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Platinum-Mediated C−H Bond Activation of Arene Solvents and Subsequent C−C Bond Formation

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The reactions of *cis*-[$PtCl_2(SOMe_2)_2$] and imines 2,6-$Cl_2C_6H_3CH{=}NCH_2(4\text{-}XC_6H_4)$ (**1a**, X = H; **1b**, X = Cl), 2,6-$Cl_2C_6H_3CH{=}NCH_2(2,6\text{-}F_2C_6H_3)$ (**1f**), and 2,6-$Cl_2C_6H_3CH{=}N(4\text{-}ClC_6H_4)$ (**1g**) carried out in toluene at 90 °C in the presence of sodium acetate dissolved in methanol produced compounds [$PtCl\{(MeC_6H_3)(2\text{-}ClC_6H_3)CHNR\}SOMe_2$] (R = $CH_2C_6H_5$ (**4a**), $CH_2(4\text{-}ClC_6H_4)$ (**4b**), $CH_2(2,6\text{-}F_2C_6H_3)$ (**4f**), and $4\text{-}ClC_6H_4$ (**4g**)), containing seven-membered platinacycles via "formal insertion" of a toluene molecule in the metallacycle. These compounds are formed in a process involving several steps, the most relevant being intermolecular C−H activation of a solvent toluene molecule and formation of a carbon−carbon bond. The reaction of *cis*-[$PtCl_2(SOMe_2)_2$] and imine 2,6-$Cl_2C_6H_3CH{=}NCH_2(4\text{-}ClC_6H_4)$ (**1b**) under analogous conditions was also carried out using other arene solvents such as benzene and *ortho*-, *meta*-, and *para*-xylene and produced in all cases seven-membered platinacycles. DFT calculations indicate that the stability of the metallacycles increases in the order *p*-xylyl < *m*-xylyl < *o*-xylyl < tolyl < phenyl and have helped to suggest a possible reaction path.

Introduction

C−C bond formation is an important process in organic synthesis; in particular, biaryl linkages are key features of diverse natural products and many important organic molecules.[1] The most common method for biaryl C−C bond construction is metal-catalyzed cross-coupling between two functionalized starting materials.[2] An ideal method to construct C−C bonds should be the direct functionalization of the ubiquitous C−H bonds[3] since, in spite of the large bond dissociation energy of the C−H bond, the fundamental features of the C−H bond cleavage reactions have been elucidated.[4] Several groups have developed group 10 transition metal catalyzed C−H activation/C−C bond formation processes that use an arene C−H bond as one of the coupling partners,[5] and the great potential of catalysis involving palladium in oxidation states higher than those of conventional palladium(0)/palladium(II) cycles has been underlined.[6] Intermolecular C−H activation leading to C−C coupling has also been described in the formation of bridging biphenyl platinum complexes.[7]

In a preliminary communication[8] we have reported the first example of a formal toluene "insertion" into a metal−carbon bond, by means of an unprecedented process involving intramolecular activation of a C_{aryl}−Cl bond of an imine, an intermolecular activation of a C_{aryl}−H bond of toluene, and the formation of a new carbon−carbon bond, between a toluene molecule and the benzal ring of the imine. The aim of this work is to explore the scope of this unexpected process taking place when toluene was used as a solvent and to analyze whether it can be extended to other arenes such as benzene or xylenes as well as to other imines. In this case, this new process could be considered as a general procedure for C−C coupling arising from intermolecular C−H activation of arene solvents.

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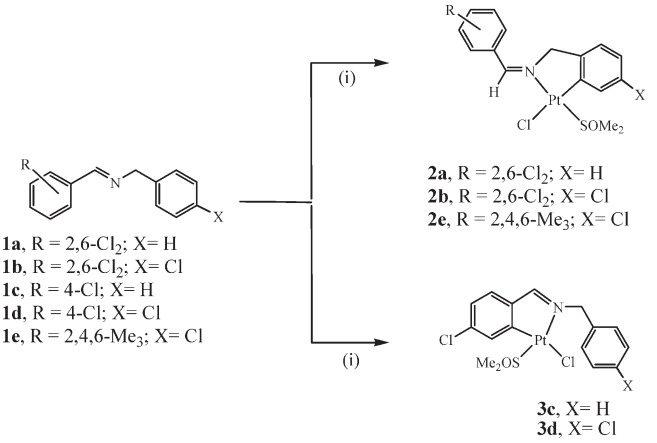
Scheme 1[a]



[a] (i) + *cis*-[$PtCl_2(dmso)_2$] + NaOAc (1:1:1) in MeOH, 65 °C, 48 h.

