (or CD_3CN) (500 μL). After complete dissolution of $Pd(OAc)_2$, $CHCl_2CHCl_2$ (2.2 μL, 0.02 mmol) was added as an internal standard, followed by 2-phenylpyridine (5.6 μL, 0.04 mmol). The solution was vigorously shaken. A series of ^{1}H NMR experiments were performed at 27 °C immediately after.

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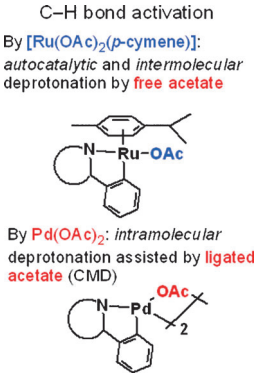
Acetate aid: The activation of the C–H bond of 1-phenylpyrazole and 2-phenyl-2-oxazoline by $[Ru(OAc)_2(p\text{-cymene})]$ is an autocatalytic intermolecular process aided by free acetate (see figure). In contrast, activation by $Pd(OAc)_2$ proceeds through a concerted metalation–deprotonation (CMD) mechanism through an intramolecular and irreversible process that is assisted by ligated acetate. A cyclometalated dimeric Pd^{II}^Pd^{II} is formed whose bielectronic electrochemical oxidation leads to a dimeric $[Pd^{III}$^$Pd^{III}]^{2+}$.



C–H activation

I. Fabre, N. von Wolff, G. Le Duc, E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand …* ▮▮▮▮–▮▮▮▮

Autocatalytic Intermolecular versus Intramolecular Deprotonation in C–H Bond Activation of Functionalized Arenes by Ruthenium(II) or Palladium(II) Complexes