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Regioselective Orthopalladation of (*Z*)-2-Aryl-4-Arylidene-5(4*H*)-Oxazolones: Scope, Kinetico-Mechanistic, and Density Functional Theory Studies of the C−H Bond Activation

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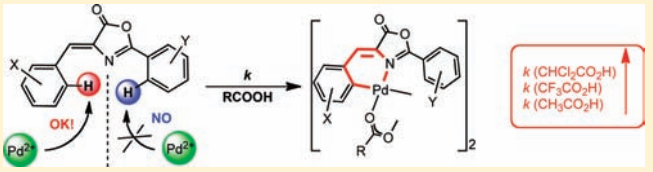
Supporting Information

ABSTRACT: Orthopalladated complexes derived from (*Z*)-2-aryl-4-arylidene-5(4*H*)-oxazolones have been prepared by reaction of the oxazolone with palladium acetate in acidic medium. The reaction is regioselective, only the *ortho* C−H bond of the arylidene ring being activated, producing a six-membered ring. The scope and reaction conditions of the orthopalladation are dependent on the acidity of the solvent. In CF_3CO_2H a large number of oxazolones can be metalated under mild conditions. As acidity decreases a lesser number of oxazolones can be efficiently palladated and harsher conditions must be used to achieve similar yields. The C−H bond activation in acidic medium agrees with an ambiphilic mechanism, as determined from kinetic measurements at variable temperature and pressure for different oxazolones substituted at the arylidene ring. The mechanism has been confirmed by density functional theory (DFT) calculations, where the formation of the six-membered ring is shown to be favored from both a kinetic and a thermodynamic perspective. In addition, the dependence of the reaction rate on the acidity of the medium has also been accounted for via a fine-tuning between the C−H agostic precoordination and the proton abstraction reaction in the overall process occurring on coordinatively saturated $[Pd(\kappa^N\text{-oxazolone})(RCO_2H)_3]^{2+}$.



INTRODUCTION

Orthopalladation represents a well established tool for the selective functionalization of organic molecules under mild reaction conditions, using either catalytic or stoichiometric processes.[1,2] The incorporation of the Pd center to the organic skeleton usually occurs via a C−H bond activation process, which in most cases is easily produced despite the inert nature of the C−H bond. This approximation to the formation of the Pd−C bonds is the most interesting in terms of efficiency and atom economy, and it has been extensively studied. Even though as a result different types of C−H bonds can be palladated using different palladium precursors,[1a] the activation of a particular C−H bond within a complex molecule is a much more difficult task. This goal is generally achieved by the introduction of a coordinating fragment, the so-called directing group.[2] A large variety of directing groups is available, resulting in a huge library of tailored-made complexes where the palladium position represents the reactive point of the molecule. Furthermore, different synthetic strategies have been developed to introduce a variety of functional groups at selected positions, thus envisaging the creation of new C−C and C−E bonds (E = halogen, O, N, S, P, or other heteroatom).[3] The number of molecules that can be modified using this strategy is increasing very quickly and, virtually, an unlimited number of new structures are accessible.

A family of compounds specially interesting is that formed by (*Z*)-2-aryl-4-arylidene-5(4*H*)-oxazolones.[4] They are versatile organic synthons, and useful intermediates in the preparative routes of many heterocycles, although their most important application is that of precursors of α-amino acids.[5] The importance of amino acids in chemistry and biology as building blocks for the synthesis of peptides is undeniable.[6] The modification of its structure (i.e., introducing substituents in the *ortho*-positions of aromatic rings) can change the activity and selectivity of the interactions of the peptide with the biomolecules.[7] Therefore, all synthetic methods, including orthopalladation, allowing

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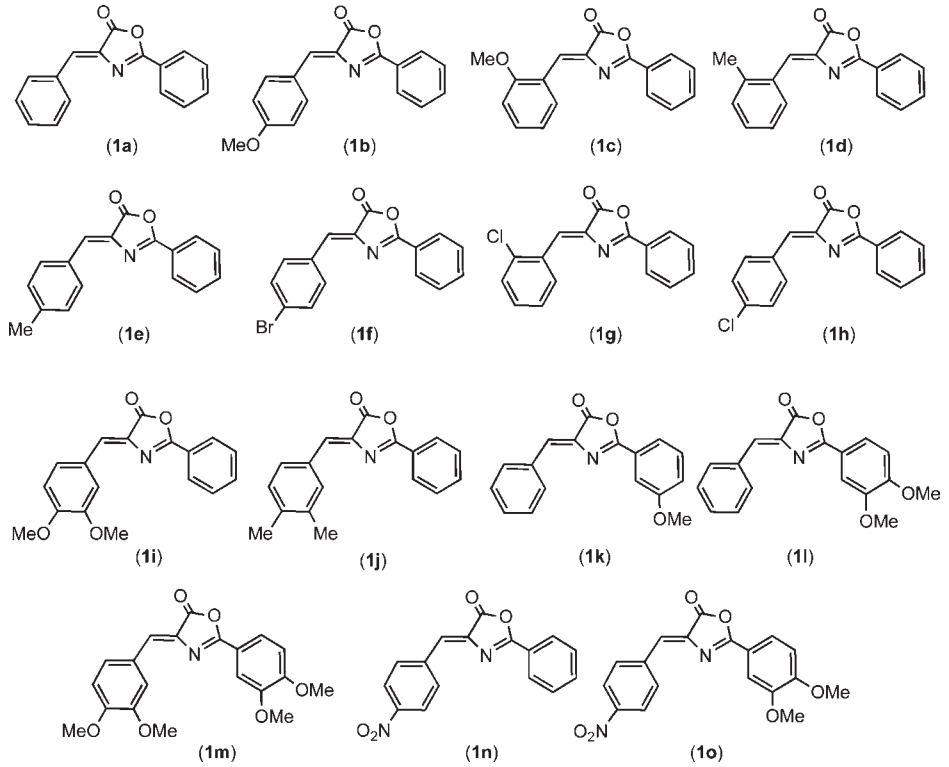

Figure 1. (*Z*)-2-aryl-4-arylidene-5(4*H*)-oxazolones used for the studied orthopalladation.

a modification of amino acids[8] and/or their derivatives or precursors, such as oxazolones,[4] are of high interest since they provide access to new families of molecules with improved activity. While orthometalated derivatives from saturated 5(4*H*)-oxazolones are limited to a few examples of complexes of Pd and Ir,[9] those of unsaturated 5(4*H*)-oxazolones were unknown until very recently.[4] Most of the reported examples have been obtained via transmetalation reactions,[4a] C−H bond activation being limited to only a few cases.[4b] As a consequence, the achievement of a general method based on the C−H bond activation remains as an important challenge.

In addition, the full understanding of the parameters governing any process necessarily demands the knowledge of the reaction mechanism. The mechanism of the C−H bond activation has been thoroughly explored, and an important number of relevant literature is available, related to both experimental and theoretical approaches.[10] In most of these studies the reaction medium contains a Brönsted base, either free or bonded to the metal center, that enables the abstraction of the proton formed on the C−H activation step.[10b−d] These mechanisms consider that the reactions occur in neutral aprotic medium; therefore, they are not valid when a neat acid is the reaction solvent. Furthermore, in some cases the reaction has been shown to be much faster in highly acidic media.[11] The consideration of the above-mentioned facts creates also the need for the study of the effect that solvents have on the mechanism operating on C−H bond activation processes, specially in the cases where protonated species are assisting the reaction by increasing its rate.