Results and Discussion

"Formal Insertion" of Toluene. As previously reported,[8] in order to explore the synthetic ability of *cis*-[$PtCl_2(SOMe_2)_2$] in the preparation of *exo*-platinacycles, the reactions of *cis*-[$PtCl_2(SOMe_2)_2$] with 2,6-$Cl_2C_6H_3CH{=}NCH_2(4\text{-}XC_6H_4)$ (**1a**, X = H; **1b**, X = Cl) were planned, with the aim that the chloro substituents in the *ortho* positions of the benzal ring would force the formation of the less common *exo*-platinacycles (Scheme 1).

When the reactions of equimolar amounts of *cis*-[$PtCl_2(SOMe_2)_2$], the corresponding imine, and sodium acetate (dissolved in a small amount of methanol) were carried out in dry toluene, heating the reaction mixture at 90 °C during 48 h, the reactions produced the new compound **4a** or **4b** (Scheme 2), in addition to the expected *exo*-cyclometalated platinum(II) compounds [PtCl{(2,6-$Cl_2C_6H_3$)$CHNCH_2$(4-XC_6H_3)}{$SOMe_2$}] (**2a**, X = H; **2b**, X = Cl).[9] Compounds **4a** and **4b** obtained as white (**4a**) or light yellow (**4b**) crystals arise from a novel process leading to seven-membered platinacycles via a "formal insertion" of a solvent toluene molecule. Compound [PtCl{(MeC_6H_3)(2-ClC_6H_3)$CHNCH_2$(4-ClC_6H_4)}{$SOMe_2$}] (**4b**) was crystallized in dichloromethane−methanol from the crude product, while [PtCl{(MeC_6H_3)$ClC_6H_3CHNCH_2C_6H_5$}{$SOMe_2$}] (**4a**) was crystallized after purifying the crude product by column chromatography (silica, ethyl acetate−hexane = 100:20). Compounds **4a** and **4b** were characterized by elemental analyses, mass spectra, and NMR spectroscopy. In the ^1H NMR spectra of both compounds in addition to the main set of signals, resonances due to a minor isomer (abundance ca. 20% (**4a′**) and 30% (**4b′**)) with the same spectral pattern were observed.[8,9] A singlet resonance coupled to platinum at 6.63 (**4a**) or 6.56 ppm (**4b**) corresponding to the major isomer is assigned to the aromatic proton adjacent to the Pt−C bond. On this basis, the major isomer is assigned to that with a *meta* arrangement between the Pt−C bond and the methyl substituent (as in the crystal structure of **4a**[8] shown in Figure 1), and the minor isomer corresponds to the *para* isomer. DFT calculations performed on **4b** and **4b′** show that the former is slightly more stable, although the difference in energies between both isomers—only 0.40 kcal/mol—is too small to be significant.

When the same reaction was performed with the imines 4-$ClC_6H_4CHNCH_2$(4-XC_6H_4) (**1c**, X = H; **1d**, X = Cl) and $Me_3C_6H_2CHNCH_2$(4-ClC_6H_4) (**1e**) (Scheme 1), the "formal insertion" of toluene was not detected and only the expected complexes were obtained: the *endo*-metallacycles [PtCl{(4-ClC_6H_3)$CHNCH_2$(4-XC_6H_4)}{$SOMe_2$}] (**3c**, X = H; **3d**, X = Cl), in the case of imines **1c** and **1d**, and the corresponding *exo*-derivative [PtCl{$MeC_6H_2CHNCH_2$(4-ClC_6H_3)}{$SOMe_2$}], **2e**, in the case of imine **1e**.[9] These results show that the presence of C−Cl bonds in the *ortho* position of the imine plays a crucial role in this process. Furthermore, compounds **4a** and **4b** could also be obtained using [$Pt(OAc)_2(SOMe_2)_2$] as platinum substrate, which suggests that the chloro bound to platinum in the final product arises from *ortho* C−Cl bond activation.

