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# Cyclopalladation and Reactivity of Amino Esters through C–H Bond Activation: Experimental, Kinetic, and Density Functional Theory Mechanistic Studies

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*This paper is dedicated to Professor Antonio Laguna on the occasion of his 65th birthday*

**Abstract:** The orthopalladation, through C–H bond activation, of a large number of amino esters and amino phosphonates derived from phenylglycine, and having different substituents at the aryl ring and the C-α atom, as well as on the N-amine atom, has been studied. The experimental observations indicated an improvement in the yields of the orthopalladated compounds when the N-amine and/or the C-α atom are substituted, when compared with the unsubstituted methyl phenylglycinate derivatives. In contrast, substitutions at the aryl ring do not promote significant changes in the orthometalation results. Furthermore, the use of hydrochloride salts of the amino esters has also been shown to have a remarkably favorable effect on the process. All these observations have been fully quantified at different temperatures and pressures by a detailed kinetic study in solution in different solvents and in the presence and absence of added Brønsted acids and chloride anions. The data collected indicate relevant changes in the process depending on these conditions, as expected from the general background known for cyclopalladation reactions. An electronic mechanism of the orthopalladation has been proposed based on DFT calculations at the B3LYP level, and a very good agreement between the trends kinetically measured and the theoretically calculated activation barriers has been obtained. The reactivity of the new orthopalladated amino phosphonate derivatives has been tested and it was found that their halogenation, alkoxylation and carbonylation resulted in formation of the corresponding functionalized *ortho*-haloaminophosphonates, *ortho*-alkoxyaminophosphonates and oxoisoindolinylphosphonates.

**Keywords:** amino acids · C–H activation · density functional calculations · kinetics · palladium

## Introduction

The use of transition metals to build or modify organic molecules is a well-established procedure, applied from the simplest compounds to the most sophisticated scaffolds.[1–3] The metal-mediated tailored breaking and formation of C–C or C–heteroatom bonds usually takes place smoothly under convenient reaction conditions by employing catalytic amounts of metals, thus saving energy, time and materials. However, to attain maximal reactivity and selectivity in the starting M–C bond formation, the processes often involves the use of prefunctionalized reagents, with associated problems of tedious multistep syntheses of the starting materials, low atom economy, and waste disposal.[1–3] Therefore, the efforts of many chemists have been directed towards the development of catalytic processes by using alternative approaches. Among the different existing possibilities, probably the most successful involves metal-mediated activation and breaking of C–H bonds as a synthetic tool for the M–C bond formation.[4] This approach avoids the cumbersome use of prefunctionalized substrates, saving preparation steps and, consequently, energy, time and money. This methodology, nevertheless, has a major drawback: the selectivity of metal site incorporation, because C–H bonds are ubiquitous in organic species. Both specific solutions based on the innate reactivity of the molecules, due to inherent electronic and/or steric biases,[5] and coordination-directed reactivity,

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as a consequence of the presence of directing groups, have been show to be very efficient ways to address this problem.[6a] Orthopalladated complexes are excellent examples of the latter, promoting smooth and site-selective C–H bond activation.[4j,p,6b] Furthermore, the reactive Pd–C bond can be transformed into new C–C or C–heteroatom bonds in a variety of ways, with oxidative coupling (involving high oxidation states) or insertion of unsaturated molecules (usually involving low oxidation states) being two possibilities.[4j,p,6a] It is clear that a precise knowledge of all the individual steps involved in the functionalization sequence is highly desirable to establish the optimal catalytic conditions. This knowledge must include the role played by the substituents of the substrate to be functionalized, as well as those originating from the ancillary ligands on the metal. From the body of data accumulated until now it is clear that both oxidation[7a,b] and C–H bond activation[7c–f] can be turnover-limiting steps; the latter being the critical step much more often. Interestingly, even ligands that do not seem to directly participate in the functionalization reactions have been shown to be relevant to assisting the process.[7g,h]

We are currently interested in the functionalization of α-amino acids, more specifically those derived from phenylglycine, by using orthopalladated complexes as intermediates.[8] The importance of the amino acids as key molecules in biological processes is unquestionable.[9] Furthermore, the increasing interest in closely related species such as α-aminophosphonic esters, due to their biological activity[10a] as enzyme inhibitors,[10b] powerful antibiotics,[10c] or antitumor compounds,[10d] among others, has prompted a large number of synthetic methods for their tailored preparation;[11] to the best of our knowledge, however, none are based on orthopalladation reactions. Stoichiometric transformations of amino acids, based on oxidative couplings[6,8] and/or insertion of small molecules,[6,12] are known, with both strategies sharing the same C–H bond activation step. However, catalytic reactions are still limited to a few examples,[13] and the functionalization of α-aminophosphonic esters is still unknown. Despite recent reports,[13a] problems in the C–H bond activation step have been associated with these lack of results. Aiming to develop more efficient functionalization processes based on C–H bond activation, we report here a comprehensive study of the influence of the substituents on the C–H bond activation step in phenylglycine-based amino acids and amino phosphonic esters. The changes at the N atom and the C-α atom are found to be critical for tuning the reaction rate, whereas, surprisingly, no changes were observed when modifications are introduced at the aryl ring. In addition, α-aminophosphonic esters have been efficiently functionalized for the first time.

## Results and Discussion

**Synthesis and characterization of orthopalladated complexes 3a–n**: The amino esters and amino phosphonates shown in Figure 1 were prepared by using previously reported methods,[8,14–18] although in most cases we introduced slight modifications (see the Supporting Information) to optimize the reported procedures. To study the individual effect of each substituent on the C(aryl)–H bond-activation step, we investigated a large set of amino ester based substrates with different substituents in all modifiable points of the molecule; i.e., the N-amine atom, the C-α atom and the aryl ring. Therefore, from the hydrochloride salt of the base scaffold **1a** (**1a**·HCl) we studied the orthopalladation of compounds with both electron-withdrawing (triflate) and electron-donating (methyl) groups at the N-amine (**1b** and **1c**), derivatives with substituents of different electronic nature (OMe, Br, and $NO_2$) at different positions of the aryl ring (*ortho*, *meta*, and *para*) (**1d**·HCl–**1h**·HCl), quaternary amino esters substituted at C-α with alkyl or aryl groups (**1i**·HCl–**1k**·HCl), including a conformationally restricted example (**1l**·HCl), and less common compounds in which the ester group was substituted by the isosteric phosphonate group (**1m**·HCl and **1n**·HCl). In such a way, we aimed to gather representative examples of all possible structural situations.

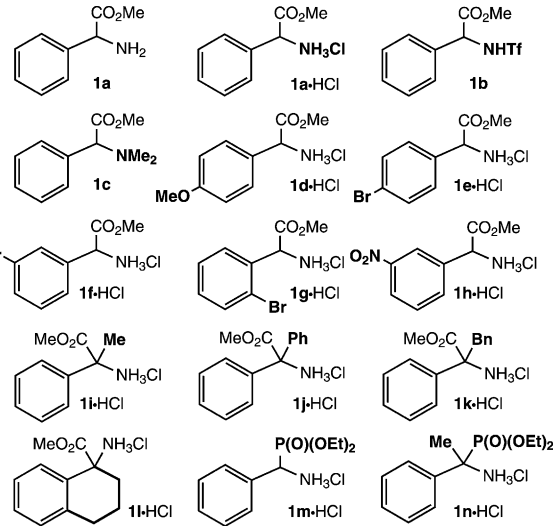
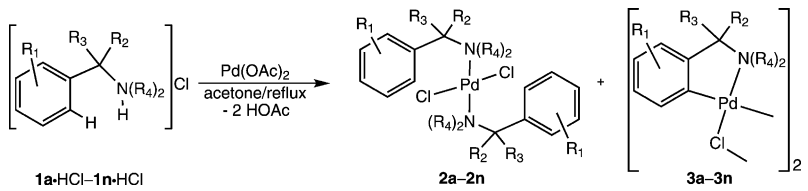



Figure 1. Amino esters and hydrochloride salts used in this work.




Scheme 1. Synthesis of the orthopalladated complexes, **3a–n**, and nonmetalated bis-amino complexes, **2a–n**, derived from phenylglycines.

The orthopalladation of **1a**·HCl was performed by following the original procedure developed by Fuchita,[19] which was taken as reference. Attempts to improve this procedure (acetone, reflux, 20 h, 58% isolated yield) were conducted, but changing from acetone to other solvents did not improve the yield. Lower conversions were obtained in MeOH, no reaction was observed in $CH_2Cl_2$, and even decomposition to 2-oxo-2-phenylacetic acid was detected when acetic acid was used as solvent. A slight increase of the reaction time up to 24 h in acetone heated to reflux allowed orthopalladated **3a** to be obtained in an improved yield of 67%, together with the non-metalated bis-amino coordination compound **2a** (32% yield). Further increases in reaction time allowed a yield of **3a** of 85% to be reached.[8d] The general process is indicated in Scheme 1, and the results obtained are summarized in Table 1; other modifications did not result in further improvements in the reaction yield. Whereas the free amino ester $PhCH(CO_2Me)NH_2$ (**1a**), in acetone heated to reflux for 24 h afforded a mixture of **2a** and **3a** containing only 30% **3a** after treatment with NaCl, the use of its ammonium triflate salt $[PhCH(CO_2Me)NH_3]OTf$ (**1a**·HOTf), also followed by treatment with NaCl, resulted in a better yield of **3a** (56%), compared with **1a**, although still lower than that of the hydrochloride **1a**·HCl. The superior performance of the ammonium salts with respect to those of the free amino esters is fully consistent with previous results.[10,19] We therefore concluded that conversion of the N-amine into the ammonium chloride was the best option for developing the general procedure. For these reasons, and also for synthetic simplicity and convenience, all reactions were performed by using amino esters in the form of their hydrochloride salts, except for **1b** and **1c** for clear reasons.

Table 1. Product distribution for the orthopalladation of amino esters shown in Figure 1 and Scheme 1.

| Amino ester | Time [h] | Complex **2** [%][a] | Complex **3** [%][a] | Reference |
|---|---|---|---|---|
| **1a**·HCl | 20/24 | not reported/32 | 58/67 | [19]/this work |
| **1b** | 48 | not observed | 56 | [8a] |
| **1c** | 24 | not observed | >65 | [8a, 15a, b] |
| **1d**·HCl | 24 | 41 | 59 | [8c] |
| **1e**·HCl | 24 | 34 | 66 | [8c] |
| **1f**·HCl | 24 | 38 | 62 | [8c] |
| **1g**·HCl | 24 | not observed | 84 | [8c] |
| **1h**·HCl | 48 | not observed | not observed | this work |
| **1i** | 22 | not observed | not reported | [13a, b] |
| **1i**·HCl | 3 | not observed | 85 | this work |
| **1j**·HCl | 24 | not observed | 85 | this work |
| **1k** | 22 | not observed | 72[b] (see text) | [13a, b] |
| **1k**·HCl | 24 | not observed | 81 (see text) | this work |
| **1l**·HCl | 24 | not observed | 81 | this work |
| **1m**·HCl | 6 | 11 | 72 | this work |
| **1n**·HCl | 2.5 | not observed | 71 | this work |

[a] Isolated yield. [b] Reaction conditions: i) toluene, 22 h, 80 °C. ii) LiBr, acetone, as reported.[13a,b]

The influence exerted by substituents at the N-amine atom is also highly dependent on their nature. We have recently reported that the orthopalladation of **1b**,[8a] containing an electron-withdrawing triflate group, requires at least 48 h to achieve a modest 56% yield, whereas metalation of dimethyl-substituted compound **1c** affords yields of more than 65% in only 24 h reaction time. Furthermore, in none of these reactions was the presence of bis-amino complexes **2** detected. Therefore, in comparison with unprotected **1a**, the results obtained here show a positive effect when the N-amine atom has at least one substituent, with higher yields of the orthometalated compounds being obtained under the same reaction conditions. Moreover, the easy C–H bond activation observed for **1c**, compared with that of **1a**, is consistent with the generally observed better orthopalladation of tertiary amines when compared with secondary and, mainly, primary amines.[20]

With respect to changes of the substituents at the aromatic ring, the differences in reactivity produce some remarkable qualitative differences that merit detailed quantification, as indicated in previous studies.[21] We have already reported that the metalation of **1d**·HCl–**1f**·HCl (*p*-OMe, *p*-Br and *m*-Br) affords the corresponding orthopalladated complexes **3d–f** with very similar reaction yields (60–66% in 24 h), which are similar to the yield obtained for unsubstituted **1a**·HCl in the same time (67%).[8c] This results indicates that the C–H bond activation step occurs in practically the same circumstances in these cases, and that the process is not tuned by changing the electronic nature of the aryl substituents, as found in other cyclopalladated systems.[21b] An exception is **1g**·HCl, which seems to give a higher yield of the palladated dinuclear complex **3g**;[8c] the fact that this complex is not obtained in pure form, and that the yield can only be estimated by the further reactivity of the mixture containing **3g**, could be responsible for the differences reported. Interestingly, a complete lack of reactivity was observed for the nitro derivative **1h**·HCl, but the yields observed for **1d**·HCl–**1f**·HCl (even considering **1g**·HCl) suggest that the reaction rate is not critically modulated by the electronic nature of the substituents. This fact suggests that the C–H bond activation step is likely based on a concerted metalation-deprotonation (CMD) ambiphilic mechanism, instead on an aromatic electrophilic substitution.[22] The same mechanism has recently been studied with respect to the orthopalladation, in carboxylic acids, of 4-arylidene-5(4*H*)-oxazolones, a type of ligand related to amino acids.[21a]