We report herein the regioselective synthesis of a large number of orthopalladated complexes from a wide range of (*Z*)-2-aryl-4-arylidene-5(4*H*)-oxazolones in carboxylic acid media via C−H bond activation, providing general access to this type of species. The reaction is regioselective with respect to the formation of six-membered rings, and the reaction rate increases as the acidity of the solvent increases. The kinetics of the reaction has been studied at variable temperature and pressure for several oxazolone ligands in different acidic media. The activation parameters obtained suggest a uniform mechanism operating in each medium for all the oxazolone ligands studied, and analogous to that indicated for simpler systems.[10j,11,12] A full density functional theory (DFT) calculation has been conducted to explain all experimental facts concerning the C−H bond activation process in acidic medium. Under acidic conditions the fully coordinated and protonated species $[Pd(RCO_2H)_3(ligand)]^{2+}$ has to be considered as the starting material for the reaction.[11,12] In all cases the reaction proceeds via the formation of an agostic C−H interaction with the metal center followed by proper proton abstraction by a coordinated carboxylic acid molecule in a sort of ambiphilic reaction mechanism.[10b]

RESULTS AND DISCUSSION

1. Orthopalladation via CH Bond Activation. A large number of different (*Z*)-2-aryl-4-arylidene-5(4*H*)-oxazolones (**1a**−**1o**, Figure 1) have been prepared in order to have the widest range of available starting materials. The number and position of the substituents have been selected to have access to all representative situations: electron-withdrawing (Cl, Br, NO_2) and electron-donating (Me, OMe) groups in *ortho* and *para* positions, or two substituents on both the 4-arylidene and 2-aryl rings. The syntheses of **1a**−**1o** have been carried out by the Erlenmeyer method,[13] with minor variations. All compounds have been previously prepared and characterized,[14−21] and the X-ray structure of **1i** has been determined (see Experimental Section and Supporting Information, Figure S1). The structure

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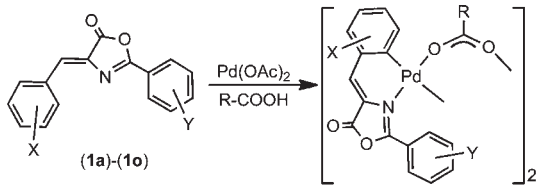
Scheme 1. Orthopalladations of 1a−1o Studied in Different Carboxylic Acids



RCOO = CH_3COO X = H, Y = H (**2a**); X = 3,4-$(OMe)_2$, Y = H (**2i**)
X = Y = 3,4-$(OMe)_2$ (**2m**)
RCOO = $ClCH_2COO$ X = 3,4-$(OMe)_2$, Y = H (**3i**)
RCOO = $CH_3C(O)COO$ X = 4-OMe, Y = H (**4b**); X = 3,4-$(OMe)_2$, Y = H (**4i**)
RCOO = CF_3COO X = H (**5a**), 4-OMe (**5b**), 2-OMe (**5c**), 2-Me (**5d**), 4-Me (**5e**), 4-Br (**5f**), 2-Cl (**5g**), 4-Cl (**5h**), 3,4-$(OMe)_2$ (**5i**), 3,4-$(Me)_2$ (**5j**)
Y = H for compounds **5a** to **5j**
X = H, Y = 3-OMe (**5k**); X = H, 3,4-$(OMe)_2$ (**5l**)
X = Y = 3,4-$(OMe)_2$ (**5m**)
X = 4-NO_2, Y = H (**5n**); X = 4-NO_2, Y = 3,4-$(OMe)_2$ (**5o**)

shows the *Z*-configuration of the arylidene moiety and a nearly planar arrangement of the whole molecular skeleton.[22]

The reactivity of **1a**−**1o** with $Pd(OAc)_2$ (OAc = acetate) in different carboxylic acids as solvents has been studied. In the weakest acidic medium (acetic acid) only substrates containing two strongly electron-donating methoxy substituents at the 4-arylidene ring (**1i** and **1m**) were metalated to an appreciable extent under harsh reaction conditions (95 °C for 2h), affording dimers **2i** and **2m** (Scheme 1). For the rest of the ligands the orthopalladation takes place with very low conversions under the same reaction conditions. For instance, **2a** is obtained from **1a** with yields around 8% after heating at 95 °C for 3 days. It is remarkable that complexes **2i** and **2m** incorporate selectively the palladium atom at the 4-arylidene ring, not at the 2-aryl ring, thus forming a six-membered palladacycle. Although a formal electrophilic substitution S_EAr on the most electron-rich ring seems a plausible explanation for this preference, the selective orientation of the metalation is not a simple electronic problem, as evidenced from the regioselective metalation of **1m**, having two methoxy groups on each side of the molecule and still producing the six-membered metallacycle exclusively. Moreover, no palladation was observed at all when one or two methoxy substituents are present on the 2-aryl ring (e.g., **1k**, **1l**, or **1o**). Clearly a more general view of the palladation process is needed to get more accurate conclusions.

Following previous observations about the acceleration of the C−H bond activation process in strong acidic media,[11,12,23] we have attempted the orthopalladation of all the oxazolones in solvents with higher acidity. Oxazolone **1i** has been selected as test substrate, because of their facile metalation in acetic acid, for comparative purposes. Its reaction with $Pd(OAc)_2$ in chloroacetic acid affords the corresponding chloroacetate complex **3i** in a similar yield (92%) to that of **2i** (91%) but under milder conditions (2 h, 65 °C (**3i**) vs 2 h, 95 °C (**2i**)). A further increase of the acidity of the reaction medium using pyruvic acid (acetic acid, pK_a = 4.75; chloroacetic acid, pK_a = 2.85; pyruvic acid, pK_a = 2.39)[24] allows the preparation of the expected dimeric pyruvate **4i** after stirring $Pd(OAc)_2$ with **1i** for 24 h at room temperature (alternatively 4 h at 60 °C or 10 min at 165 °C). That is, the process can be optimized either by decrease of the reaction temperature, keeping long reaction times, or by decrease of the reaction time but performing the reaction at high temperatures. Given the thermal decarboxylation process of pyruvic acid,[25] the use of high temperatures and long reaction times are unsuitable, and the best reaction conditions are a compromise between temperature and time. Using optimized reaction conditions, we achieved the orthopalladation of other derivatives under reasonable conditions, that is, **4b** can be obtained in a moderate 31% yield reacting $Pd(OAc)_2$ with **1b** at 60 °C for 4 h. The use of trifluoroacetic acid (pK_a = 0.52)[24c] as solvent further decreases the reaction time to only 5 min for oxazolone **1i**, compound **5i** being obtained at 25 °C in 95% yield. The use of this solvent has allowed for the orthopalladation of the whole series of oxazolones **1a**−**1o** (Figure 1, Table 1, Scheme 1). The optimized orthopalladation conditions for each oxazolone are collected in Table 1, together with the yields of isolated compounds. Clearly the reaction yield seems to be related with the nature of the substituents. In general, the mildest conditions are those for **1i**, since this is the most activated substrate.