In order to rule out the possibility that *exo*-metallacycles could be precursors of compounds **4**, an equimolar mixture of **2b** and NaOAc (in a small amount of methanol) was heated at 90 °C during 48 h in toluene, after which time the *exo*-metallacycle was recovered unchanged. In addition, when the reaction of compound [$Pt(OAc)_2(SOMe_2)_2$] and imine **1b** was carried out in d_8-toluene (90 °C, 48 h), to produce d_6-**4b**, no changes were observed in the ^1H NMR spectrum for the signals corresponding to the imine protons, which indicates that H−D exchange does not occur in the N-donor ligand.

The low yields obtained for compounds **4a** and **4b** (15% and 30%, respectively) can be related to the formation of the *exo*-derivative as a byproduct. For this reason and in order to expand the process to new ligands, imines **1f** and **1g** were investigated in this work. These ligands were selected because the presence of two fluorine atoms in the *ortho* positions for **1f** or the unlikely formation of a four-membered cycle for **1g** prevents formation of an *exo*-metallacycle. Seven-membered metallacycles **4f** and **4g**, analogous to **4a** and **4b**, were obtained with these imines; however the yield of the process did not increase significantly. The low yields are probably due to decomposition and hydrolyses processes, as evidenced by formation of metallic platinum and aldehyde. The reaction with imine **1h**, containing two nitrogen atoms, was also carried out under the same conditions; however in this case the only product was coordination compound **Ih**, which suggests that the presence of a labile ligand is required for further reaction to take place. NMR spectra of compounds **4f**, **4g**, and **Ih** are consistent with the proposed formulas. For **4f** and **4g** two isomers were detected in the crude reaction mixture, but only one isomer could be isolated and characterized in each case.

Further work was focused on imine **1b**, and since according to the stoichiometry of the reaction (see below) two equivalents of HCl should be formed, the reaction was tested under the same conditions as above but using two equivalents of sodium acetate. Under these conditions, a higher yield of compound **4b** (45%) was obtained. Further increase in the amount of sodium acetate did not produce an increase in the obtained yield. On the other hand, an increase in the reaction time produced the formation of higher amounts of metallic platinum and lower yields for **4b**.

"Formal Insertion" of Other Arenes. In order to expand the scope of this novel process, the activation of other aromatic solvents such as benzene and *ortho*-, *meta*-, and *para*-xylene was explored in this work. Intermolecular aromatic C−H bond activation at platinum(II) compounds containing N-donor ligands is now well established,[4,10,11] and the factors that influence the selectivity and reactivity of activation of benzene, toluene, or xylenes have been studied.[12]