As indicated in Table 1, a remarkable change in reactivity was observed for the orthopalladation of quaternary amino esters **1i**·HCl–**1l**·HCl, which contain a fully substituted C-α atom. In all these cases the reaction occurs with selective formation of the orthopalladated derivatives **3i–l**, in very good yields (typically higher than 81%), and without formation of coordination compounds **2**. It is clear that the preparation of complexes **3** from **1i**·HCl–**1l**·HCl is favored with respect to **1a**·HCl, because better yields were obtained under the same experimental conditions, even in shorter reaction times in some instances. Table 1 also reflects the difference between the reactivity of **1i**·HCl and **1k**·HCl and that reported for their free amino esters **1i** and **1k**.[13a,b]

Once again, orthopalladated compounds **3** were obtained with better yields starting from the hydrochloride salts. Interestingly, whereas the reaction of **1k**·HCl with $Pd(OAc)_2$ under the standard conditions regioselectively afforded **3k**, which contains the palladium incorporated at the *ortho* position of the Ph ring, thus forming a five-membered metallacycle, the reaction of **1k** with $Pd(OAc)_2$ in toluene at 80 °C for 22 h produced a mixture of isomers derived from the $Pd^{II}$ incorporation to both Ph and Bn rings (75 and 15 %, respectively).[13a,b] Clearly, the method reported here gives a better yield of the orthopalladated compound, with the regioselectivity also being improved.

Changing the planar trigonal carbomethoxy group with an isosteric tetrahedral diethyl phosphonate moiety affords amino phosphonates **1m**·HCl and **1n**·HCl, the orthometalation of which has not been previously reported. The reaction of **1m**·HCl with $Pd(OAc)_2$ in acetone under the standard reaction conditions (Scheme 1) afforded a good yield (ca. 70 %) of complex **3m**. Optimization of the reaction conditions allowed **3m** to be obtained in an improved reaction time of 6 h with the same yield (Table 1). In the case of quaternary derivative **1n**·HCl, we observed the same reactivity trends as those described above for quaternary salts; that is, orthopalladation of **1n**·HCl gave **3n** faster (ca. 70 % yield in 2.5 h) than **1m**·HCl gave **3m**. Once again, the change from an amino ester unit to the diethyl phosphonate moiety does not hinder the formation of the orthopalladated complexes, indeed, it constitutes an improvement of the reaction conditions when related substrates are compared.

Characterization of complexes **3i–n** was carried out on the basis of their spectroscopic (IR and NMR) and analytical (elemental analysis and/or high-resolution mass spectra) data. The NMR spectra of **3i–n**, measured in $[D_6]$acetone, display in all cases a single set of signals, wherein peaks due to the presence of the $\{PdC_6H_4\}$ units, as well as those due to the other functional groups are present. The observation of a single set of signals is remarkable, given the fact that these dimers contain two stereogenic centers, thus two diastereoisomers (*RR*/*SS* and *RS*/*SR*) are expected. In addition, each dimer can have an arrangement of the cyclometalated units in *cisoid*/*transoid* dispositions, therefore, if a static behavior is assumed at room temperature, then more than one set of signals would be expected. The NMR spectra of these species are temperature dependent, and the $^1$H NMR spectra of **3i** and **3j** at −73 °C show the splitting of all the signals, appearing as two sets of peaks, strongly suggesting the presence of a dynamic equilibria at 25 °C. The rapid transformation of the two dimeric diastereoisomers through i) breakage of the chloride bridging system by a weakly coordinating ligand, for instance the solvent $[D_6]$acetone, ii) formation of a mononuclear species, and iii) recombination of the mononuclear species to form a new dinuclear complex by solvent decoordination, can be responsible for this simplification of the NMR spectra. The crystal structure of **3j** was determined by X-ray diffraction methods; Figure 2 depicts the molecular structure, as well as selected bond distances and angles.

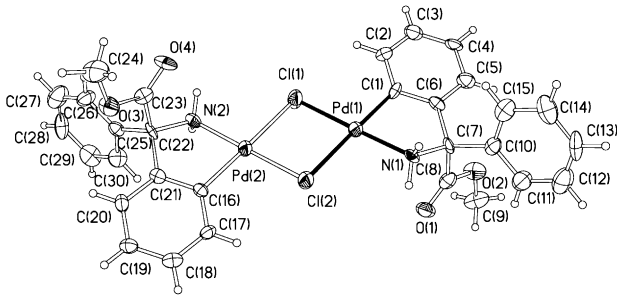
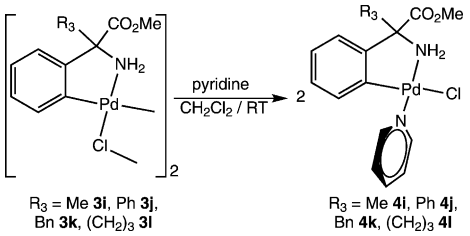



Figure 2. View of complex **3j**. Displacement ellipsoids are scaled to 50 % probability level. Selected bond lengths [Å] and angles [°] for **3j**: Pd1−C1 1.957(8), Pd1−N1 2.028(6), Pd1−Cl1 2.327(2), Pd1−Cl2 2.467(2), Pd2−C16 1.969(7), Pd2−N2 2.030(6), Pd2−Cl2 2.347(2), Pd2−Cl1 2.445(2), N1−C7 1.514(8), C6−C7 1.515(10), C7−C10 1.544(10), C7−C8 1.559(11), C8−O1 1.180(9), C8−O2 1.333(9), O2−C9 1.463(9), N2−C22 1.489(8), C21−C22 1.522(10), C22−C25 1.520(10), C22−C23 1.555(10), C23−O4 1.200(9), C23−O3 1.317(9), O3−C24 1.459(9); C1-Pd1-N1 81.4(3), C1-Pd1-Cl1 96.0(2), N1-Pd1-Cl2 96.32(17), Cl1-Pd1-Cl2 86.32(7), C16-Pd2-N2 81.6(3), C16-Pd2-Cl2 97.3(2), N2-Pd2-Cl1 94.96(17), Cl2-Pd2-Cl1 86.42(7), Pd2-Cl2-Pd1 93.07(7), Pd1-Cl1-Pd2 94.14(8).

In spite of the apparent similarity of **3j** and **3a**, the structure of the former shows notable differences compared with that previously determined for the latter.[8d] The most interesting point corresponds to the *transoid* arrangement of the cyclopalladated rings in **3j**, probably minimizing intramolecular steric interactions. This disposition opposes the *cisoid* arrangement determined for **3a**, even though the metrical parameters are the same within experimental error. Furthermore, **3j** crystallizes in the monoclinic space group $P2_1/n$, indicating that the two enantiomers are present in the unit cell and that the crystal is racemic.

Although the characterization of complexes **3i–l** on the basis of the data gathered through different techniques is unambiguous, the low solubility of the dimers did not allow complete NMR spectra (especially $^{13}$C NMR spectra) to be recorded, and some signals were not observed. To carry out a full characterization of the orthopalladated ligands, we transformed the insoluble dimers **3i–l** into more soluble pyridine adducts **4i–l** (Scheme 2), by breakage of the corresponding chloride bridge with pyridine.

Complexes **4i–l** were obtained in good yields as air-stable, white solids, the elemental analyses and mass spectra of which were in good agreement with the structures indicated in Scheme 2. The NMR spectra of **4i–l** show the expected signals associated with the presence of $\{PdC_6H_4\}$ (**4i–k**) or




Scheme 2. Formation of pyridine adducts **4i–l**.

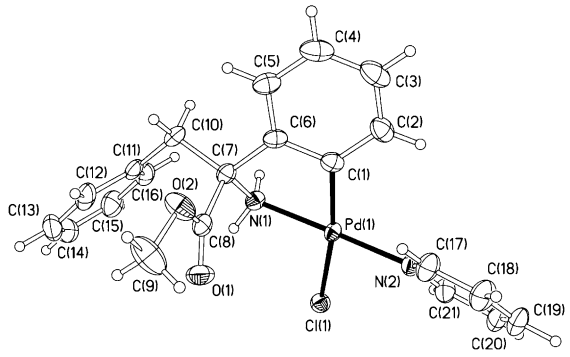



Figure 3. View of complex **4k**. Displacement ellipsoids are scaled to 50% probability level. Selected bond lengths [Å] and angles [°] for **4k**: Pd1–C1 1.980(3), Pd1–N1 2.036(2), Pd1–N2 2.045(2), Pd1–Cl1 2.4381(7), N1–C7 1.489(3), C6–C7 1.523(4), C7–C8 1.528(4), C7–C10 1.548(3), C10–C11 1.513(4), O1–C8 1.195(3), O2–C8 1.331(3), O2–C9 1.450(4); C1-Pd1-N1 80.24(10), C1-Pd1-N2 95.95(10), N1-Pd1-Cl1 90.01(6), N2-Pd1-Cl1 94.05(7), N1-C7-C6 104.4(2), N1-C7-C8 106.1(2), C6-C7-C8 112.3(2), N1-C7-C10 111.2(2), C6-C7-C10 114.0(2), C8-C7-C10 108.6(2).

$\{PdC_6H_3\}$ (**4l**) units, thus allowing unambiguous characterization of the cyclopalladated ligands (see the Supporting Information). In addition, the molecular structure of **4k** was determined by X-ray diffraction methods. Figure 3 shows a drawing of the molecule and some selected bond distances and angles. The environment of the Pd atom is square-planar, slightly distorted, and it is surrounded by the metalated carbon, the aminic and pyridinic nitrogen atoms and the chloride ligand, with the latter being *trans* to the palladated carbon. The molecular drawing shows the orthopalladation of the Ph ring directly bonded to the C-α atom, and not that of the benzyl group, confirming the structure proposed on the basis of the NMR data. As previously discussed, this contrasts with previous reports that structurally characterized the orthopalladation of the benzyl group in $[PdCl(C_6H_4CH_2C(Ph)(CO_2Me)NH_2)PPh_3]$.[13a]

**Mechanistic studies on the orthopalladation reaction: kinetics**: In view of the important differences and trends observed in the preparative procedures of the cyclometalated derivatives of the ligands indicated in Figure 1, a detailed kinetic study of the process was conducted. The cyclometalation reaction of the free amino ester ligands **1a**, **1c**, and **1i**, and hydrochlorides **1a**·HCl, **1d**·HCl, **1e**·HCl, **1i**·HCl, and **1m**·HCl with $Pd(OAc)_2$ was studied by time-resolved UV/Vis spectroscopy. The data obtained from the equimolecular reactions imply the metalation of $\{Pd^{II}(aminoester)\}$ units is a one-step process as already established for reactions of other cyclometalating ligands with $Pd(OAc)_2$.[13a,23] Recording the reaction rates at different temperatures, pressures and solvent conditions produced the set of kinetic, thermal, and pressure activation parameters indicated in Table 2, once the relevant Eyring or ln *k* vs. *P* plots were conducted (Figure 4). Parallel NMR spectroscopic monitoring of the process indicated the C–H bond-activation nature of the reaction rate studied.

Table 2. Rate constants and activation parameters obtained for the reaction of some amino esters and hydrochlorides (Figure 1) with $Pd(OAc)_2$ in different media. Literature data for $NH_2CMe(CO_2Me)Bn$ and $NH_2CBn(CO_2Me)Ph$, **1k**, are included for comparison.

| Compound | Solvent | $10^{-4}\times{}^{300}k$ [$s^{-1}$] | $\Delta H^{\ddagger}$ [kJ $mol^{-1}$] | $\Delta S^{\ddagger}$ [J $K^{-1}$ $mol^{-1}$] | $\Delta V^{\ddagger}$ [$cm^{-3}$ $mol^{-1}$] |
|---|---|---|---|---|---|
| **1a** | acetone | 0.67 | 58±5 | −134±15 | −13±3 |
| **1a** | toluene | 0.41 | 61±7 | −128±21 | −17±2 |
| **1a** | acetic acid | 0.28 | 56±4 | −148±13 | +11±2 |
| **1c** | acetone | 3.3 | 75±4 | −64±14 | nd[d] |
| **1c** | toluene | 5.3 | 39±4 | −180±12 | −13±3 |
| **1c** | acetic acid | 0.16 | 43±6 | −196±18 | +15±1 |
| **1i** | acetone | 8.6 | 69±1 | −76±3 | −14±2 |
| **1i** | toluene | 0.78 | 96±4 | −6±14 | −13±2 |
| **1i** | acetic acid | 3.7 | 55±3 | −149±8 | 2±2 |
| **1a**·HCl | acetone | 3.7 | 51±7 | −143±21 | −5±4 |
| **1d**·HCl | acetone | 3.7 | 51±7 | −143±21 | −5±4 |
| **1e**·HCl | acetone | 3.7 | 51±7 | −143±21 | −5±4 |
| **1i**·HCl | acetone | 10 | 73±2 | −61±6 | −12±2 |
| **1m**·HCl | acetone | 18 | 60±6 | −100±21 | −3±1 |
| **1k**[a,b] | toluene | 9.3 | 70±1 | −72±1 | nd[d] |
| **1k**[a,c] | toluene | 4.0 | 76±2 | −59±7 | nd[d] |

[a] Data from ref. [13a]. [b] Metallation forming a five-membered ring. [c] Metalation forming a six-membered ring. [d] nd = not determined.