Table 1. Optimized Conditions for the Orthopalladation of 1a−1o (Figure *1*) in CF_3CO_2H

entry	complex	*T* (°C)	*t* (h)	yield (%)[a]	X	Y
1	**5a**[b]	75	4	64[c]	H	H
2	**5b**	75	4	87	4-OMe	H
3	**5c**	75	4	87	2-OMe	H
4	**5d**	75	4	72	2-Me	H
5	**5e**	75	4	83	4-Me	H
6	**5f**	75	4	82	4-Br	H
7	**5g**	75	4	68	2-Cl	H
8	**5h**	75	4	57	4-Cl	H
9	**5i**	25	0.1	95	3,4-$(OMe)_2$	H
10	**5j**	75	2	74	3,4-$(Me)_2$	H
11	**5k**	75	4	91	H	3-OMe
12	**5l**	81	3	55	H	3,4-$(OMe)_2$
13	**5m**	95	2	83	3,4-$(OMe)_2$	3,4-$(OMe)_2$
14	**5n**	75	3	46	4-NO_2	H
15	**5o**	75	2	57	4-NO_2	3,4-$(OMe)_2$

[a] Isolated complex yield. [b] See ref 4b. [c] The yield was improved with respect to that in ref 4b.

For the unsubstituted **5a** the obtained yield is moderate (entry 1, 64%), but under the same reaction conditions the presence of electron-releasing groups, such as methyl or methoxy (**5b**−**e**, entries 2−5), produces an improvement of the yield (72−87%) regardless of their position. Similarly, the introduction of two strongly electron-donating groups (entries 9 and 10) produces a definite improvement of the yield (up to 95% for **5i**), even under smooth reaction conditions. Nevertheless, slightly electron-withdrawing substituents such as Cl or Br (**5f**−**h**, entries 6−8) also improve the yield of the palladated compound, albeit in a lower percentage. All these facts suggest that the electronic nature of the substituents is important, but not critical, in governing the regioselectivity of the reaction.

As indicated in Scheme 1, orthopalladation of the oxazolones to produce **5a**−**o** is completely regioselective in all studied cases, only the *ortho* CH bond of the arylidene ring being activated, affording six-membered palladacycles. We have not observed the formation of the 5-membered ring even in minor quantities. Even though the nature of the substituents on the arylidene ring has a definite effect on the yield, the regioselectivity of the reaction is independent of their nature. This independence is confirmed by the study of the reactivity of **1k**−**1o** (Table 1, entries 11−15).

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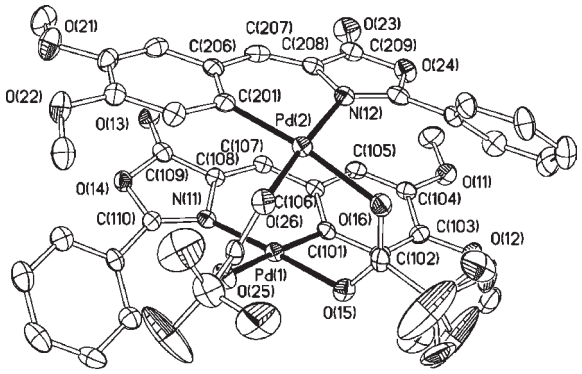

Figure 2. Molecular drawing of **5i**. Selected bond distances (Å) and angles (deg): Pd(1)−C(101) 1.986(3), Pd(1)−N(11) 2.034(2), Pd(1)−O(15) 2.0523(18), Pd(1)−O(25) 2.1621(18), Pd(1)−Pd(2) 2.9759(3), N(11)−C(110) 1.302(3), N(11)−C(108) 1.409(3), O(13)−C(109) 1.197(3), O(14)−C(110) 1.372(3), O(14)−C(109) 1.406(3), C(101)−Pd(1)−N(11) 92.22(10), C(101)−Pd(1)−O(15) 90.56(9), N(11)−Pd(1)−O(15) 177.07(8), C(101)−Pd(1)−O(25) 171.16(9), N(11)−Pd(1)−O(25) 95.58(8), O(15)−Pd(1)−O(25) 81.71(7), C(101)−Pd(1)−Pd(2) 96.29(7), N(11)−Pd(1)−Pd(2) 98.52(6), O(15)−Pd(1)−Pd(2) 82.07(6), O(25)−Pd(1)−Pd(2) 78.46(5).

Even the presence of one (**1k**) or two (**1l**, **1m**, **1o**) methoxy groups at the 2-phenyl ring does not produce a change in the orientation of the orthometalation, and six-membered palladacycles **5k**, **5l**, **5m**, and **5o** were obtained in moderate to excellent yields. The alternative approach, followed with oxazolones **1n** and **1o** (which contain the strongly deactivating 4-NO_2 substituent at the 4-arylidene moiety) does not produce any changes either, and **5n** and **5o** are obtained (46 and 57% yield, respectively). It is clear that the electronic effects based on the orientations predicted by the simple S_EAr reactions do not apply for the outcome of the reaction as indicated above.

Compounds **2**−**5** have been characterized by analytic and spectroscopic methods, and complexes **3i** and **5i** have also been characterized by X-ray diffraction techniques. The molecular drawing of **5i** is shown in Figure 2. The whole molecules of **3i** and **5i** are isostructural, and show the expected open-book structures in both cases (see Supporting Information).

2. Mechanistic Studies on the Orthopalladation Reaction: Kinetics. The cyclometalation reaction of different oxazolones (**1a**, **1b**, **1c**, and **1i**, Figure 1) by palladium acetate in solution to produce the corresponding six-membered cyclometalated compounds, has been studied under second order conditions ([Pd]/[oxazolone] = 0.7−1.3) to avoid the formation of the nonreactive bis-coordinated complexes. The reactions were followed spectrophotometrically in the solvent of choice (acetic, dichloroacetic, and trifluoroacetic acids), and the absorbance versus time traces derived at the wavelength where larger differences were observed. The monitoring of reactions in pyruvic acid could not be performed because of extensive decarboxylation. Dichloroacetic acid was used instead of chloroacetic given the better spectroscopic behavior of the former, while keeping an acidic character intermediate between acetic and trifluoroacetic acids. The nature of the starting material is thus modified according to the carboxylic acid acting as solvent, given the high lability of the Pd^{II} center, that enables a facile acetate by solvent carboxylate substitution. Additional measurements of the overall reaction via time-resolved ^{1}H NMR spectroscopy have also been conducted, to confirm that the monitored reaction effectively corresponds to the intramolecular cyclometalation (C−H bond activation) to produce the characterized six-membered ring. Some experiments with oxazolone **1i** have also been carried out in diluted triflic acid (CF_3SO_3H) solutions in acetic acid (Supporting Information, Figure S2). The ^{1}H NMR monitoring of these reaction mixtures again agrees with the formation of the desired organometallic complex **2i** under the conditions used. Hydrolysis of the oxazolone ligands is not observed, and it is only occurring under severe acidic conditions. In all cases the coordination of the oxazolone to the dimeric palladium center is fast in relation to the cyclometalation reaction, given the relatively high temperatures needed for the C−H bond activation.[10j,11] Consequently all the values found for the observed first-order rate constants, k_{obs}, for the systems studied correspond to the actual C−H bond activation process from the coordinated oxazolone complex. These values as a function of oxazolone, temperature, and pressure are collected in Supporting Information, Table S1. From these first order rate constants the thermal activation parameters and activation volumes, collected in Table 2 and Figure 3, are derived[26] for each solvent and oxazolone system.