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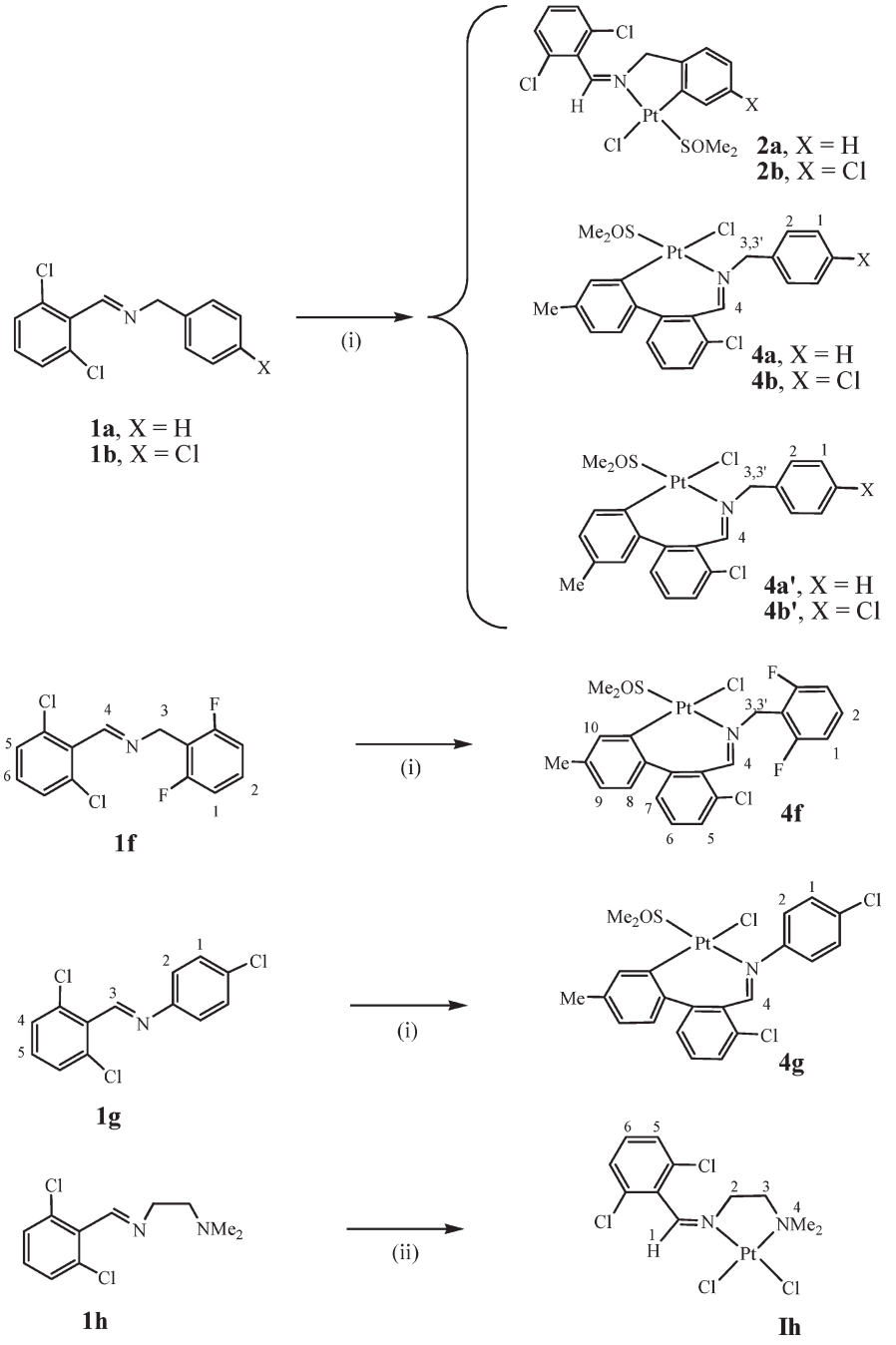
Scheme 2[a]



[a] (i): + *cis*-[$PtCl_2(dmso)_2$] + NaOAc−MeOH (1:1:1 or 1:1:2) (see text) in toluene, 90 °C, 48 h. (ii): + *cis*-[$PtCl_2(dmso)_2$] + NaOAc−MeOH (1:1:2) in toluene, 90 °C, 72 h.

The reactions were carried out from imine **1b**, *cis*-[$PtCl_2(SOMe_2)_2$], and NaAcO under the same experimental conditions described above, in the corresponding aromatic solvent. The activation of the arenes used as solvents took place in all cases, with formation of the corresponding seven-membered metallacycles (Scheme 3). Again, formation of the *exo* derivative **2b** is observed in all cases, and isolation of the desired compounds was possible by means of column chromatography separation.

$^1H-^1H$ COSY and NOESY NMR spectra of all these compounds allow proposing the structures depicted in Scheme 3 for the different isomers. In the case of *meta*-xylene the formation of the two possible isomers (**7b** and **7b′**) was observed. The NMR spectra show, in addition to the main set of signals, resonances due to a minor isomer (ca. 36%). In this case, the major isomer shows a singlet not coupled to platinum at 6.63 ppm, and the minor isomer shows a singlet at 6.40 ppm coupled to platinum ($J(H-Pt) = 51.8$ Hz). DFT calculations performed on the **7b**/**7b′** couple show that the former is 1.4 kcal/mol lower in energy. This difference in energy is larger than in the toluene derivatives, due to the steric hindrance in **7b′** between the methyl group from the xylene and the iminic aromatic ring. In all other cases, only one isomer was observed. This is the expected situation for benzene due to the absence of substituents, leading to compound **5b**.