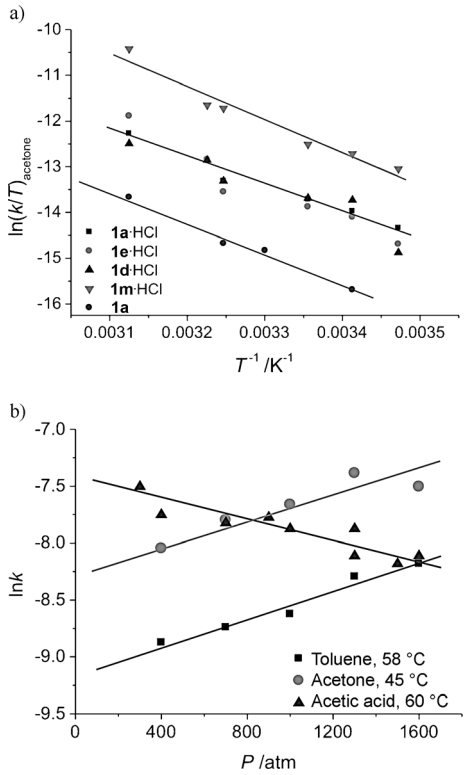



Figure 4. a) Eyring plot for the C–H bond activation process for **1a**·HCl, **1e**·HCl, **1d**·HCl, **1m**·HCl, and **1a** by $Pd(OAc)_2$ in acetone solution. b) Plot of ln *k* vs. *P* for the C–H bond activation of **1a** by $Pd(OAc)_2$ in different solvents.

It is clear from the data collected in Table 2 that the "usual" dramatic acceleration of the cyclometalation process in acetic acid observed for previously studied systems in-

volving N-imine directing groups does not hold in this case.[21b,23a,24] A similar behavior has also been observed in kinetico-mechanistic studies carried out for the cyclopalladation of benzyl amines,[25] which can be attributed to the effective protonation of the more basic N-amine directing group, thus decreasing the concentration of the active {$Pd^{II}$(amine)} cyclometalating unit by the existence of a protonation equilibrium. In fact, the existence of protonated amines in highly acidic media has been found to be relevant for the cyclopalladation of some amino-imino ligands,[26] and for other systems in which the weak nature of the $Pd^{II}$-directing group bond has been found to be relevant.[27] As a consequence, in the present case, the determined rate constants, when protic medium is used, are composites of an equilibrium and a first-order rate constant ($k = K_{\text{amine deprotonation}} \times k_{\text{CH activation}}$), and no further comparison with the processes carried out in the more innocent acetone or toluene solution is possible at this stage. Given these implications, a study of the free amino esters **1c** and **1i** was conducted.

For the fully unsubstituted amino ester ligand **1a**, the data collected are consistent with the expected highly ordered and entropy-demanding transition state, which is accompanied by an important volume contraction.[13a,21a,b] In this respect, it is noticeable that no significant differences in the activation parameters are observed for the reactions carried out in acetone or toluene solution, which is indicative of the innocent and nonparticipative nature of these solvents in the process. These differences (or similarities), have already been established as very significant for other organometallic systems of diverse nature.[28,29] For *N*,*N*-dimethyl substituted ligand **1c**, the values obtained in toluene solution also relate to a highly ordered and compressed transition state, this time though, the value determined for $\Delta H^{\ddagger}$ was much lower, in line with the better donor character of the substituted amine. This effect would not be expected for an electrophilic substitution reaction on the aromatic carbon,[30] and has to be related to the induced increase in the leaving capability of the acetate ligand attached to the palladium center, which actuates as the proton abstractor for the reaction in a so called ambiphilic mechanism (Figure 5).[21a,b,22e] In this respect, the fact that the kinetic and activation parameters determined for the cyclometalation of hydrochlorides **1a**·HCl, **1d**·HCl, and **1e**·HCl by $Pd(OAc)_2$ (Table 2, Figure 1), are the same within experimental error is again consistent with the nonelectrophilic nature of the process involved.[8c,21c] Surprisingly, the values collected in Table 2 for the reaction of **1c** in acetone are rather different from the expected values; we can speculate that the generation of acetic acid from the transition state indicated in Figure 5, as free acid in acetone, can lead to a partial protonation of the basic tertiary amine, thus disrupting its coordination to form effective cyclometalating {$Pd^{II}$(amine)} units.

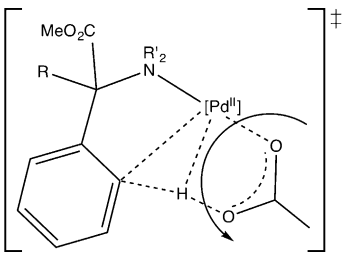



Figure 5. Transition state proposed for the ambiphilic mechanism involved in the cyclometalation of palladium acetate by aminoesters.

For the cyclopalladation reaction with methyl C-α substituted ligand **1i**, the results indicate a definite acceleration of the process, which has already been observed in the metalation of similar systems,[13a,24b] as well as in the preparative procedures indicated above. In acetone solution the effect is mainly attributable to a decrease in the entropic demands, while maintaining the values for $\Delta H^{\ddagger}$ and $\Delta V^{\ddagger}$. Nevertheless, in toluene solution, the activation parameters show a much larger decrease in entropy demands, compensated for by a large increase in $\Delta H^{\ddagger}$ and accompanied by a similar value for $\Delta V^{\ddagger}$. Taking into account the differences between the two solvents used, the data in toluene solution should be considered the most suitable for initial discussion. Clearly, the rather important steric demands of the ligand to form the transition state indicated in Figure 5, has to be accompanied by less negative values of the activation entropy, while increasing the enthalpic demands for the process. In acetone solution the inductive effect on the methyl substituent at C-α seems to be the dominating feature. The N-amine becomes slightly more basic and can be easily protonated in acetone from the acetic acid liberated from the transition state, as indicated above for tertiary amines. Again, the values of the rate constant are then a composite of kinetic and thermodynamic parameters, which make them much more difficult to interpret directly (see the comments on the data in acetic acid solution above). In this respect it is important to note that the values obtained for the thermal activation parameters for the cyclopalladation of **1i** in acetone solution are midway between those in toluene and acetic acid solutions. The same effect has already been described in the cyclopalladation of the phenylalanine-derived ligand $NH_2CMe(CO_2Me)CH_2Ph$.[13a]

Finally, the fact that the hydrochloride salts of the amino esters show cyclopalladation reaction rates in acetone solution that are higher than those for the free amino esters has also to be considered (Table 2, **1a**·HCl, **1d**·HCl, **1e**·HCl, **1i**·HCl, and **1m**·HCl). Under the conditions used, two factors have to be taken into account: i) the presence of a single equivalent of chloride anion/ligand, and ii) the presence of a single equivalent of acid in a polar medium. To establish whether one or both factors are involved in such an increased reactivity, a detailed kinetic study was carried on the reactions with ligand **1a** in acetone solution in the presence of chloride anions [provided as $(NBu_4)Cl$] and protons (provided as HTrifl or $HBF_4 \cdot Et_2O$); furthermore, the effect of an ion-rich medium was also studied by the use of $(NBu_4)ClO_4$ solutions. The use of other coordinating acids was avoided in view of the data obtained in previous studies.[21,31] Table 3 contains a summary of the data obtained at 25 and 35 °C under these conditions; the results can thus be

Table 3. Values of the rate constants for the cyclometalation of **1a** by palladium acetate ($5.3\times10^{-4}$ M equimolecular ratio) in acetone solution and in the presence of additives.

| Amino ester | $T$ [°C] | Additive | Concentration | [Pd]/[Cl]/[H$^+$] | $10^{-4}\times k$ [s$^{-1}$] |
|---|---|---|---|---|---|
| **1a**·HCl | 35 | – | – | – | 5.1 |
| **1a** | 35 | – | – | – | 1.3 |
| **1a** | 35 | $(NBu_4)Cl$ | 0.00054 | 1:1:0 | 5.0 |
| **1a** | 35 | $HBF_4$ | 0.00025 | 1:0:0.5 | 1.4 |
| **1a** | 35 | $HBF_4$ | 0.00050 | 1:0:1 | 6.0 |
| **1a** | 35 | $(NBu_4)Cl + HBF_4$ | 0.00054 + 0.00054 | 1:1:1 | 6.5 |
| **1a** | 25 | – | – | – | 0.67 |
| **1a**·HCl | 25 | – | – | – | 3.5 |
| **1a**·HCl | 25 | $(NBu_4)ClO_4$ | 0.0018 | – | 4.2 |
| **1a**·HCl | 25 | $(NBu_4)ClO_4$ | 0.0044 | – | 3.5 |
| **1a**·HCl | 25 | $(NBu_4)ClO_4$ | 0.0065 | – | 4.5 |
| **1a**·HCl | 25 | $(NBu_4)Cl$ | 0.0011 | 1:2:0 | 4.2[a] |
| **1a**·HCl | 25 | $(NBu_4)Cl$ | 0.0020 | 1:4:0 | –[b] |
| **1a**·HCl | 25 | $(NBu_4)Cl$ | 0.0022 | 1:4:0 | 5.0[a] |
| **1a**·HCl | 25 | $(NBu_4)Cl$ | 0.0034 | 1:6:0 | –[b] |
| **1a**·HCl | 25 | $(NBu_4)Cl$ | 0.0034 | 1:6:0 | 4.0[a] |
| **1a**·HCl | 25 | HTrifl | 0.0005 | 1:0:1 | 50 |
| **1a**·HCl | 25 | HTrifl | 0.001 | 1:0:2 | 15 |

[a] A secondary reaction was observed that becomes dominant. [b] No reaction was observed when palladium acetate was pretreated with $(NBu_4)Cl$.

compared with those obtained with hydrochloride salt **1a**·HCl.

It is clear that the presence of $(NBu_4)ClO_4$ does not affect the reaction rate of cyclopalladation of **1a** significantly, thus indicating that the polarity of the medium is not directly responsible for the acceleration observed (Table 3, entries 9–11). As for the presence of chloride anions, the addition of one equivalent of $(NBu_4)Cl$ to **1a** produced an acceleration similar to that observed when the hydrochloride salt was used (Table 3, entries 2 and 3), indicating that the main component of the acceleration process corresponds to the presence of one equivalent of chloride. It is clear that the presence of a chloride ligand in the coordination sphere of the Pd center enhances the reaction rate for electronic reasons. Interestingly, the presence of increasing quantities of chloride ligand triggers the operation of a secondary reaction (probably producing $[PdCl_4]^{2-}$) that inhibits the cyclopalladation reaction (Table 3, entries 12–16).[32]

The presence of noncoordinating acids such as triflic or tetrafluoroboric (Table 3, entries 4, 5, 17, and 18) produced only a slight rate enhancement in a rather small concentration range going from ca. 2 to 5 fold the Pd concentration. This fact indicates an extremely fine tuning between the protonation of the acetate ligand in Figure 5, which has been shown to produce significant acceleration in the cyclopalladation rate constants,[21] and that of the amine group from the ligand, which prevents its coordination and consequent cyclometalation (see above). Protonation of the dangling acetate oxygen in the structure shown in Figure 5 produces a clear increase in the observed rate constant due to a change in the structure of the transition state for the process, but protonation of the free amine prevents the formation of the metalating {Pd$^{II}$(aminoester)} units. It is also clear that the substitution of one of the acetate ligands by a chloride further enhances the reaction rate in such a weak protic medium (Table 3, entry 9). An excess of both species promotes either decoordination of the amine directing group or substitution of the acetate by chloride ligands, thus preventing either cyclopalladation or proton abstraction from the system.