Both the values for the enthalpies and entropies of activation are within the range obtained for other palladium acetate C−H bond activations via formal electrophilic substitution in acetic acid.[11] Nevertheless, their absolute values are larger ($\Delta H^{\ddagger}$) and more negative ($\Delta S^{\ddagger}$), in accordance with the relative slowness of the reaction observed. Further, the values determined for $\Delta V^{\ddagger}$ are slightly less negative than those found for the above-mentioned reactions, indicating a less compressive arrangement of the transition state. The good correlation of the values determined for $\Delta S^{\ddagger}$ and $\Delta V^{\ddagger}$ indicate that no direct involvement of the external solvent in the transition state is present in this reaction, contrarily to what has been observed for other substitution and redox reactions in potentially hydrogen-bonded organized media.[27] As a whole, the results agree with the presence of a highly ordered transition state such as that proposed previously, shown in Figure 4, where a neighboring terminal acetic acid ligand acts as proton acceptor to produce $CH_3CO_2H_2^+$ as a leaving group.[11f,12]

From the data indicated in Table 2 important differences are evident to occur on changing the reaction media (RCO_2H, R = CH_3, $CHCl_2$, CF_3) where the C−H bond activation is taking place. The reactions carried out in acetic acid are the slowest, this not being a consequence solely of the values of $\Delta H^{\ddagger}$, and the rather negative values determined for $\Delta S^{\ddagger}$ add up to produce larger values for $\Delta G^{\ddagger}$. The compensation plots for the systems studied, shown in Figure 5, are a good indication of this fact. As for differences generated from the electronic characteristics of the substituents of the cyclometalated six-membered ring, no significant changes are observed on the presence of electron-releasing MeO substituents on the ring,[10j,11] as would be expected for the ambiphilic nature of the reaction mechanism.[10b] Furthermore, given the fact that these substituents are not hindering the C−H bond being metalated (only the unhindered C−H bond is activated in **1i** ligand), no definite trends are even observed for the values of the entropies and volumes of activation.[10j,28]

The transition state proposed in Figure 4, although agreeing with the individual data for the orthometalation reaction, does not seem to justify the trends indicated in Table 2 and Figure 5, which are somehow related with the relative acidity of the solvent involved.

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Table 2. Values of the Rate Constants and Relevant Activation Parameters Obtained for the Reaction of Oxazolones 1a, 1b, 1c, and 1i with Palladium Acetate in Different Media

oxazolone	medium	$^{343}k^{a}/s^{-1}$	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	$\Delta V^{\ddagger}_{(T)}$/cm^3 mol$^{-1}{}_{(K)}$
1a[b]	CH_3CO_2H	1.0×10^{-5}	84 ± 4	-98 ± 12	n.m.
	$CHCl_2CO_2H$	9.6×10^{-3}	67 ± 1	-90 ± 3	n.m.
	CF_3CO_2H	1.9×10^{-3}	80 ± 1	-68 ± 2	n.m.
1b[b]	CH_3CO_2H	2.7×10^{-5}	75 ± 4	-113 ± 12	$-9.3 \pm 0.5_{(351)}$
	$CHCl_2CO_2H$	7.7×10^{-3}	63 ± 5	-102 ± 17	n.m.
	CF_3CO_2H	4.5×10^{-4}	83 ± 4	-70 ± 12	n.m.
1c	CH_3CO_2H	4.5×10^{-5}	86 ± 3	-81 ± 11	n.m.
	$CHCl_2CO_2H$	1.9×10^{-2}	56 ± 1	-120 ± 1	n.m.
	CF_3CO_2H	9.1×10^{-4}	54 ± 2	-150 ± 5	n.m.
1i	CH_3CO_2H	3.5×10^{-5}	89 ± 5	-76 ± 16	$-8.2 \pm 0.6_{(343)}$
		0.36[c]	43 ± 7[c]	-124 ± 22[c]	n.m.
	$CHCl_2CO_2H$	1.8×10^{-2}	67 ± 1	-86 ± 1	$-10 \pm 1_{(298)}$
	CF_3CO_2H	3.9×10^{-3}	65 ± 1	-106 ± 5	$-8.2 \pm 1.3_{(321)}$

[a] Extrapolated from Eyring plots. [b] Two equivalent positions considered, $k = k_{obs}/2$. [c] Triflic acid (CF_3SO_3H) added, second order rate constants M^{-1} s^{-1}; n.m. = Not measured.

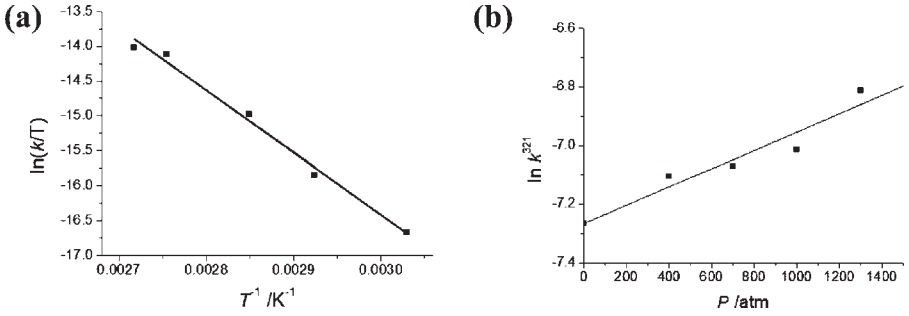

Figure 3. (a, left) Eyring plot for the C−H bond activation of **1b** by $Pd(OAc)_2$ in acetic acid. (b, right) Plot of ln k versus P for the C−H bond activation of **1i** by $Pd(OAc)_2$ in CF_3CO_2H.

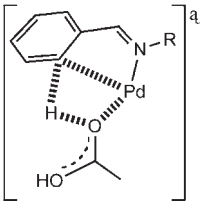

Figure 4. Proposed transition state for the C−H bond activation step from kinetic data.

This is especially true for the important acceleration obtained for the reaction in CH_3CO_2H in the presence of variable quantities of triflic acid (CF_3SO_3H) that ensures the predominance of the fully protonated $[Pd(CH_3CO_2H)_3(\kappa^1\text{-}N_{oxazolone})]^{2+}$ material. A competition effect between the Lewis basicity of the coordinated carboxylic acid and the Brönsted acidity of the $RCO_2H_2^+$ leaving species (dashed bonds in Figure 4) should play a key role in the full oxazolone proton abstraction process.