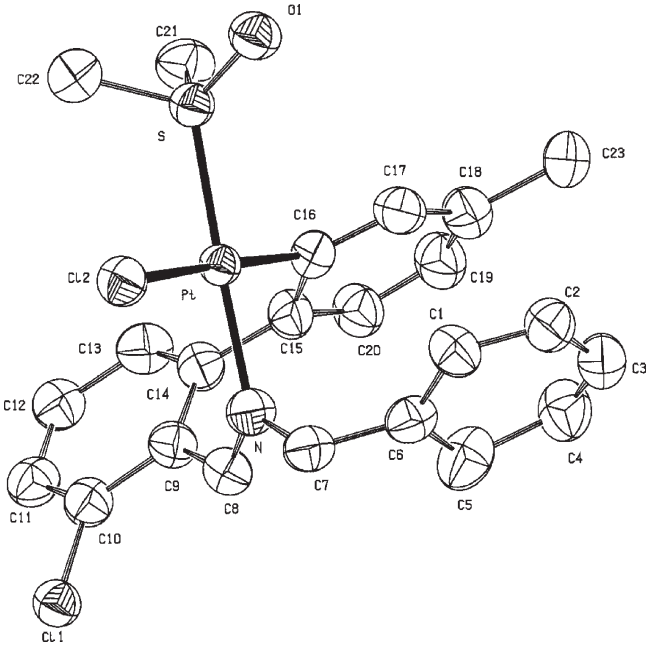


Figure 1. Molecular structure of compound **4a** showing 50% probability ellipsoids (ref 8).

However, for *ortho*-xylene three possible isomers could be expected. The presence of a singlet coupled to platinum assigned to H_9 and showing a cross-peak with Me^2 in the NOESY NMR spectrum indicate that the obtained isomer **6b** is that having the methyl groups *para* to platinum and to the biaryl linkage, respectively. This isomer is the less sterically hindered of the three possible isomers derived from *ortho*-xylene. DFT calculations were carried out on the three possible isomers, **6b**, **6b′** (methyl groups *ortho* to the platinum and *para* to the biaryl linkage, respectively) and **6b″** (methyl groups *para* to the platinum and *ortho* to the biaryl linkage, respectively). The optimized geometries are shown in Figure 2. The most stable isomer is indeed **6b**, while **6b′** is 2.4 kcal/mol higher in energy; this difference is larger than in both **4b**/**4b′** and **7b**/**7b′** couples, in which both isomers are observed. Moreover, **6b″** is 6.2 kcal/mol higher in energy than **6b**. On the other hand, in spite of the steric hindrance due to the presence of methyl groups in adjacent positions to the activated sites, formation of compound **8b** derived from *para*-xylene was also possible.

The ^{195}Pt NMR spectra show one signal at about −3800 ppm for compounds **5b**, **6b**, and **8b**, while two resonances at −3768.7 and −3782.4 ppm are observed for the product arising from *meta*-xylene, in agreement with the presence of two isomers. The resonance at lower field corresponds to the major isomer; it has been reported that the presence of a methyl group in an *ortho* position produces a downfield shift of the ^{195}Pt resonance.[13] In agreement with this, the value observed for **8b** (−3758.7 ppm) appears at lower field than those observed for **5b** and **6b**.

In order to compare the relative stability of the seven-membered metallacycles, we have calculated, at the DFT level, the energy increment corresponding to the following hypothetical one-step processes, which correspond to the reaction in the absence and presence of sodium acetate, respectively:

$$\begin{aligned} &\textit{cis}\text{-}[PtCl_2(SOMe_2)_2] + \text{L-Cl} + \text{H-Ar-H} \\ &\rightarrow [PtCl(\text{Ar-L})(SOMe_2)] + 2HCl + SOMe_2 \end{aligned} \quad (1)$$

$$\begin{aligned} &\textit{cis}\text{-}[PtCl_2(SOMe_2)_2] + \text{L-Cl} + \text{H-Ar-H} \\ &+ 2AcO^- \rightarrow [PtCl(\text{Ar-L})(SOMe_2)] + 2Cl^- \\ &+ SOMe_2 + 2HAcO \end{aligned} \quad (2)$$

where L-Cl, H-Ar-H, and [PtCl(Ar-L)($SOMe_2$)] represent respectively the imine ligand, the arene, and the seven-membered cyclometalated compound **4** arising from formation of a bond between the arene and the ligand fragments.