**Mechanistic information on the orthopalladation reaction: DFT calculations**: DFT calculations on the orthopalladation reaction have been carried out based on the concerted metalation-deprotonation ambiphilic mechanism (CMD), which is the accepted sequence for this type of reaction occurring in nonprotic innocent solvents.[33] We have already used this reaction mechanism to successfully explain the regioselectivity found in the C–H bond activation step of different iminophosphoranes.[34] The mechanism is based on the formation of an agostic C–H interaction between the metal and the precoordinated substrate, followed by proton abstraction by a carboxylate acting as an internal base. The last step is assisted by the metal and culminates in the formation of the metal–carbon bond. In this study, two situations have to be considered: i) orthopalladation of the free amino esters for which the starting material can be modeled as [Pd($\kappa^2$-OAc)($\kappa^1$-OAc)($\kappa^1$-*N*-aminoester)], as for similar compounds;[33,34] ii) orthopalladation of the corresponding hydrochlorides for which the implication of a chloride ligand has to be considered during the process.

As for the orthopalladation of free amino esters, the study of the energetics involved in the accepted general mechanism indicated above is summarized in Figure 6 for ligand **1a**. The formation of the agostic species $\mathbf{I_{Nag}}$ from the starting material $\mathbf{R_N}$, [Pd($\kappa^2$-OAc)($\kappa^1$-OAc)($\kappa^1$-*N*-**1a**)], shows a relative barrier of 16.0 kcal mol$^{-1}$. The rate-determining step, which represents a barrier of 25.5 kcal mol$^{-1}$, corresponds to subsequent breakage of the C–H bond and concerted abstraction of the proton by the acetate ligand, with

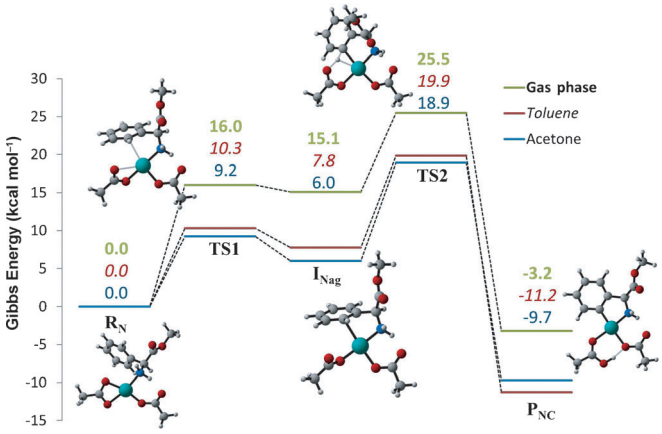



Figure 6. Gibbs energy profile for the orthopalladation of **1a** in the gas phase and in different solvents.

concomitant formation of the Pd–C bond. The reaction is exothermic and affords the final species $\mathbf{P_{NC}}$, which contains the orthopalladated amino ester and two acetate groups connected by a hydrogen bond. The effect of the solvent (acetone and toluene) was taken into account by using the continuum model in a single-point calculation on the gas-phase optimized structures. Clearly, the use of acetone (a polar solvent) is beneficial for the reaction, due to a better stabilization of the polar agostic intermediate and the respective transition states.

Given the remarkable qualitative[8c] and quantitative independence of the reaction rate with respect to the substituents in the aromatic ring, we have studied the effect on the energetic profile of the reaction of the electronic structure of the aromatic ring on which the C–H position to be activated is located. In this respect, both electron-donating (MeO) and electron-withdrawing (Br) groups were included in the *para* position of the aromatic ring for the DFT calculations. Furthermore, the effect of multiple electron-donating substituents was evaluated by including two OMe groups in the *meta* and *para* positions. The obtained results are summarized in Figure 7, which also shows that the orthopalladation of **1e** seems to occur as a single-step process; the agostic intermediate $\mathbf{I_{Nag}}$ and the preceding transition state **TS1** were not found. The differences between the calculated activation barriers for the orthopalladation processes of all these ligands were less than 0.4 kcal mol$^{-1}$, i.e, the same within error. Clearly the process can be seen as being effectively independent of the substituents on the aryl ring containing the metalating C–H bond, and that the mechanism through which the reaction occurs is concerted metalation-deprotonation (ambiphilic), and not electrophilic substitution.

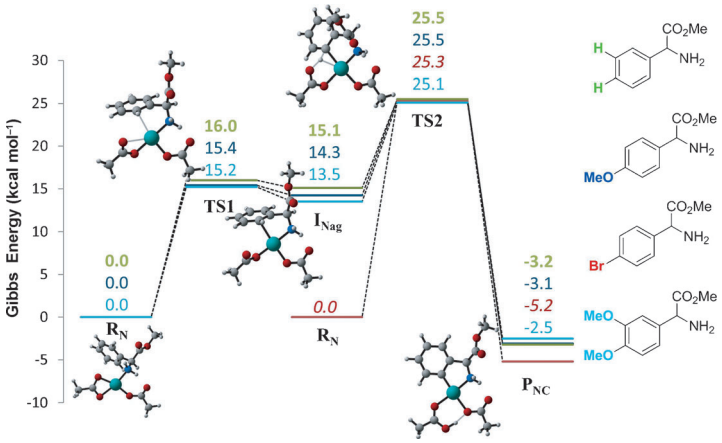



Figure 7. Gibbs energy profiles computed for the orthopalladation of aryl-substituted derivatives of **1a** in the gas phase.

In contrast, a remarkable increase in the reaction rates has been observed when either quaternary amino esters (containing alkyl substituents at the C-α atom) or disubstituted amino groups are cyclometalated. Thus, we extended our calculations to include these substrates. As for the quaternary amino esters, a comparison of the energetic profiles of **1a** and its methyl (**1i**) and *tert*-butyl substituted derivatives is shown in Figure 8. Both substituents lead to a notable stabilization of the transition state for the rate-determining step, due to the Thorpe–Ingold effect,[35] especially in the case of **1i**. Interestingly, the formation of the agostic intermediate for the *tert*-butyl system requires more energy, probably due to the clear steric requirements. On the other hand, with respect to the *N*,*N*-dimethyl substituted derivative **1c** (see Figure S1), the inclusion of *N*-Me groups promotes a remarkable decrease in the activation barrier of more than 9 kcal mol$^{-1}$, in perfect agreement with the easy orthopalladation observed experimentally for **1c** (see Table 1 and Table 2), compared with that of **1a**. The large relative stabilizations observed for all intermediates in the orthopalladation of **1c** seem to be related to the stronger donor character of the $NMe_2$ group compared with that of the unsubstituted amine, again in good agreement with the easier orthometalation of tertiary amines, compared with their primary counterparts.[20]

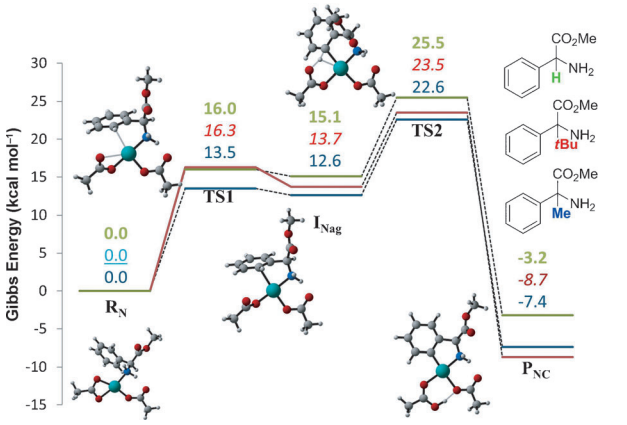



Figure 8. Calculated energy profiles for the orthopalladation of methyl phenylglycinate **1a** with different substituents at the C-α atom in the gas phase.

We have shown that the reaction model based on a concerted metalation-deprotonation, or ambiphilic mechanism, reflects the trends observed experimentally. A further step in the theoretical analysis of the orthopalladation of amino esters involves consideration of hydrochlorides as starting compounds (**1a**·HCl, and **1d**·HCl–**1n**·HCl). The model used for the DFT calculations so far in nonpolar solvents,[22e,33] [Pd($\kappa^2$-OAc)($\kappa^1$-OAc)($\kappa^1$-*N*-aminoester)], does not correspond to the isolated neutral noncyclometalated dimers [Pd(μ-OAc)(OAc)($NH_2CH_2Ar$)]$_2$, which have been found to be relevant intermediates in the orthopalladation of benzylamines and related species.[12b,c] If the use of such a model produces calculated data that fully agree with the experimental results, then species such as [Pd($\kappa^2$-OAc)(Cl)($\kappa^1$-*N*-$NH_2CH_2Ar$)][20a] can be considered as part of a valid model for the formation of the isolated compounds of type **3** indicated in Scheme 1. Similar compounds with mixtures of ace-

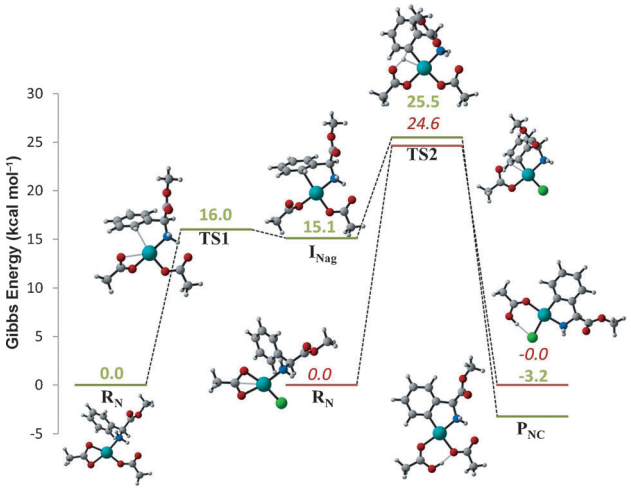



Figure 9. Gibbs energy profile for the orthopalladation of **1a** (green) and **1a**·HCl (red) in the gas phase.

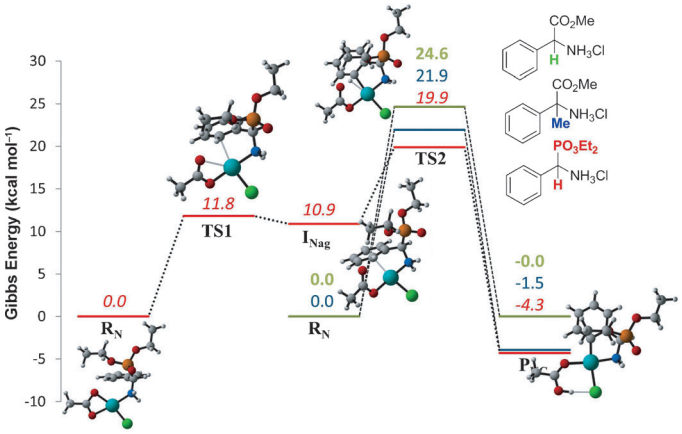


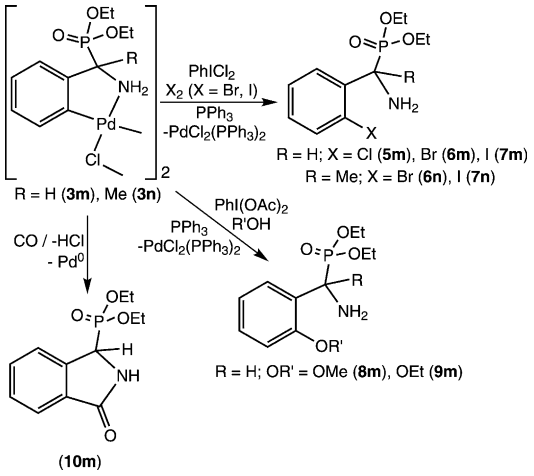

Figure 10. Calculated energy profiles for the orthopalladation of hydrochloride salts having different substituents at C-α atom in the gas phase.

tate/chloride ligands have also been found to be relevant for related metalation reactions.[36] The computed reaction pathway for **1a**·HCl starting from [Pd(κ²-OAc)(Cl)(κ¹-$NH_2$CH-($CO_2$Me)Ar)] is shown in Figure 9, and it is compared with that computed for **1a**.

The orthopalladation of **1a**·HCl seems to occur in a single-step process, as observed for **1e**. This difference with respect to the orthopalladation of **1a** is not significant because the agostic intermediate has been found to be a short-life species in the cases where it is detected, being in a very shallow energy valley. On the other hand, the rate-determining steps (**TS2**) in the two pathways are structurally similar. The only noticeable change is a slight shortening of the intramolecular bond distances of the moving H to the donor C and receptor O atoms from **1a** (1.376 and 1.367 Å, respectively) to **1a**·HCl (1.366 and 1.357 Å). Energetically, the results obtained show that the activation barrier found for the orthopalladation of **1a**·HCl is lower (24.6 kcal mol$^{-1}$) than that found for **1a** (25.5 kcal mol$^{-1}$), in good agreement with the acceleration observed experimentally (see Table 1, Table 2 and Table 3). In the same way, the presence of substituents at the aromatic ring or at the C-α atom has been evaluated for the hydrochloride salts. Initially both electron-donating (MeO, **1d**·HCl) and electron-withdrawing (Br, **1e**·HCl) groups in *para* positions (Figure S2) were considered. In a second instance, methyl-substituted quaternary amino ester **1i**·HCl and isosteric aminophosphonate derivative **1m**·HCl were also studied (Figure 10).