3. Mechanistic Information on the Orthopalladation Reaction: DFT Calculations. Contrarily to what has been observed for other cyclometalated ligands on Pd^{II},[10j,11] and to the general rules established for the process,[10k,29] for the oxazolones involved in this study only six-membered cyclometalated species

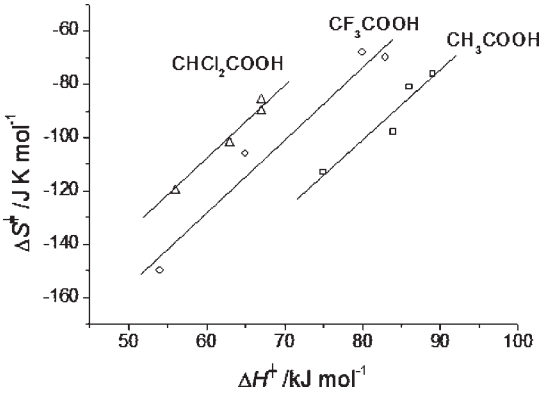

Figure 5. Isokinetic compensation plot for all the oxazolone C−H bond activation systems kinetically studied as a function of the different RCO_2H reaction media.

are formed, despite the possibility of generating five-membered analogues. This remarkable regioselectivity, the observed total absence of cyclometalation process in nonprotic solvents,[4b] and the recent establishment of how protonation of the acetate ligands contribute to a facile C−H bond activation,[12] prompted us to calculate the energy profiles of the reactions via DFT.

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Initially calculations have been carried out considering the accepted sequence for the metalation reaction in nonprotic solvents[10f] leading to both five- and six-membered metallacycles and using toluene, acetic acid, methanol, and water as continuous solvent media. The process can be visualized as the establishment of a C−H interaction with the Pd^{II} center followed by the proper proton abstraction from the cyclometalated phenyl ring, in what has been recently classified as an ambiphilic mechanism.[10b] The calculated energy profile for the C−H bond activation of oxazolone **1a** in acetic acid is shown in Supporting Information, Figure S3a. The data indicates the thermodynamic slight preference for the six-membered metallacycle, although a prohibitively high activation energy for both cyclometalated complexes is needed for the process to occur from $[Pd(\eta^2\text{-}CH_3CO_2)(CH_3CO_2)(\kappa^1\text{-}N_{oxazolone})]$. Additionally, intramolecular hydrogen bonding is needed to justify the stability of the final cyclometalated compounds of the observed process. As found for similar imine ligand systems already published,[12] protonation of this species to $[Pd(\eta^2\text{-}CH_3CO_2)(CH_3CO_2H)(\kappa^1\text{-}N_{oxazolone})]^+$ in acetic acid as solvent, despite producing better results and thermodynamically favoring the six-membered metallacycle, still implies an unreasonably high activation barrier for the process (Supporting Information, Figure S3b). In this case even the activation barrier leading to the six-membered metallacycle is slightly more demanding in energy, not justifying the nonappearance of the five-membered compound. Furthermore, the assistance from an external (solvent) carboxylic acid has been shown ineffective for an improvement on the energetic demands of the process.[12] From this point, and given the fact that calculations from a partially deprotonated $[Pd(CH_3CO_2)(CH_3CO_2H)_2(\kappa^1\text{-}N_{oxazolone})]^+$ species do not produce better results, the calculation of the energy profiles from the reasonable[30] starting $[Pd(CH_3CO_2H)_3(\kappa^1\text{-}N_{oxazolone})]^{2+}$ material in 12 M CH_3CO_2H (or in CF_3SO_3H/CH_3CO_2H solutions) was pursued. Figure 6a collects the summary of the data in acetic acid, showing that the energy barriers needed for the process diminish to much more reasonable values, even though the presence of fairly constrained species is required.[31] Furthermore, although the final five- and six-membered metallacycles show the same relative thermodynamic stability trend than before, the de facto energy barrier calculated for the formation of the six-membered metallacycle is definitively smaller than that for the competitive five-membered analogue, given the relative higher energy calculated for the initial coordination compound **5**×**1**. This difference is directly related to the prearrangement of the relevant acetic acid ligand as receptor of the hydrogen from the metallating ring of the oxazolone. This is reminiscent of the intramolecular effect found for a η^2-η^1 rearrangement of different carboxylates thus producing a lower activation barrier for C−H activation the process.[10c]

It is thus clear that the preference for a particular metallacycle is not only based on thermodynamic grounds, the kinetic parameters play, at least in this case, also a crucial role. Similar regioselective orthopalladations[32] of iminophosphorane ligands have been recently studied, and the ultimate reasons of the selectivity based on kinetic parameters determined through DFT methods.[32b,d]

Given the fact that the data in Table 2 indicate a neat acceleration of the C−H activation process on increasing the acidity/decreasing the donor characteristics of the carboxylate ligands on the Pd^{II} center, the same energetic profiles were derived for the system in 13 M trifluoroacetic acid.[33] Figure 6b shows the summary of the calculated data. The data agree very well with the important acceleration of the cyclometalation reaction on going from CH_3CO_2H to CF_3CO_2H medium. Furthermore, the preference for the six-membered final ring is even more prononunced with respect to the five-membered cyclometalated compound. The relevant calculated bond distances for the different transition states involved in the four reaction paths indicated in Figure 6 are collected in Table 3. Figure 7 also collects the calculated bond lengths for transition states $6TS_{X12}$, $6TS_{Y12}$, $6TS_{X23}$ and $6TS_{Y23}$. As in the case of the acetic acid complexes, the energy needed for the prearrangement of the accepting trifluoroacetic acid ligand and oxazolone ligand in the five-membered metallacycle is about 20 kJ/mol higher. It is interesting to note that for the polar solvents studied (acetic acid, methanol, and water) the differences encountered in the energy reaction profiles are fully equivalent, as indicated in Supporting Information, Figure S4.

From the calculated data represented in Figure 7 it is important to note that the limiting step for the experimental six-membered ring cyclometalation process observed corresponds to that going via TS_{12} in acetic acid but via TS_{23} in trifluoroacetic acid. That is, the limiting step moves from the proton attachment to the leaving carboxylate (agostic interaction of the Pd^{II} center with the C−H bond) to the C−H bond rupture (proton abstraction) on changing the solvent from CH_3CO_2H to CF_3CO_2H. This fact is in excellent agreement with the kinetico-mechanistic experiments carried out. Compensation plots in Figure 5 indicate a definite change for the different solvents used, even showing that for $CHCl_2CO_2H$ the limiting step will probably differ further.

Detailed data analysis in Table 3 gives a very clear explanation of the important acceleration observed for the formation of the six-membered metallacycle in trifluoroacetic acid medium when compared with acetic acid (**6X** versus **6Y** path). From the data it is clear that, in TS_{12} for this process, the leaving CF_3CO_2H group is much more connected to the aromatic hydrogen than CH_3CO_2H, and its decoordination from the Pd center is also more advanced. We are dealing with a latter transition state for the proton transfer to the leaving $RCO_2H_2^+$ group. With respect to the proper C−H bond breaking process, achieved in TS_{23}, the data also indicates that the transition state in CF_3CO_2H medium is also in a latter position with a much longer $C-H_{(activated)}$ distance. As for the kinetic selectivity for the six-membered metallacycle in both processes, the same considerations hold. Both in CH_3CO_2H and CF_3CO_2H media the attachment of the preorganized aromatic hydrogen to the coordinated carboxylate oxygen is more efficient for the six-membered metallacycle formation, thus assisting better the process. As a whole, though, the kinetic preference for the metallacycle formation is more pronounced in CF_3CO_2H medium. The effect is clearly related with the proton acceptance of the coordinated trifluoroacetic acid that thus weakens the existing Pd−O bond in a process that is facilitated for steric reasons in the six-membered metallacycle formation.