Results are shown in Table 1. In the cases where the "formal insertion" of the aromatic hydrocarbon (toluene, *ortho*- and *meta*-xylene) could lead to more than one isomer, only the most stable one has been taken into account. The stability of the metallacycles increases in the order *p*-xylyl < *m*-xylyl < *o*-xylyl < tolyl < phenyl, thus suggesting that the steric hindrance between the methyl groups and the aromatic ring that completes the biaryl group is the most important factor that causes the differences in the relative energies. On the other hand, we have included the calculations for the formation of compound **4g**; the comparison with **4b** can be useful to assess the importance of the substituents of the nitrogen atom in the stability of the metallacycles. In fact, the presence of the $-CH_2-$ moiety between the nitrogen atom and the aromatic ring stabilizes the metallacycle about 6 kcal/mol. As there are no appreciable differences in steric hindrance between the nitrogen substituents and the rest of the molecule in **4b** and **4g** (the optimized geometries are shown in Figure 3), these differences are due probably to changes in the relative basicity of the nitrogen atom. Finally, the comparison of the energy increments corresponding to processes 1 and 2 confirms that the addition of sodium acetate is necessary for the reaction to take place.

Seven-membered metallacycles analogous to those obtained for imines **1a, 1b**, **1f**, and **1g** have been previously reported,[14] and their formation arises from platinum(IV) precursors as shown in Scheme 4. In all cases, the C−C coupling takes place

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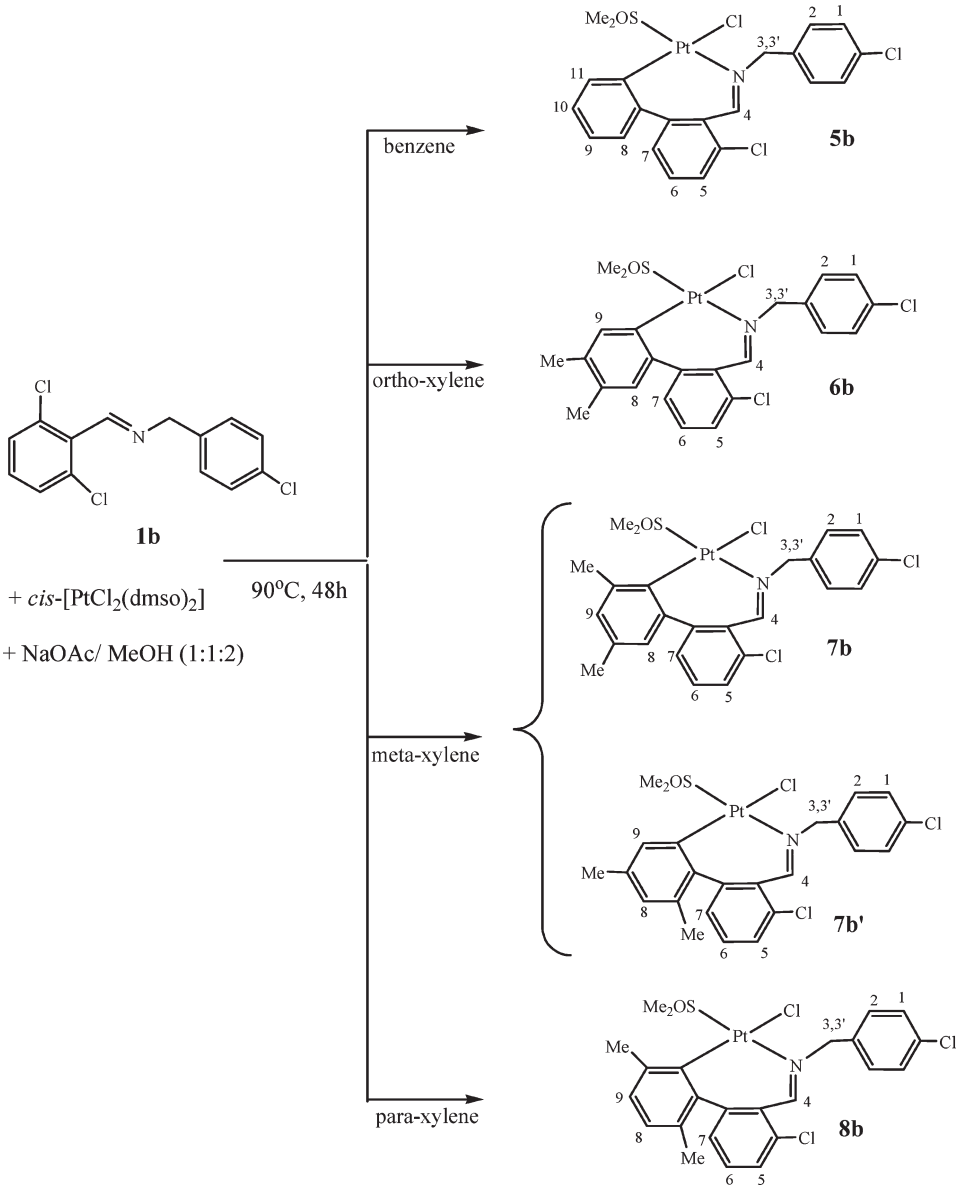
Scheme 3