In all studied cases we observe the same trend as that of the unsubstituted couple **1a**·HCl/**1a**; that is, the activation barriers for the hydrochlorides (**1d**·HCl, **1e**·HCl, **1i**·HCl) are smaller than those for the free amines (**1d**, **1e**, **1i**; compare Figure 7 and Figure S2), in good agreement with the experimental results. In the same way, the presence of substituents at the aryl ring does not induce remarkable changes, whereas substituents at C-α promotes notable decreases of the activation barriers. In this respect it is worth indicating the important acceleration expected for aminophosphonate **1m**·HCl, due to a stabilization of the transition state **TS2** of almost 5 kcal mol$^{-1}$ with respect to **1a**·HCl, as experimentally observed. Therefore, it is clear that both the C-α and the N atoms are the most sensitive points in the original structure; changes of substituents at these positions trigger remarkable effects in the reaction rate of the orthopalladation. Unexpectedly, the aromatic ring (i.e., the part of the molecule where C–H bond activation occurs) is actually less sensitive, or not at all, to modification and/or change of the substituents.

**Reactivity of 3m and 3n: *ortho*-functionalization of aminophosphonate derivatives**: The reactivity of cyclopalladated complexes **3m** and **3n** in processes involving oxidative couplings (halogenation, alkoxylation) or insertion of small unsaturated molecules, such as CO, has also been investigated. The studied reactions and the obtained products are summarized in Scheme 3. The trends observed can be easily compared to those reported previously for the isosteric amino esters.[8a,c,d]




Scheme 3. Reactivity of **3m** and **3n** to give functionalized aminophosphonates.

The oxidative halogenations were carried out by using different reagents, depending of the halogen to be introduced. In the case of chlorinations, $PhICl_2$ gave the best performance for **3m**,[37] whereas a complex reaction was observed for **3n**. Although extensive decomposition was observed when $Cl_2$ was used in both cases, $Br_2$ and $I_2$ were suitable reagents in the case of brominations and iodinations, respectively, for the two complexes. The reaction of **3m** and **3n** with the corresponding reagent under stoichiometric conditions takes place in two steps, as previously reported.[8d,12e] Initially, intermediate coordination complexes of stoichiometry $[PdCl_2L_2]$ (L = *ortho*-functionalized aminophosphonate) are formed, which were not isolated. The process presumably involves the formation of a $Pd^{IV}$ species and subsequent reductive elimination during formation of the C–X bond. During the reaction, $PdX_2$ was formed as a byproduct and removed by filtration. The decoordination of *ortho*-functionalized aminophosphonate (L) from the intermediate species is normally conducted by treatment of $[PdCl_2L_2]$ with a chelating ligand (1,10-phenantroline),[8d,12e] which forms a very insoluble complex $[PdCl_2(N,N\text{-phen})]$ thus promoting quantitative release of the functionalized species L. In our case, 1,10-phen does not appear to be a good ligand for releasing purposes, and optimum results were instead achieved by using $PPh_3$ (1:2 molar ratio). In this way, $Pd^{II}$ was removed quantitatively as $[PdCl_2(PPh_3)_2]$, and any excess of free $PPh_3$ could be separated by column chromatography (see Experimental) from the desired halogenated derivatives $H_2NC(R)[P(O)(OEt)_2](C_6H_4\text{-}2\text{-}X)$ [Scheme 3; R = H, X = Cl (**5m**), Br (**6m**), I **7m**; R = Me, X = Br (**6n**), I (**7n**)]. Characterization of **5m**–**7n** was carried out on the basis of their analytical and spectroscopic data. Elemental analyses and mass spectra were consistent with the stoichiometries shown in Scheme 3. The $^1H$ and $^{13}C$ NMR spectra, which show a single set of signals each, clearly display peaks due to the presence of the $\{C_6H_4\}$ unit, whereas the existence of a C–X bond (X = Cl, Br, I) is evident in the $^{13}C$ NMR spectra from the observation of peaks at 133.7 (**5m**, Cl), 124.3 (**6m**, Br), and 100.9 ppm (**7m**, I).

The incorporation of alkoxy functional groups at the ortho position of aminophosphonates by following a similar methodology, has also been achieved. Given the fact that iodonium salts promote successful oxidative couplings (see above),[38] the reactivity of **3m** with alcohols in the presence of an I(III) salt was attempted.[39] Thus, the reaction of **3m** with $PhI(OAc)_2$ (1:4 molar ratio) in methanol (or ethanol) at room temperature afforded the corresponding coordination complexes $[PdCl_2L_2]$, described above, with the L ligands being the *ortho*-alkoxy substituted aminophosphonates (methoxy or ethoxy, respectively). As indicated previously, the reaction of these species with $PPh_3$ induces the precipitation of $[PdCl_2(PPh_3)_2]$ and release of the alkoxyaminophosphonates $H_2NC(H)[P(O)(OEt)_2](C_6H_4\text{-}2\text{-}X)$ [Scheme 3; R = OMe (**8m**), OEt (**9m**)], which were subsequently isolated and purified. Characterization of **8m** and **9m** was straightforward from their analytical and spectroscopic parameters, mainly from the NMR spectra from which it was possible to assign signals due to the presence of the $C_6H_4$-bonded OMe and OEt groups.

Insertion of small unsaturated molecules into the Pd–C bonds (for instance CO) also represents a classical tool with which to achieve regioselective functionalization of organic substrates;[40] thus, reaction of **3m** with CO (1 atm) in $CH_2Cl_2$ at room temperature was studied. The reaction occurs with formation of black palladium. Its removal, followed by simple evaporation of the resulting solution, afforded a white solid that was characterized as the isoindolinone-type derivative **10m** (Scheme 3). The reaction implies CO bonding, migratory insertion into the $Pd–C_{ortho}$ bond, reductive elimination by C–N coupling and final elimination of HCl from the resulting ammonium salt. The reactivity pattern is identical to that observed with the isosteric amino ester,[8c,d] but when the reaction was carried out in methanol, instead of $CH_2Cl_2$, the same isoindolinone **10m** was obtained. This is a remarkable result because it implies that the cyclization step is faster than the formation of the ester, in contrast to results obtained with the amino ester derivative.[8a]

Even though **5m**–**10m** are the first aminophosphonates to be regioselectively modified by using a transition metal, the results obtained here show a close similarity to those reported previously with the isosteric amino esters. This suggests that replacing the ester by a phosphonate group produces a parallel reactivity, at least for the studied cases. The effect of the changes seem to be limited to the tuning of the rate at which the reactions take place.

## Conclusion

Interesting trends concerning the orthopalladation of different phenylglycine-derived amino esters and aminophosphonates substituted at the N atom, the aryl ring, and the C-α atom, under optimized reaction conditions, have been observed during preparative procedures. The introduction of substituents at the N atom and the C-α atom (quaternary amino esters), as well as replacing the amino ester by aminophosphonate, facilitate the preparative procedures relative to the unsubstituted amino esters. On the other hand, the presence of substituents at the aryl ring does not seem to exert a critical influence on the process, indicating a mechanism for the C–H bond activation step that is not based on electrophilic substitution. Quantification of these trends by undertaking a detailed kinetico-mechanistic study indicates that orthopalladation of substituted amino esters occurs at a faster rate on substitution of either the C-α or amine N atoms, whereas no effect was evident upon the introduction of different substituents on the metalating aryl ring. The data also indicate that the corresponding hydrochlorides metalate at a faster rate. The process behaves according to the expected ambiphilic nature of the CMD mechanism, with important changes in entropy and volume requirements to reach the transition state. DFT modeling of the reaction, considering such mechanism, produces a series of trends in

the activation barriers that are fully consistent with the experimental kinetico-mechanistic data obtained. These trends can be easily related to the presence of the substituents introduced. Interestingly, the replacement of an acetate by a chloride in the mechanistically relevant species, [Pd($\kappa^2$-OAc)($\kappa^1$-X)($\kappa^1$-*N*-aminoester)], also produces a favorable difference in the activation energy, as found in the experimental handling of the process: the reaction is faster starting from [Pd($\kappa^2$-OAc)($\kappa^1$-Cl)($\kappa^1$-*N*-aminoester)] than from [Pd($\kappa^2$-OAc)($\kappa^1$-OAc)($\kappa^1$-*N*-aminoester)]. The reactivity of the orthopalladated aminophosphonate complexes in oxidative couplings and insertion of small unsaturated molecules allows the corresponding *ortho*-functionalized aminophosphonate species to be obtained, in a similar process to that described for amino esters.

## Experimental Section

**General methods**: Solvents were dried and distilled by using standard procedures before use. Elemental analyses (CHN) were carried out with a Perkin–Elmer 2400-B microanalyzer. Infrared spectra (4000–380 $cm^{-1}$) were recorded with a Perkin–Elmer Spectrum One IR spectrophotometer. $^1$H, $^{13}$C, and $^{31}$P NMR spectra were recorded at RT (unless otherwise stated) with Bruker AV300 and AV400 spectrometers ($\delta$ in ppm, *J* in Hz) at a $^1$H operating frequency of 300.13 and 400.13 MHz, respectively. $^1$H and $^{13}$C NMR spectra were referenced against solvent signal as internal standard, whereas $^{31}$P NMR spectra were referenced to $H_3PO_4$ (85%). ESI$^+$ mass spectra were recorded with 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. MALDI$^+$ mass spectra were recorded from $CHCl_3$ solutions with a MALDI-TOF Microflex (Bruker) spectrometer (DCTB as matrix). HRMS and ESI (ESI+) mass spectra were recorded with an MicroToF Q, API-Q-ToF ESI with a mass range from 20 to 3000 *m*/*z* and mass resolution 15000 (FWHM).

Compound **1a**·HCl is commercially available and was used without further purification. The amino esters **1b**[14] and **1c**,[8a,15] and the hydrochlorides **1d**·HCl,[8c] **1e**·HCl,[8c] **1f**·HCl,[8c] and **1g**·HCl[8c] have been prepared as previously described. Hydrochlorides of the quaternary amino esters **1i**·HCl, **1j**·HCl, **1k**·HCl, **1l**·HCl,[16] as well as aminophosphonates **1m**·HCl[17] and **1n**·HCl,[18] were prepared through modifications or adaptations of previously reported methods; their syntheses are detailed in the Supporting Information. The orthopalladated derivatives **3a–g** were already known (**3a**,[19] **3b**,[8a] **3c**,[8a,15] **3d**,[8c] **3e**,[8c] **3f**,[8c] and **3g**[8c]); they were synthesized by following reported procedures and identified by comparison of their spectroscopic data with those published. Compounds closely related to **3l** and **3k** have been reported recently,[13a,b] but they differ in the nature of the halide bridge (μ-Cl in **3l** and **3k** whereas μ-Br in the reports[13a,b]) and in the method of synthesis (solvents, temperature, time). $PhICl_2$ was also prepared by following published procedures.[37]

**Synthesis of orthopalladated complexes**

*[Pd(μ-Cl){$C_6H_4$(CMe($CO_2$Me)$NH_2$)-2}]$_2$ (**3i**)*: To a suspension of amino ester hydrochloride **1i**·HCl (1000.0 mg, 4.637 mmol) in acetone (40 mL), $Pd(OAc)_2$ (1040.0 mg, 4.637 mmol) was added and the resulting suspension was heated to reflux for 3 h. During this time, the color of the suspension changed noticeably to orange. After this time, the suspension was allowed to reach RT and $Et_2O$ (40 mL) was added. The precipitated orange solid was filtered, washed with $Et_2O$ (30 mL), dried in vacuum and identified as **3i**. Yield: 1270 mg (85%); $^1$H NMR (300.13 MHz, [D$_6$]acetone): $\delta$ = 1.88 (s, 3H; $CH_3$), 3.78 (s, 3H; $OCH_3$), 5.14 (br. s, 2H; $NH_2$), 6.79–7.02 (m, 3H; $C_6H_4$), 7.13 ppm (m, 1H; $C_6H_4$); $^{13}$C{$^1$H} NMR (75.47 MHz, [D$_6$]acetone): $\delta$ = 27.62 ($CH_3$), 53.53 ($OCH_3$), 71.75 ($C_\alpha$), 124.48 (CH, $C_6H_4$), 125.31 (CH, $C_6H_4$), 126.81 (CH, $C_6H_4$), 134.42 (CH, $C_6H_4$), 173.84 ppm (CO); the two quaternary carbon atoms of the $C_6H_4$ ring were not observed, in spite of the use of long accumulation trials; IR: $\tilde{\nu}$ = 3286, 3210 ($\nu_{NH2}$), 1724 ($\nu_{C=O}$) $cm^{-1}$; MS (ESI$^+$): *m*/*z*: 595.6 [*M*−$CO_2$]$^+$; elemental analysis calcd (%) for $C_{20}H_{24}Cl_2N_2O_4Pd_2$ (640.16): C 37.52, H 3.78, N 4.38; found: C 37.58, H 3.81, N 4.33.