In the same line, the nonrelevant hydrogen bond lengths calculated for all the transition states involved in the four possible reaction paths indicate that distances are longer for the CF_3CO_2H compounds ($6TS_Y$, Figure 7), in accordance with the higher acidity of the ligand indicated above. Surprisingly, though, all the $Pd-O_{(coordinated\ carboxylate)}$ calculated distances are the same within error, indicating that the hydrogen bonding interactions are capable of compensating for the lower Lewis basicity of the ligands (translated into lower M−L bond strength and longer M−L distances), possibly because of the formation of

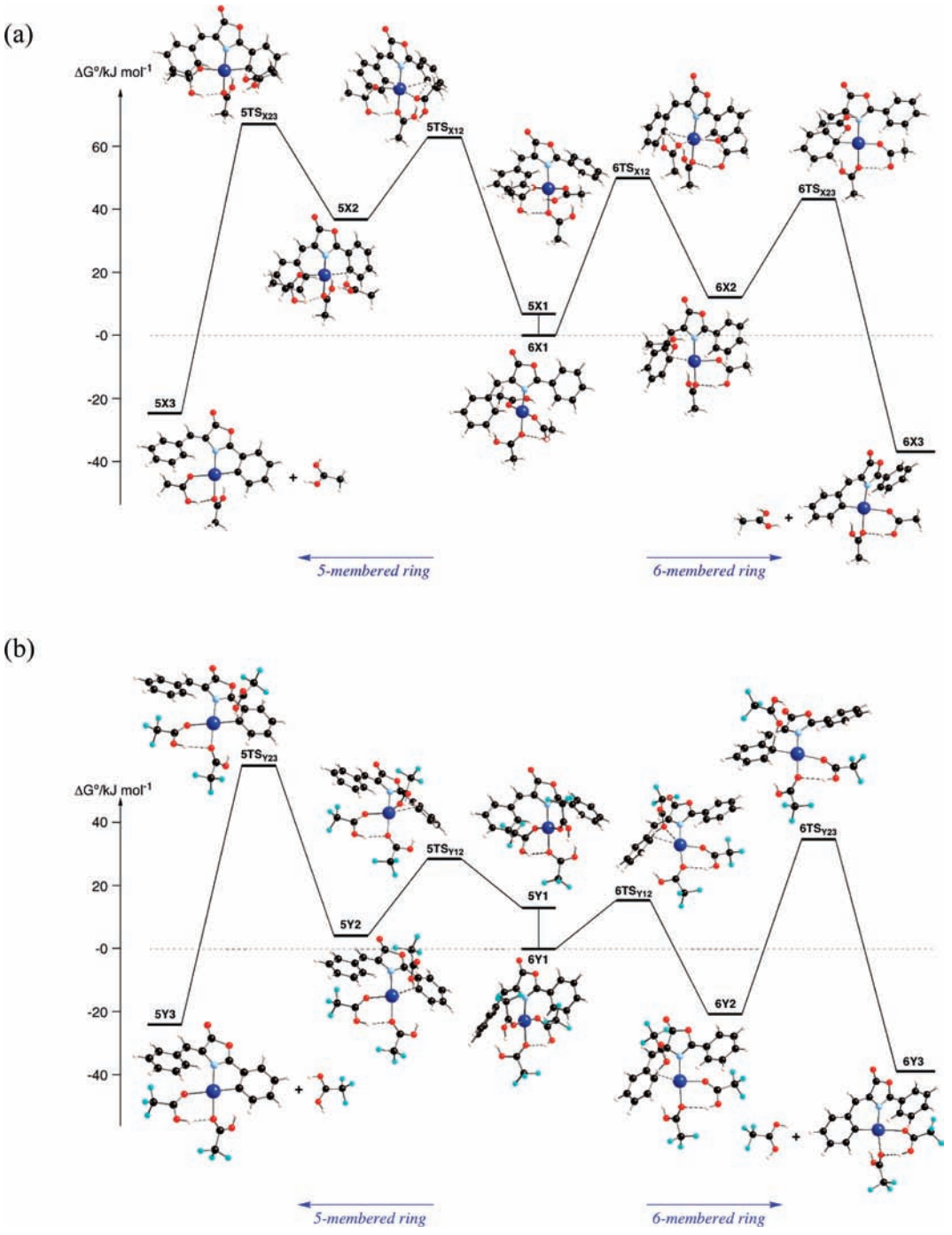

Figure 6. Energy profile for the C−H bond activation of (a) $[Pd(CH_3CO_2H)_3(\kappa^1\text{-}N_{oxazolone})]^{2+}$ and (b) $[Pd(CF_3CO_2H)_3(\kappa^1\text{-}N_{oxazolone})]^{2+}$ in acetic acid.

rather stable Pd-OC(R)OH-O- cycles.[34] It is clear that the assumption of a continuous model for the solvent for systems prone to hydrogen bonding has to be considered very carefully; in these systems hydrogen bonding networks play a crucial role.

It is also important to note the about 20 kJ/mol difference between species **5×1** and **6×1** (or **5Y1** and **6Y1**), shown in Figure 6 and not existing either in compounds $[Pd(\eta^2\text{-}CH_3CO_2)(CH_3CO_2)(\kappa^1\text{-}N_{oxazolone})]$ (**5M1** and **6M1**) or $[Pd(\eta^2\text{-}CH_3CO_2)(CH_3CO_2H)(\kappa^1\text{-}N_{oxazolone})]^+$ (**5A1** and **6A1**) (Supporting Information, Figure S3). These differences indicate a destabilization for the arrangement of the relevant carboxylate ligand for the abstraction of the hydrogen from the metallating C−H bond in the starting material for the five-membered metallacycle with respect to the competing six-membered one. That is, the need of an initial non-hydrogen bonded carboxylic acid ligand to assist in the abstraction of the proton from the metallating oxazolone is less energy demanding for formation of the six-membered cyclometalated complex.

Finally it is remarkable that the values for $\Delta H^{\ddagger}$ for the process on the $CHCl_2CO_2H$ solvento complexes are in the lower side,

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while $\Delta S^{\ddagger}$ are in the same range than for all the reactions taking place. DFT calculations have been conducted on the 6-membered cyclometalated ring formation with $CHCl_2CO_2H$ solvento complexes to explain the rather surprising rate and activation parameter values obtained. Figure 8 collects the relative energies for TS_{12}, TS_{23}, and the intermediate species (having an agostic C−H interaction with the palladium center) with the same structures than their analogous acetic and trifluoroacetic acid solvates. It is clear that the important rate acceleration observed with respect to the trifluoroacetic system does not correspond to changes in transition state energies, but to the fact that the intermediate **6Z2** species is considerably less stabilized (Supporting Information, Table S3); the actual calculated total energetic demands being 82, 72, and 60 kJ/mol for the CH_3CO_2H, CF_3CO_2H, and $CHCl_2CO_2H$ systems, respectively. It is thus clear that the main reason for the acceleration of the process for $CHCl_2CO_2H$ solution corresponds to enhanced stability of the **6×2**, **6Z2**, and **6Y2** species on increasing the electronegativity/acidity of the solvent.