between a freely rotating aryl group and a rigid aryl ring of a metallacycle. The process here reported is more complex since it requires both intramolecular $C_{aryl}-Cl$ activation of the coordinated imine to produce a [C,N] metallacycle and intermolecular $C_{aryl}-H$ bond activation of the aromatic solvent presumably to form a $Pt-C_{aryl}$ σ-bond with elimination of HCl, as preliminary steps to undergo the "formal insertion" of toluene in the metallacycle with elimination of another HCl molecule.

A competition experiment was carried out for the synthesis of **8b** in a mixture of *para*-xylene and d_{10}-*para*-xylene (molar ratio 1:1). The analysis of the H/D content of the isolated product by proton NMR spectra provides a KIE value, $k_H/k_D = 2.75$. Analogous values have been reported for activation of aromatic C−H bonds both at platinum(IV) (k_H/k_D = 2.3 and 3.0 for toluene and benzene, respectively)[10,15] and at platinum(II) species ($k_H/k_D = 2.8$ for *ortho*-xylene).[16]

In order to gain some insight into the mechanistic aspects of the formation of seven-membered cyclometalated complexes with inserted arene systems, we have performed DFT calculations on several possible intermediate systems. With the aim of facilitating the interpretation of the results and also of removing the difficulty of dealing with different isomers, we have taken the "formal insertion" of benzene as a model. We have performed the calculations in gas phase and in benzene, and we have calculated the energetics of the different reaction steps both in the presence and in the absence of sodium acetate (see Table S1, Supporting Information). The results of the calculations in benzene and in the presence of sodium acetate are shown in Scheme 5 and will be discussed next.

The first step consists in the dissociation of a $SOMe_2$ ligand and the coordination of the imine to the platinum(II) center, resulting in an energy increment of 3.69 kcal/mol. The resulting coordination compound, **B**, could react in several ways. In the absence of sodium acetate the most favored path is the oxidative addition of a C−Cl bond to give the endocyclic platinum(IV) compound **D**. In the presence of base, the formation of the exocyclic platinum(II) derivative

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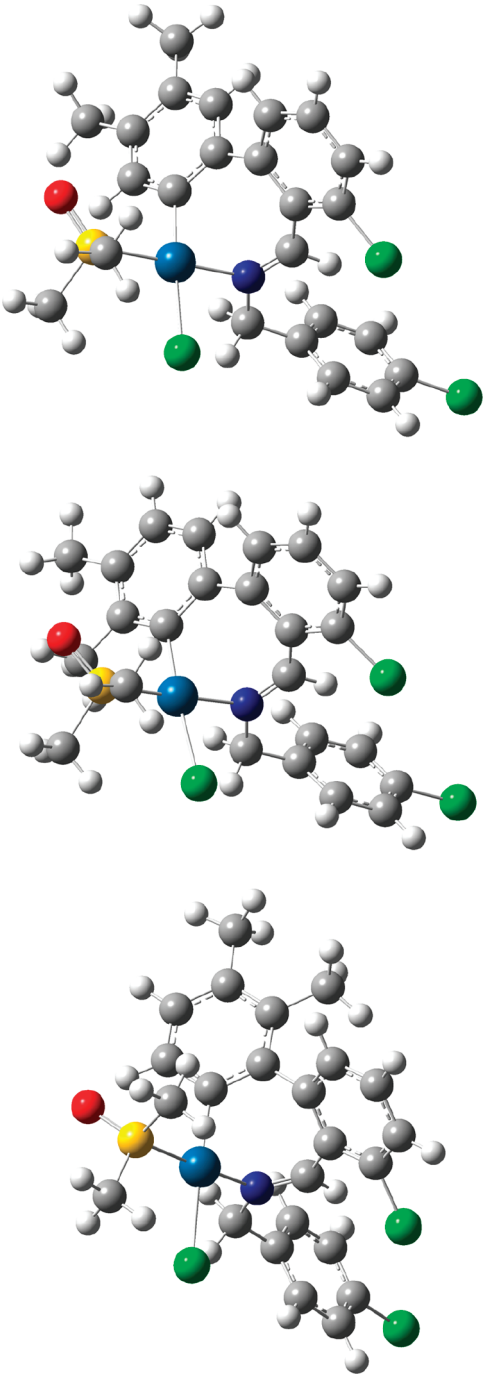