*[Pd(μ-Cl){$C_6H_4$((CPh)($CO_2$Me)$NH_2$)-2}]$_2$ (**3j**)*: Compound **3j** was obtained by using a method similar to that described for **3i** with slight modifications. To a solution of amino ester hydrochloride **1j**·HCl (700.0 mg, 2.52 mmol) in acetone (20 mL), $Pd(OAc)_2$ (565.6 mg, 2.52 mmol) was added and the resulting mixture was heated to reflux for 24 h. After this time the resulting solution was allowed to reach RT, and *n*-hexane (40 mL) was added. The pale-yellow solid formed was filtered, washed with additional *n*-hexane (30 mL), dried in vacuum and identified as **3j**. Yield: 817.3 mg (85%); $^1$H NMR (300.13 MHz, [D$_6$]acetone): $\delta$ = 3.87 (s, 3H; $OCH_3$), 5.26 (s, 1H; NH), 5.58 (s, 1H; NH), 6.76 (dd, $^3J$(H,H) = 7.6, $^4J$(H,H) = 1.8 Hz, 1H; $C_6H_4$), 6.90 (t, $^3J$(H,H) = 7.2 Hz, 1H; $C_6H_4$), 6.96 (td, $^3J$(H,H) = 7.3, $^4J$(H,H) = 1.4 Hz, 1H; $C_6H_4$), 7.20 (d, $^3J$(H,H) = 7.1 Hz, 1H; $C_6H_4$), 7.26–7.35 (m, 2H; $C_6H_5$), 7.35–7.47 ppm (m, 3H; $C_6H_5$); $^{13}$C{$^1$H} NMR (75.47 MHz, [D$_6$]acetone): $\delta$ = 53.67 ($OCH_3$), 124.78 (CH, $C_6H_4$), 126.74 (CH, $C_6H_4$), 127.11 (CH, $C_6H_4$), 128.19 (CH, $C_6H_5$), 129.29 (2 overlapped CH, $C_6H_5$), 134.32 (CH, $C_6H_4$), 142.03 (C, $C_6H_5$), 144.22 (C, $C_6H_4$), 150.70 (C, $C_6H_4$), 172.31 ppm (CO); the signal due to the C-α carbon was not detected; IR: $\tilde{\nu}$ = 1727 $cm^{-1}$; MS (ESI$^+$): *m*/*z*: 719.7 [*M*−$CO_2$]$^+$; elemental analysis calcd (%) for $C_{30}H_{28}Cl_2N_2O_4Pd_2$ (764.3): C 47.14, H 3.69, N 3.67; found: C 47.28, H 3.60, N 3.61.

*[Pd(μ-Cl){$C_6H_4$(CBn($CO_2$Me)$NH_2$)-2}]$_2$ (**3k**)*: Compound **3k** was obtained by following an experimental procedure identical to that described for **3j**. Amino ester hydrochloride **1k**·HCl (200.0 mg, 0.686 mmol) was heated to reflux with $Pd(OAc)_2$ (153.8 mg, 0.686 mmol) in acetone (10 mL) for 24 h to give **3k** as a pale-yellow solid. Yield: 219.6 mg (81%); $^1$H NMR (300.13 MHz, [D$_6$]acetone): $\delta$ = 3.47 (m, 1H; $CH_2$), 3.76 (m, 1H; $CH_2$), 3.80 (s, 3H; $OCH_3$), 4.56–5.00 (m, 2H; $NH_2$), 6.90 (m, 1H; $C_6H_4$), 7.05 (m, 1H; $C_6H_4$), 7.10–7.23 (m, 2H; $C_6H_4$), 7.27–7.38 (m, 3H; $C_6H_5$), 7.38–7.50 ppm (m, 2H; $C_6H_5$); $^{13}$C{$^1$H} NMR (75.47 MHz, [D$_6$]acetone): $\delta$ = 46.87 ($CH_2$), 53.20 ($OCH_3$), 124.67 (CH, $C_6H_4$), 125.19 (CH, $C_6H_4$), 126.93 (CH, $C_6H_4$), 129.41 (CH, $C_6H_5$), 130.76 (CH, $C_6H_5$), 131.15 (C, $C_6H_5$), 144.55 (C, $C_6H_4$), 172.19 ppm (CO); the signal due to the C-α carbon, two signals of the $C_6H_4$ ring and another due to the $C_6H_5$ fragment were not observed; IR: $\tilde{\nu}$ = 3330, 3253 ($\nu_{NH2}$), 1730 $cm^{-1}$ ($\nu_{C=O}$); MS (ESI$^+$): *m*/*z*: 747.7 [*M*−$CO_2$]$^+$; elemental analysis calcd (%) for $C_{32}H_{32}Cl_2N_2O_4Pd_2$ (792.32): C 48.51, H 4.07, N 3.54; found: C 48.70, H 3.92, N 3.57.

*[Pd(μ-Cl){$C_6H_3$((CH$_2$)$_3$C($CO_2$Me)$NH_2$)-8}]$_2$ (**3l**)*: Compound **3l** was obtained by following an experimental procedure identical to that described for **3j**. Amino ester hydrochloride **1l**·HCl (200.0 mg, 0.827 mmol) was heated to reflux with $Pd(OAc)_2$ (185.8 mg, 0.827 mmol) in acetone (10 mL) for 24 h to give **3l** as a grey solid. Yield: 475.2 mg (81%). elemental analysis calcd (%) for $C_{24}H_{28}Cl_2N_2O_4Pd_2$ (692.20): C 41.64, H 4.08, N 4.05; found: C 41.52, H 4.11, N 4.01. IR: $\tilde{\nu}$ = 3279, 3228 ($\nu_{NH2}$), 1720 $cm^{-1}$ ($\nu_{C=O}$). Compound **3l** was insoluble in the usual solvents, making its characterization by NMR methods impossible.

*[Pd(μ-Cl){$C_6H_4$(CH[P(O)(OEt)$_2$]$NH_2$)-2}]$_2$ (**3m**) and [PdCl$_2${$NH_2$CH[P(O)(OEt)$_2$]Ph}$_2$] (**2m**)*: To a suspension of **1m**·HCl (2 g, 7.16 mmol) in acetone (100 mL), $Pd(OAc)_2$ (1.61 g, 7.16 mmol) was added and the resulting mixture was heated to reflux for 6 h. The resulting solution was evaporated to a small volume (ca. 1 mL), and the residue was subjected to column chromatography (2.5 cm diameter, 25 cm height) over silica gel (ethyl acetate as eluent). The first orange band collected was that containing orthopalladated complex **3m**, which was isolated by evaporation of the solvent to dryness, addition of *n*-hexane (20 mL) and further stirring. The solid thus obtained was filtered, washed with additional *n*-hexane (10 mL) and dried in vacuum. Yield: 2.05 g (72%). Further elution with ethyl acetate gave a second orange band, from which complex **2m** (0.50 g, 11%) could be isolated after evaporation of the solvent and addition of *n*-hexane (15 mL).

*Characterization of* ***3m***: $^1$H NMR (400.13 MHz, [D$_6$]acetone): $\delta$ = 1.28 (t, $^3J$(H,H) = 7.0 Hz, 3H; CH$_3$), 1.34 (t, $^3J$(H,H) = 7.0 Hz, 3H; CH$_3$), 4.00–4.07 (m, 2H; OCH$_2$), 4.24 (m, 1H; OCH$_2$), 4.40 (m, 1H; OCH$_2$), 4.59 (d, $^2J$(P,H) = 17.4 Hz, 1H; CH), 6.81 (m, 1H; C$_6$H$_4$), 6.92 (m, 1H; C$_6$H$_4$), 7.05–7.13 ppm (m, 2H; C$_6$H$_4$); $^{13}$C{$^1$H} NMR (100.61 MHz, [D$_6$]acetone): $\delta$ = 16.52 (d, $^3J$(P,C) = 5.6 Hz, CH$_3$), 16.64 (d, $^3J$(P,C) = 5.8 Hz, CH$_3$), 61.20 (d, $^1J$(P,C) = 148 Hz, CH), 64.12 (br., OCH$_2$), 64.30 (d, $^2J$(P,C) = 7.0 Hz, OCH$_2$), 123.27, 124.91, 126.14, 133.72, 144.45, 146.70 ppm (C$_6$H$_4$); $^{31}$P{$^1$H} NMR (161.97 MHz, [D$_6$]acetone): $\delta$ = 20.32 ppm (s); IR: $\tilde{\nu}$ = 3209 ($\nu_{NH}$), 1230 cm$^{-1}$ ($\nu_{P=O}$); MS (ESI$^+$): *m*/*z* (%): 732.7 (40) [*M*−Cl]$^+$; elemental analysis calcd (%) for C$_{22}$H$_{34}$Cl$_2$N$_2$O$_6$P$_2$Pd$_2$: C 34.40, H 4.46, N 3.65; found: C 34.58, H 4.54, N 3.70.

*Characterization of* ***2m***: $^1$H NMR (400.13 MHz, CDCl$_3$): $\delta$ = 1.22–1.32 (m, 6H; CH$_3$), 4.08–4.16 (m, 2H; OCH$_2$), 4.18–4.26 (m, 2H; OCH$_2$), 4.67 (d, $^2J$(P,H) = 16.7 Hz, 1H; CH), 6.76 (m, 1H; C$_6$H$_5$), 6.83 (m, 1H; C$_6$H$_5$), 7.07 (m, 1H; C$_6$H$_5$), 7.38 (m, 1H; C$_6$H$_5$), 7.56 ppm (m, 1H; C$_6$H$_5$); $^{31}$P{$^1$H} NMR (161.97 MHz, CDCl$_3$): $\delta$ = 22.30 ppm; IR: $\tilde{\nu}$ = 3221 ($\nu_{N-H}$), 1226 cm$^{-1}$ ($\nu_{P=O}$); MS (ESI$^+$): *m*/*z* (%): 628.8 (100) [*M*−Cl]$^+$; elemental analysis calcd (%) for C$_{22}$H$_{36}$Cl$_2$N$_2$O$_6$P$_2$Pd: C 39.81, H 5.47, N 4.22; found: C 39.74, H 5.47, N 4.11.

*[Pd(μ-Cl){C$_6$H$_4$(CMe[P(O)(OEt)$_2$]NH$_2$)-2}]$_2$* (***3n***): Complex **3n** was obtained by following the same experimental method described for **3m**, with the exception that **3n** precipitated from the reaction medium and chromatographic purification was not necessary. A suspension of **1n**·HCl (100 mg, 0.34 mmol) and Pd(OAc)$_2$ (76.4 mg, 0.34 mmol) in acetone (20 mL) was heated to reflux for 2.5 h, giving **3n** as an orange solid. Yield: 96.3 mg (71%) $^1$H NMR (400.13 MHz, [D$_6$]acetone): $\delta$ = 1.21 (m, 3H; CH$_3$), 1.37 (m, 3H; CH$_3$), 1.82 (d, $^3J$(P,H) = 15.0 Hz, 3H; α-CH$_3$), 3.78–4.00 (m, 2H; OCH$_2$), 4.20–4.43 (m, 2H; OCH$_2$), 6.83 (m, 1H; C$_6$H$_4$), 6.92–7.00 (m, 2H; C$_6$H$_4$), 7.12 ppm (m, 1H; C$_6$H$_4$); $^{31}$P{$^1$H} (161.97 MHz, [D$_6$]acetone): $\delta$ = 23.38 ppm; IR: $\tilde{\nu}$ = 3204 ($\nu_{N-H}$), 1228 cm$^{-1}$ ($\nu_{P=O}$); MS (ESI$^+$): *m*/*z* (%): 430.9 (19) [*M*/2+Cl]$^+$, 402.9 (100) [*M*H/2]$^+$; elemental analysis calcd (%) for C$_{24}$H$_{38}$Cl$_2$N$_2$O$_6$P$_2$Pd$_2$: C 36.20, H 4.81, N 3.52; found: C 36.48, H 4.86, N 3.48.