CONCLUSION

The orthopalladation of (*Z*)-4-arylidene-2-aryl-5(4*H*)-oxazolones via CH bond activation has been achieved for a notable number of oxazolones with different substituents. The process is completely regioselective, and allows the incorporation of the Pd atom at the 4-arylidene ring forming a six-membered palladacycle, the reaction being accelerated in increasing acidic media. The formation of the six-membered palladacycle is kinetic- and thermodynamically favored versus the formation of the five-membered ring, as shown by the elucidation of the mechanism of the reaction by DFT methods.

The data obtained indicate that the formation of solvento $[Pd(RCO_2H)_3(\kappa^1\text{-}N_{oxazolone})]^{2+}$ complexes represents a crucial role for the readiness of the cyclometalation reaction of oxazolones as already established for other systems, both experimentally and in silico. The effect of triflic acid as accelerating additive for the reaction is clearly caused by its compensation of the increased acidity of the coordinated RCO_2H ligands, that should reduce the amount of fully protonated solvento species present in the reaction medium. That is, the acceleration observed for the CF_3CO_2H solvento compounds versus those from CH_3CO_2H is not directly related with the neat acidity of the solvent. A very fine-tuning between Lewis and Brönsted basicity of the carboxylic acid used as solvent and as ligands is the key factor for the trends observed. While for the weakest acidity system (CH_3CO_2H) the limiting step for the metalation process corresponds to the initial

Table 3. Relevant Calculated Distances (Å) for the Transition States Indicated in Figure 6

	CH_3CO_2H				CF_3CO_2H			
	5-member		6-member		5-member		6-member	
	TS_{12}	TS_{23}	TS_{12}	TS_{23}	TS_{12}	TS_{23}	TS_{12}	TS_{23}
$C-H_{activated}$	1.10	1.38	1.10	1.36	1.10	1.49	1.10	1.48
$Pd-O_{leaving}$	2.76		2.72		2.76		3.36	
$H_{activated}-O_{leaving}$	2.62	1.29	2.26	1.30	2.62	1.22	2.10	1.22

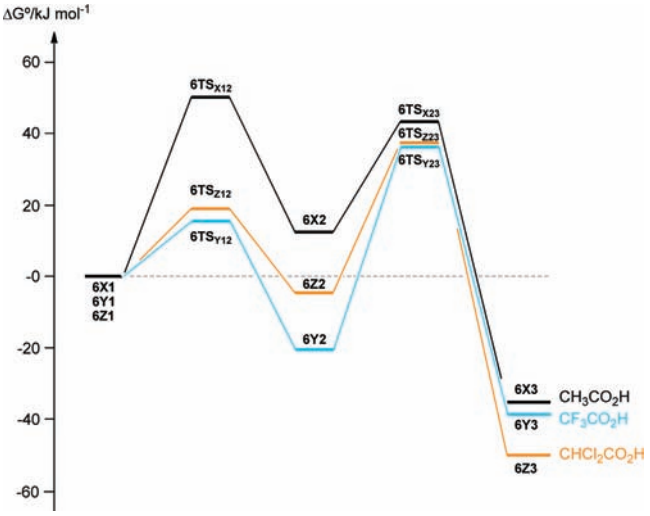

Figure 8. Calculated energy profile for the C−H bond activation for the formation of 6-membered metallacycles of $[Pd(RCO_2H)_3(\kappa^1\text{-}N_{oxazolone})]^{2+}$ (R = CH_3, **6×1**; CF_3, **6Y1**; $CHCl_2$, **6Z1**) in acetic acid.

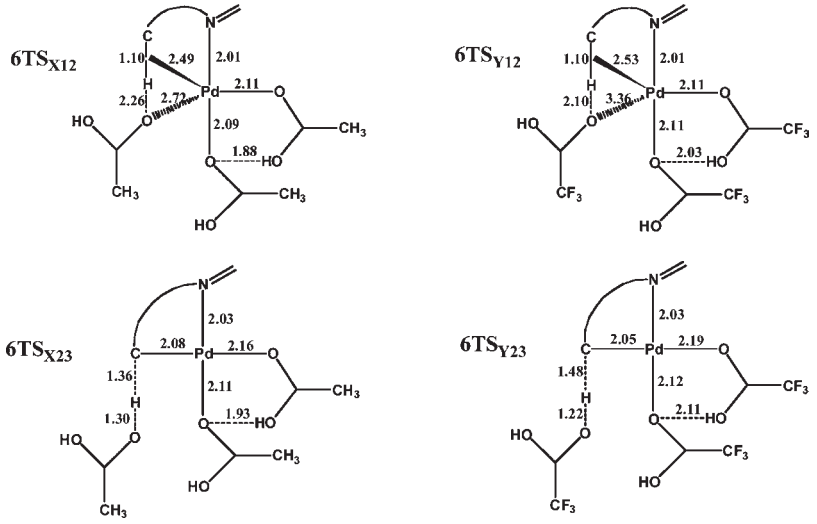

Figure 7. Calculated bond lengths (Å) for the 6-membered transition states involved in Figure 6.

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Pd···H−C agostic interaction, for the systems with much larger acidities (CF_3CO_2H and $CHCl_2CO_2H$) this initial interaction is less energy demanding and the limiting step involves the proper proton abstraction from the carbon. Furthermore, the relative stability of the intermediate species having this Pd···H−C agostic interaction is found to notably increase with the electronegativity of the solvent system; consequently, the lesser electronegative character of the $CHCl_2CO_2H$ ligand produces a less stable system than the equivalent CF_3CO_2H compound. As a consequence, cyclometalation of the oxazolone ligands in $CHCl_2CO_2H$ results in the faster reaction for all the systems studied because both the initial Pd···H−C agostic interaction is less energy demanding and the stability of the intermediate formed is lower.

EXPERIMENTAL SECTION

General Methods. Solvents were dried and distilled using standard procedures before use. Elemental analyses (CHN) were carried out on a Perkin-Elmer 2400-B microanalyzer. Infrared spectra (4000−380 cm^{-1}) were recorded on a Perkin-Elmer Spectrum One IR spectrophotometer. ^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$, DMSO-d_6, and CD_2Cl_2 solutions at 25 °C on Bruker AV300 and AV400 spectrometers (δ in ppm, J in Hz) at ^1H operating frequency of 300.13 and 400.13 MHz, respectively. ^1H and ^{13}C spectra were referenced using the solvent signal as internal standard, while ^{19}F spectra were referenced to $CFCl_3$ (85%). ESI^+ mass spectra were recorded using an Esquire 3000 ion-trap mass spectrometer (Bruker Daltonic GmbH) equipped with a standard ESI/APCI source. Samples were introduced by direct infusion with a syringe pump. Nitrogen served both as the nebulizer gas and the dry gas. The mass spectra ($MALDI^+$) were recorded from $CHCl_3$ solutions on a MALDI-TOF Microflex (Bruker) spectrometer (DCTB as matrix). Oxazolones **1a**,[14] **1b**,[15] **1c**,[16] **1d**−**e**,[15c,16] **1f**−**h**,[15c,16b,17] **1i**,[18] **1j**,[16] **1k**−**m**,[19,20] **1n**,[16b,21] and **1o**[4b] were synthesized according to published methods. Complexes **2n**, **5a**, **5k**, **5l**, and **5m** have been previously reported.[4b]

Orthopalladated Complexes. The full preparative procedures and characterization for the new orthopalladated complexes are collected in the Supporting Information. We include here a representative example.