**Reactivity of the orthopalladated complexes 3m and 3n**

*{H$_2$NC(H)[P(O)(OEt)$_2$](2-ClC$_6$H$_4$)}* (***5m***): To a fresh solution of PhICl$_2$[37] (71.6 mg, 0.26 mmol) in CH$_2$Cl$_2$ (10 mL), complex **3m** (100 mg, 0.13 mmol) was added. The resulting mixture was stirred at RT for 24 h and then filtered over a Celite bed, washing repeatedly with 5 mL fractions of CH$_2$Cl$_2$. The resulting solution was evaporated to 10 mL, then PPh$_3$ (68.3 mg, 0.26 mmol) was added. After a few seconds a voluminous yellow precipitate of [PdCl$_2$(PPh$_3$)$_2$] appeared. This suspension was stirred at RT for 2 h, then the solid was removed by filtration and the resulting solution was concentrated to 2 mL. This residue was subjected to column chromatography over silica gel with ethyl acetate as eluent. The first colorless fraction collected was identified as unreacted PPh$_3$. Further elution developed a second yellow band, from which **5m** was isolated as a yellow oil by evaporation of the solvent. Yield: 52.2 mg (72%); $^1$H NMR (400.13 MHz, CDCl$_3$): $\delta$ = 1.12 (t, $^3J$(H,H) = 7.1 Hz, 3H; CH$_3$), 1.32 (t, $^3J$(H,H) = 7.0 Hz, 3H; CH$_3$), 1.91 (br. s, 2H; NH$_2$), 3.82 (m, 1H; OCH$_2$), 3.94 (m, 1H; OCH$_2$), 4.09–4.22 (m, 2H; OCH$_2$), 4.82 (d, $^2J$(P,H) = 18.7 Hz, 1H; CH), 7.20 (m, 1H; C$_6$H$_4$), 7.29 (m, 1H; C$_6$H$_4$), 7.35 (m, 1H; C$_6$H$_4$), 7.66 ppm (m, 1H; C$_6$H$_4$); $^{13}$C{$^1$H} NMR (100.61 MHz, CDCl$_3$): $\delta$ = 16.3 (d, $^3J$(C,P) = 5.7 Hz; CH$_3$), 16.6 (d, $^3J$(C,P) = 5.7 Hz, CH$_3$), 49.8 (d, $^1J$(C,P) = 152.3 Hz; CH), 62.9 (d, $^2J$(C,P) = 7.4 Hz, OCH$_2$), 63.0 (d, $^2J$(C,P) = 7.4 Hz, OCH$_2$), 127.3 (d, $J$(C,P) = 2.8 Hz; CH, C$_6$H$_4$), 129.0 (d, $J$(C,P) = 2.9 Hz; CH, C$_6$H$_4$), 129.2 (d, $J$(C,P) = 4.3 Hz; CH, C$_6$H$_4$), 129.5 (d, $J$(C,P) = 2.0 Hz; CH, C$_6$H$_4$), 133.7 (d, $^3J$(C,P) = 8.9 Hz; C-Cl, C$_6$H$_4$), 136.4 ppm (s; C, C$_6$H$_4$); $^{31}$P{$^1$H} NMR (161.97 MHz, CDCl$_3$): $\delta$ = 24.46 ppm; IR: $\tilde{\nu}$ = 3376, 3298 ($\nu_{N-H}$), 1235 cm$^{-1}$ ($\nu_{P=O}$); MS (ESI$^+$): *m*/*z* (%): 278.0 (70%) [*M*+H]$^+$; HRMS (ESI-TOF): *m*/*z*: calcd for C$_{11}$H$_{18}$ClNO$_3$P 278.0707 [*M*+H]$^+$; found: 278.0731; elemental analysis calcd (%) for C$_{11}$H$_{17}$ClNO$_3$P: C 47.58, H 6.17, N 5.04; found: C 47.89, H 6.25, N 4.88.

*{H$_2$NC(H)[P(O)(OEt)$_2$](2-BrC$_6$H$_4$)}* (***6m***): To a solution of **3m** (100 mg, 0.13 mmol) in CH$_2$Cl$_2$ (20 mL), Br$_2$ was added (13.2 μL, 0.26 mmol), and the resulting suspension was stirred at RT for 20 h. The precipitated PdBr$_2$ was removed by filtration through a Celite bed, which was washed with CH$_2$Cl$_2$ (2×5 mL). The clear solution was washed with an aqueous solution of sodium sulfite (32.7 mg, 0.26 mmol in 10 mL water) to eliminate any Br$_2$ in excess, and the organic fraction was dried with anhydrous MgSO$_4$. Further workup of the resulting solution was similar to that described for **5m**. Thus, the solution was treated with PPh$_3$ (68.3 mg, 0.26 mmol) for 2 h at RT, the precipitated [PdCl$_2$(PPh$_3$)$_2$] was removed and the residue was purified by chromatography (silica gel, ethyl acetate), to afford **6m** as a yellow oil. Yield: 32.8 mg (40%); $^1$H NMR (400.13 MHz, CDCl$_3$): $\delta$ = 1.14 (t, $^3J$(H,H) = 6.9 Hz, 3H; CH$_3$), 1.35 (t, $^3J$(H,H) = 7.1 Hz, 3H; CH$_3$), 1.95 (br. s, 2H; NH$_2$), 3.83 (m, 1H; OCH$_2$), 3.96 (m, 1H; OCH$_2$), 4.11–4.25 (m, 2H; OCH$_2$), 4.82 (d, $^2J$(P,H) = 18.7 Hz, 1H; CH), 7.15 (m, 1H; C$_6$H$_4$), 7.35 (m, 1H; C$_6$H$_4$), 7.55 (m, 1H; C$_6$H$_4$), 7.69 ppm (m, 1H; C$_6$H$_4$); $^{13}$C{$^1$H} NMR (100.61 MHz, CDCl$_3$): $\delta$ = 16.3 (d, $^3J$(P,C) = 5.6 Hz; CH$_3$), 16.6 (d, $^3J$(P,C) = 5.8 Hz; CH$_3$), 52.5 (d, $^1J$(P,C) = 152.1 Hz; CH), 63.0 (d, $^2J$(P,C) = 7.3 Hz; OCH$_2$), 63.1 (d, $^2J$(P,C) = 7.3 Hz; OCH$_2$), 124.3 (d, $^3J$(P,C) = 9.6 Hz; C-Br, C$_6$H$_4$), 127.9 (d, $J$(P,C) = 2.8 Hz; CH, C$_6$H$_4$), 129.3 (d, $J$(P,C) = 2.1 Hz; CH, C$_6$H$_4$), 129.4 (d, $J$(P,C) = 3.6 Hz; CH, C$_6$H$_4$), 132.9 (d, $J$(P,C) = 1.9 Hz; CH, C$_6$H$_4$), 138.1 ppm (s; C, C$_6$H$_4$); $^{31}$P{$^1$H} NMR (161.97 MHz, CDCl$_3$): $\delta$ = 24.32 ppm; MS (ESI$^+$): *m*/*z* (%): 321.9 (18%) [*M*]$^+$; HRMS (ESI-TOF): *m*/*z*: calcd for C$_{11}$H$_{18}$BrNO$_3$P 322.0202 [*M*+H]$^+$; found 322.0206; elemental analysis calcd (%) for C$_{11}$H$_{17}$BrNO$_3$P: C 41.01, H 5.32, N 4.35; found: C 40.72, H 5.18, N 4.38; IR: $\tilde{\nu}$ = 3374, 3296 ($\nu_{N-H}$), 1234 cm$^{-1}$ ($\nu_{P=O}$).

*{H$_2$NC(H)[P(O)(OEt)$_2$](2-IC$_6$H$_4$)}* (***7m***): The synthesis of **7m** was carried out by following the same experimental procedure described for **6m**. Thus, **3m** (100 mg, 0.13 mmol) was reacted with I$_2$ (66.4 mg, 0.26 mmol) and PPh$_3$ (68.3 mg, 0.26 mmol) in CH$_2$Cl$_2$ (20 mL) to give **7m** as a yellow oil. Yield: 27.1 mg (28%); $^1$H NMR (400.13 MHz, CDCl$_3$): $\delta$ = 1.13 (t, $^3J$(H,H) = 7.0 Hz, 3H; CH$_3$), 1.35 (t, $^3J$(H,H) = 7.1 Hz, 3H; CH$_3$), 1.92 (br. s, 2H; NH$_2$), 3.80 (m, 1H; OCH$_2$), 3.95 (m, 1H; OCH$_2$), 4.17–4.22 (m, 2H; OCH$_2$), 4.76 (d, $^2J$(P,H) = 18.7 Hz, 1H; CH), 6.97 (m, 1H; C$_6$H$_4$), 7.37 (m, 1H; C$_6$H$_4$), 7.66 (m, 1H; C$_6$H$_4$), 7.83 ppm (m, 1H; C$_6$H$_4$); $^{13}$C{$^1$H} NMR (100.61 MHz, CDCl$_3$): $\delta$ = 16.4 (d, $^3J$(C,P) = 5.7 Hz, CH$_3$), 16.7 (d, $^3J$(C,P) = 5.8 Hz, CH$_3$), 57.9 (d, $^1J$(C,P) = 151.5 Hz, CH), 63.0 (d, $^2J$(C,P) = 7.4 Hz, OCH$_2$), 63.1 (d, $^2J$(C,P) = 7.3 Hz, OCH$_2$), 100.9 (d, $^3J$(C,P) = 10.4 Hz, C-I, C$_6$H$_4$), 128.8 (d, $J$(C,P) = 3.1 Hz, CH, C$_6$H$_4$), 129.0 (d, $J$(C,P) = 4.4 Hz, CH, C$_6$H$_4$), 129.7 (d, $J$(C,P) = 2.9 Hz, CH, C$_6$H$_4$), 139.7 (d, $J$(C,P) = 1.5 Hz, CH, C$_6$H$_4$), 141.5 ppm (s, C, C$_6$H$_4$); $^{31}$P{$^1$H} NMR (161.97 MHz, CDCl$_3$): $\delta$ = 24.80 ppm; MS (ESI$^+$): *m*/*z* (%): 370.1 (32) [*M*+H]$^+$; HRMS (ESI-TOF): *m*/*z*: calcd for C$_{11}$H$_{18}$INO$_3$P: 370.0063 [*M*+H]$^+$; found: 370.0060; elemental analysis calcd (%) for C$_{11}$H$_{17}$INO$_3$P: C 35.79, H 4.64, N 3.79; found: C 35.60, H 4.68, N 4.00; IR: $\tilde{\nu}$ = 3374, 3296 ($\nu_{N-H}$), 1234 cm$^{-1}$ ($\nu_{P=O}$).

*{H$_2$NC(Me)[P(O)(OEt)$_2$](2-BrC$_6$H$_4$)}* (***6n***): The synthesis of **6n** was carried out by following the same experimental procedure described for **6m**, except that compound **3n** was used as starting material. Thus, **3n** (100 mg, 0.125 mmol) was reacted with Br$_2$ (13.3 μL, 0.26 mmol) and PPh$_3$ (68.3 mg, 0.26 mmol) in CH$_2$Cl$_2$ (20 mL) to give **6n** as a yellow oil. Yield: 36.8 mg (41%); $^1$H NMR (400.13 MHz, CDCl$_3$): $\delta$ = 1.29 (t, $^3J$(H,H) = 6.9 Hz, 3H; CH$_3$), 1.30 (t, $^3J$(H,H) = 7.0 Hz, 3H; CH$_3$), 1.90 (d, $^3J$(P,H) = 15.7 Hz, 3H; α-CH$_3$), 2.42 (br., 2H; NH$_2$), 4.03–4.16 (m, 4H; OCH$_2$), 7.09 (m, 1H; C$_6$H$_4$), 7.29 (m, 1H; C$_6$H$_4$), 7.60 (m, 1H; C$_6$H$_4$), 7.76 ppm (m, 1H; C$_6$H$_4$); $^{13}$C{$^1$H} NMR (100.61 MHz, CDCl$_3$): $\delta$ = 16.6 (d, $^3J$(C,P) = 2.4 Hz; CH$_3$), 16.7 (d, $^3J$(C,P) = 2.3 Hz; CH$_3$), 25.7 (d, $^2J$(C,P) = 1.7 Hz; α-CH$_3$), 58.0 (d, $^1J$(C,P) = 152.0 Hz; C), 63.1 (d, $^2J$(C,P) = 7.7 Hz; OCH$_2$), 63.4 (d, $^2J$(C,P) = 7.5 Hz; OCH$_2$), 121.7 (d, $^3J$(C,P) = 8.2 Hz; C-Br, C$_6$H$_4$), 128.6 (d, $J$(C,P) = 12.1 Hz; CH, C$_6$H$_4$), 132.1 (d, $J$(C,P) = 2.8 Hz; CH, C$_6$H$_4$), 132.2 (d, $J$(C,P) = 9.9 Hz; CH, C$_6$H$_4$), 136.3 (d, $J$(C,P) = 0.9 Hz; CH, C$_6$H$_4$), 139.8 ppm (s; C, C$_6$H$_4$); $^{31}$P{$^1$H} NMR (161.97 MHz, CDCl$_3$): $\delta$ = 26.60 ppm; IR: $\tilde{\nu}$ = 3370, 3300 ($\nu_{N-H}$), 1236 cm$^{-1}$ ($\nu_{P=O}$); MS (ESI$^+$): *m*/*z* (%): 335.8 (2.5) [*M*+H]$^+$, 279.0 (100) [*M*−C$_4$H$_9$]$^+$, 197.9 (10) [*M*−P(O)(OEt)$_2$]$^+$; elemental analysis calcd (%) for C$_{12}$H$_{19}$BrNO$_3$P: C 42.88, H 5.70, N 4.17; found: C 43.01, H 5.67, N 4.04.

*{H$_2$NC(Me)[P(O)(OEt)$_2$](2-IC$_6$H$_4$)}* (***7n***): The synthesis of **7n** was carried out by following the same experimental procedure described for **6m**, except that compound **3n** was used as starting material. Thus, **3n** (100 mg, 0.125 mmol) was reacted with I$_2$ (67.4 mg, 0.26 mmol) and PPh$_3$

(68.3 mg, 0.26 mmol) in $CH_2Cl_2$ (20 mL) to give **7n** as a yellow oil. Yield: 25.2 mg (26%); $^1$H NMR (400.13 MHz, $CDCl_3$): $\delta = 1.27$ (t, $^3J(H,H) = 5.7$ Hz, 6H; $CH_3$), 1.88 (d, $^3J(P,H) = 15.6$ Hz, 3H; α-$CH_3$), 2.31 (br., 2H; $NH_2$), 4.00–4.14 (m, 4H; $OCH_2$), 7.07 (m, 1H; $C_6H_4$), 7.28 (m, 1H; $C_6H_4$), 7.40–7.69 ppm (m, 2H; $C_6H_4$); $^{31}$P{$^1$H} NMR (161.97 MHz, $CDCl_3$): $\delta = 26.36$ ppm; IR: $\tilde{\nu} = 3365$, 3301 ($\nu_{N-H}$), 1240 cm$^{-1}$ ($\nu_{P=O}$); elemental analysis calcd (%) for $C_{12}H_{19}INO_3P$: C 37.62, H 5.00, N 3.66; found: C 37.44, H 5.02, N 3.69.

*{$H_2NC(H)[P(O)(OEt)_2](2\text{-}MeOC_6H_4)$} (**8m**)*: To a suspension of **3m** (100 mg, 0.13 mmol) in methanol (10 mL), $PhI(OAc)_2$ (167.7 mg, 0.52 mmol) was added. The mixture was stirred at RT for 20 h, then the suspended solid was removed by filtration through a Celite bed, which was washed with $CH_2Cl_2$ (2×5 mL). The solid was discarded and the combined solutions were evaporated to dryness. The remaining residue was redissolved in $CH_2Cl_2$ (30 mL) and the clear solution was washed with an aqueous solution of sodium sulfite (10%, 2×15 mL). The organic fraction was dried with anhydrous $MgSO_4$. Further workup of the resulting solution was similar to that described for **5m**. Thus, the solution was treated with $PPh_3$ (68.3 mg, 0.26 mmol) for 3 h at RT, the precipitated $[PdCl_2(PPh_3)_2]$ was removed and the residue was purified by chromatography (silica gel, ethyl acetate), to afford **8m** as a yellow oil. Yield: 6.7 mg (10%); $^1$H NMR (400.13 MHz, $CDCl_3$): $\delta = 1.07$ (t, $^3J(H,H) = 7.1$ Hz, 3H; $CH_3$), 1.24 (t, $^3J(H,H) = 7.1$ Hz, 3H; $CH_3$), 2.82 (br., $NH_2$), 3.77 (s, 3H; $OCH_3$), 3.86–3.92 (m, 2H; $OCH_2$), 3.98–4.09 (m, 2H; $OCH_2$), 4.72 (d, $^2J(P,H) = 17.9$ Hz, 1H; CH), 6.81 (m, 1H; $C_6H_4$), 6.92 (m, 1H; $C_6H_4$), 7.15–7.75 ppm (m, 2H; $C_6H_4$); $^{31}$P{$^1$H} NMR (161.97 MHz, $CDCl_3$): $\delta = 26.01$ ppm; elemental analysis calcd (%) for $C_{12}H_{20}NO_4P$: C 52.74, H 7.38, N 5.13; found: C 52.50, H 7.47, N 5.06.

*{$H_2NC(H)[P(O)(OEt)_2](2\text{-}EtOC_6H_4)$} (**9m**)*: The synthesis of **9m** was carried out by following the same experimental procedure described for **8m**, except that ethanol was used as solvent. Thus, **3m** (100 mg, 0.13 mmol) was reacted with $PhI(OAc)_2$ (167.7 mg, 0.52 mmol) in ethanol (10 mL) and with $PPh_3$ (68.3 mg, 0.26 mmol) in $CH_2Cl_2$ (20 mL) to give **9m** as a yellow oil. Yield: 8.6 mg (12% yield); $^1$H NMR (400.13 MHz, [$D_6$]acetone): $\delta = 1.08$ (t, $^3J(H,H) = 7.0$ Hz, 3H; $CH_3$), 1.25 (t, $^3J(H,H) = 7.1$ Hz, 3H; $CH_3$), 1.36 (t, $^3J(H,H) = 7.0$ Hz, 3H; $CH_3$), 3.79 (m, 1H; $OCH_2$), 3.89 (m, 1H; $OCH_2$), 3.95–4.02 (m, 2H; $OCH_2$), 4.04–4.12 (m, 2H; $OCH_2$), 4.75 (d, $^2J(P,H) = 17.9$ Hz, 1H; CH), 6.79 (m, 1H; $C_6H_4$), 6.91 (m, 1H; $C_6H_4$), 7.25 (m, 1H; $C_6H_4$), 7.40 ppm (m, 1H; $C_6H_4$); $^{31}$P{$^1$H} NMR (161.97 MHz, [$D_6$]acetone): $\delta = 26.21$ ppm; elemental analysis calcd (%) for $C_{13}H_{22}NO_4P$: C 54.35, H 7.72, N 4.88; found: C 53.89, H 7.65, N 4.90.

*Diethyl (3-oxoisoindolin-1-yl)phosphonate (**10m**)*: A solution of cyclopalladated complex **3m** (100 mg, 0.13 mmol) in $CH_2Cl_2$ (20 mL) was stirred under a CO atmosphere (1 atm) at RT for 24 h. During this time the decomposition of the palladacycle was evident as black palladium appeared and its amount increases along the reaction time. After 24 h, the resulting black suspension was filtered through a Celite bed to remove Pd(0), and the resulting pale-yellow solution was evaporated to dryness. Treatment of the residue with *n*-hexane (20 mL) and continuous stirring gave **10m** as a white solid, which was filtered, washed with additional *n*-hexane (10 mL) and dried by suction. Yield: 40.2 mg (58%). $^1$H NMR (400.13 MHz, $CDCl_3$): $\delta = 1.08$ (t, $^3J(H,H) = 7.1$ Hz, 3H; $CH_3$), 1.29 (t, $^3J(H,H) = 7.1$ Hz, 3H; $CH_3$), 3.78 (m, 1H; $OCH_2$), 3.98 (m, 1H; $OCH_2$), 4.12–4.23 (m, 2H; $OCH_2$), 4.96 (d, $^2J(P,H) = 13.6$ Hz, 1H; CH), 6.91 (br., 1H; NH), 7.54 (td, $^3J(H,H) = 7.5$, $^4J(H,H) = 1.3$ Hz, 1H; $C_6H_4$), 7.62 (td, $^3J(H,H) = 7.6$, $^4J(H,H) = 1.1$ Hz, 1H; $C_6H_4$), 7.75 (dd, $^3J(H,H) = 7.6$, $^4J(H,H) = 0.5$ Hz, 1H; $C_6H_4$), 7.92 ppm (dd, $^3J(H,H) = 7.5$, $^4J(H,H) = 0.5$ Hz, 1H; $C_6H_4$, $C_6H_4$); $^{13}$C{$^1$H} NMR (100.61 MHz, $CDCl_3$): $\delta = 16.2$ (d, $^3J(C,P) = 5.5$ Hz; Me), 16.4 (d, $^3J(C,P) = 5.6$ Hz; Me), 54.0 (d, $^1J(C,P) = 155.6$ Hz; C-P), 63.4 (d, $^2J(C,P) = 7.3$ Hz; $CH_2$), 63.8 (d, $^2J(C,P) = 7.0$ Hz; $CH_2$), 124.2 (CH, $C_6H_4$), 124.3 (CH, $C_6H_4$), 129.0 (d, $J(C,P) = 2.2$ Hz, CH; $C_6H_4$), 131.7 (d, $J(C,P) = 4.7$ Hz; C, $C_6H_4$), 132.2 (d, $J(C,P) = 2.5$ Hz; CH, $C_6H_4$), 140.0 (d, $^2J(C,P) = 6.6$ Hz; C, $C_6H_4$), 170.6 ppm (s; CO); $^{31}$P{$^1$H} NMR (161.97 MHz, $CDCl_3$): $\delta = 18.07$ ppm; IR: $\tilde{\nu} = 3195$ ($\nu_{N-H}$), 1694 ($\nu_{C=O}$), 1252 cm$^{-1}$ ($\nu_{P=O}$); MS (ESI$^+$): *m*/*z* (%): 269.9 (90) $[M+H]^+$; HRMS (ESI-TOF) *m*/*z*: calcd for $C_{12}H_{16}NNaO_4P$ 292.0709 $[M+Na]^+$; found: 292.0722.

**X-ray crystallography**: Crystals of **3j** and **4k** of sufficient quality for X-ray measurements were grown by vapor diffusion of $Et_2O$ into $CH_2Cl_2$ solutions of the crude products at 25°C. A single crystal was mounted in each case 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. X-ray data collection was performed with Bruker Smart Apex CCD or Oxford Diffraction Xcalibur2 diffractometers using graphite-monocromated Mo-Kα radiation ($\lambda = 0.71073$ Å). In all cases, a hemisphere of data was collected based on ω-scan or $\phi$-scan runs. The diffraction frames were integrated by using the programs SAINT[41] or CrysAlis RED[42] and the integrated intensities were corrected for absorption with SADABS.[43] The structures were solved and developed by Patterson and Fourier methods.[44] All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen 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.[45] CCDC-934779 (**3j**) and 934780 (**4k**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**Kinetic measurements**: Reactions at atmospheric pressure were followed by UV/Vis time-resolved spectroscopy in the full 750–300 nm range with a HP8543 or Cary 50 instrument equipped with a thermostated multicell transport (±0.1°C). Observed rate constants were derived from the absorbance versus time traces at wavelengths for which a maximum increase and/or decrease of absorbance was observed. No dependence of the rate constant values on the selected wavelengths was found, as expected for reactions in which good retention of isosbestic points is observed. For runs at elevated pressure, a previously described pressurizing system and high-pressure cell were used.[24b,46a] In these cases, the changes in spectra with time were recorded with a J&M TIDAS instrument in the full wavelength range. The general kinetic technique was previously described.[13a,24c,28,46b] The solutions for the kinetic runs were prepared by mixing the calculated amounts of palladium acetate and ligand solutions in the solvent of choice to produce a 1:1 final concentration ratio. The solutions also included any additional reactants in the calculated concentrations for the desired final reaction conditions. In all cases, no dependence on the concentration of palladium [$(2–5)\times10^{-4}$ M range] was detected. Rate constants were derived from exponential least-square fitting by the standard routines.[47] Table S1 (see the Supporting Information) summarizes 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 10–15% range of the calculated value. All post-run fittings were done by standard commercially available fitting programs.

**Computational details**: Calculations were carried out with the GAUSSIAN03 software package.[48] The hybrid density function method known as B3LYP was applied.[49] Relativistic effective core potentials from the Stuttgart-Dresden group were used to represent the innermost electrons of the palladium atom and its basis set of valence double-ζ quality associated known as SDD.[50] The basis set for the light elements (C, N, O, and H) was also double-ζ quality split-valence and includes polarization functions in all atoms (known as 6–31 g(d)).[51] The geometries for minima were fully optimized in all isomers and transition states were located to connect two minima; these were confirmed by a vibrational analysis. Energies in solution were taken into account by PCM calculations,[52] keeping the geometry optimized for the gas phase (single-point calculations). In solvent calculations, the basis set for atoms other than Pd were expanded to the 6–311g++(d,p) triple-ζ basis sets. All energies reported here are in units of kcal mol$^{-1}$ and if not stated otherwise the energy referred to in the text are Gibbs energies in the gas phase. Gibbs energies in solution were computed as $\Delta G_{sol} = \Delta E_{solv}^{BS2} + (\Delta G_{gas}^{BS1} - \Delta E_{gas}^{BS1})$. Where $\Delta E_{solv}^{BS2}$ is the solution potential energy, being the sum of the potential energy of the solute and the Gibbs energy of the solvent. All DFT calculation data for the coordinates and absolute energies are available in tabular format (Tables S2–S3) and electronic files included in the Supporting Information.

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