Synthesis of 2i. To a stirred solution of **1i** (0.500 g, 1.616 mmol) in glacial acetic acid (30 mL), palladium acetate (0.363 g, 1.616 mmol) was added. The solution was refluxed for 2 h at 95 °C meanwhile the color of the solution changed from pale brown to intense red. After cooling the resulting solution was diluted with water, the product extracted with CH_2Cl_2 (100 mL) and the organic solution evaporated under reduced pressure to small volume (ca. 3 mL). Hexane addition (40 mL) and further stirring affords **2i** as a dark red solid (Yield 0.697 g, 91%). ^1H NMR ($CDCl_3$) δ = 1.15 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 6.84 (s, 1H, $H_{6''}$), 6.94 (s, 1H, $H_{3''}$), 7.40 (t, ^3J = 7.8 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.45 (s, 1H, $H_{7''}$), 7.53 (t, ^3J = 6.8 Hz, 1H, $H_{4'}$), 7.79 (d, ^3J = 7.5 Hz, 2H, $H_{2'}$, $H_{6'}$). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ = 22.54 (1C, $\underline{C}H_3COO$), 55.73, 56.08 (2C, $2O\underline{C}H_3$), 114.55 (1C, $C_{6''}$), 115.98 (1C, $C_{3''}$), 121.26, 122.94, 123.81, 134.60 (4C, $C_{1'}$, $C_{1''}$, C_2, $C_{2''}$), 127.79 (2C, $C_{3'}$, $C_{5'}$), 130.99 (2C, $C_{2'}$, $C_{6'}$), 133.33 (1C, $C_{4'}$), 139.41 (1C, $C_{7''}$), 147.03, 150.02 (2C, $C_{4''}$, $C_{5''}$), 161.72 (1C, C_1), 166.21 (1C, C_3), 179.61 (1C, $CH_3\underline{C}OO$). IR: ν = 1783 cm^{-1} (C═O), 1651 cm^{-1} (C═N). MS (MALDI +) m/z, (rel. int. %): 888.1 (20.2%) $[M - CH_3COO^-]^+$, 473.2 (100%) $[M/2]^+$, 414.1 (93.5%) $[M/2 - CH_3CO_2^-]^+$. Anal. Calcd for $C_{40}H_{34}N_2O_{12}Pd_2$ (946.02): C, 50.70; H, 3.62; N, 2.96. Found: C, 50.33; H, 3.39; N, 2.64.

X-ray Crystallography. Crystals of **1i**, **3i**, and **5i** of good quality were grown by vapor diffusion of Et_2O into CH_2Cl_2 or $CHCl_3$ solutions of the crude products at 25 °C. In each case, a single crystal was mounted at the end of a quartz fiber in a random orientation, covered with perfluorinated oil and placed under a cold stream of N_2 gas. Data collection was performed on Bruker Smart Apex CCD or Oxford Diffraction Xcalibur2 diffractometers using graphite-monocromated Mo-Kα radiation (λ = 0.71073 Å). In all cases, a hemisphere of data was collected based on ω-scan and ϕ-scan runs. The diffraction frames were integrated using the programs SAINT[35] or CrysAlis RED,[36] and the integral intensities were corrected for absorption with SADABS.[37] The structures were solved and developed by Fourier methods.[38] All non-hydrogen atoms were refined with anisotropic displacement parameters. H atoms were placed at idealized positions and treated as riding atoms. Each H atom was assigned an isotropic displacement parameter equal to 1.2 times the equivalent isotropic displacement parameter of its parent atom. The structures were refined to F_o^2, and all reflections were used in the least-squares calculations.[39] Crystallographic data (excluding structure factors) for the structure of **1i**, **3i**, and **5i** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 816893 (**1i**), CCDC 816894 (**3i**), and CCDC 816895 (**5i**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44-(0)1223−336033 or e-mail: deposit@ccdc.cam.ac.uk).

Kinetics. The reactions at atmospheric pressure were followed by UV−vis spectroscopy in the full 750−300 nm range on a HP8543 or Cary 50 instruments equipped with a thermostatted multicell transport (±0.1 °C). Observed rate constants were derived from the absorbance versus time traces at the wavelengths where a maximum increase and/or decrease of absorbance was observed. No dependence of the values on the selected wavelengths was detected, as expected for reactions where good retention of isosbestic points is observed. For runs at elevated pressure, a previously described pressurizing system and high pressure cell were used.[11e,40] In these cases the changes in spectra with time were recorded on a J&M TIDAS instrument in the full wavelength range.

The general kinetic technique is that previously described.[11f−h,41] The solutions for the kinetic runs were prepared by dissolving the calculated amounts of the palladium compounds in the desired solvent (CH_3COOH, $CHCl_2COOH$, CF_3COOH, CH_3COOH/CF_3SO_3H). In all cases no dependence on the concentration of palladium was detected, and it was kept in the $(2-5) \times 10^{-4}$ M margin. Rate constants were derived from exponential least-squares fitting by the standard routines.[42] Supporting Information, Table S1 collects all the obtained k_{obs} values for the complexes studied as a function of the starting complex, temperature, and pressure. Least-square errors for the rate constants were always in the range of 10−15% of the calculated value. All post-run fittings to rate laws were done by standard commercially available fitting programs.

Computational Details. Calculations were carried out using the GAUSSIAN03 or 09 packages.[43] The hybrid density functional method known as B3LYP was applied.[44] Relativistic effective core potentials from Stuttgart-Dresden group were used to represent the innermost electrons of the palladium atom and its associated basis set of valence double-ζ quality known as SDD.[45] The basis set for the light elements (C, N, O, and H) was also double-ζ quality split-valence and includes a polarization functions in all atoms (known as SVP).[46] The geometries for minima were fully optimized in all isomers, and transition states were located to connect two minima, and they were confirmed by a vibrational analysis. Energies in solution were taken into account by PCM calculations using GAUSSIAN03[43a] for toluene, methanol, and water (ε = 2.379, 32.63, and 78.4, respectively) and GAUSSIAN09[43b] for acetic acid (ε = 6.2528),[47] keeping the geometry optimized for gas phase (single-point calculations). All DFT calculation data for the coordinates and absolute energies are available in tabular format in the Supporting Information, Tables S2 and S3.

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■ ASSOCIATED CONTENT

Supporting Information. Full experimental section, CIF of compounds **1i**, **3i**, and **5i**, and geometries of all singular points calculated by DFT. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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