Figure 2. Optimized geometries for **6b** (upper), **6b′** (middle), and **6b″** (lower).

C and the activation of a solvent C−H bond to render the coordination compound **E** are more favored. The oxidative addition of a C−Cl bond on compound **E** results in the formation of the endocyclic cycloplatinated compound **F**; this complex can also be formed from **D** via an activation of an arene C−H bond followed by the loss of a chloride ligand. Both reactions are exergonic in the presence of sodium acetate.

The most energetically favored path for the formation of the final compound **G** from platinum(IV) compound **F** consists in (1) formation of a C−C bond, through reductive elimination of Pt(IV) to Pt(II), yielding **H**, and (2) activation of the C−H bond of the aromatic ring, leading to the final

Table 1. Energy Increments (in kcal/mol) Corresponding to the Formation of Seven-Membered Metallacycles in the Absence (A) and in the Presence (B) of Sodium Acetate (reactions 1 and 2 described in the text, respectively)

compound	A	B
4b	12.04	−38.68
4g	18.09	−32.64
5b	10.61	−40.11
6b	12.30	−38.42
7b	14.23	−36.49
8b	16.80	−33.92

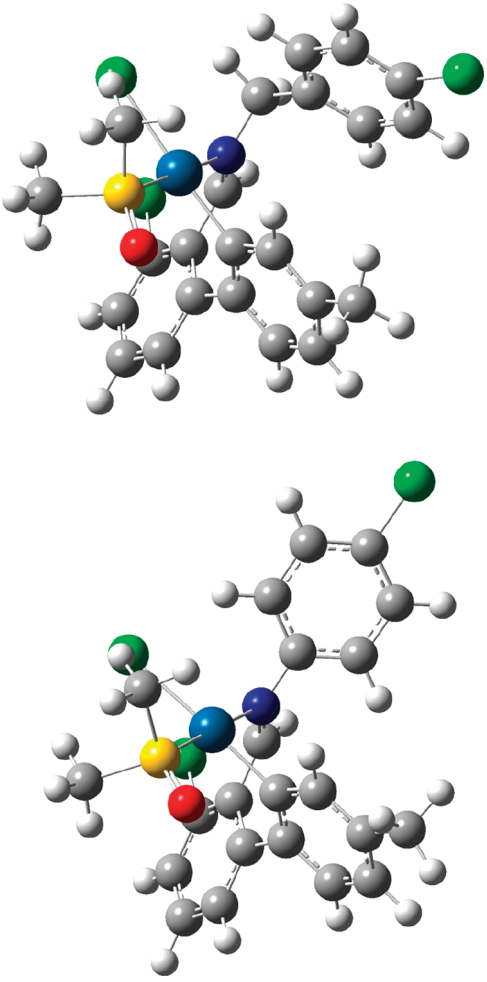

Figure 3. Optimized geometries for **4b** (upper) and **4g** (lower).

product **G**. An analogous process involving reductive elimination from a platinum(IV) compound with formation of a C−C bond followed by intramolecular C−H activation has been postulated for analogous systems involving fluorinated arenes.[17] As a whole, our calculations suggest that the preferred path to form the final compound **G** would feature the intermediates **B**, **E**, **F**, and **H**.

However, although decoordination of the labile ligand $SOMe_2$ to yield **I** is an endergonic process, previous mechanistic studies[18] indicate that prior dissociation of a ligand to form a five-coordinate intermediate is involved in C−C

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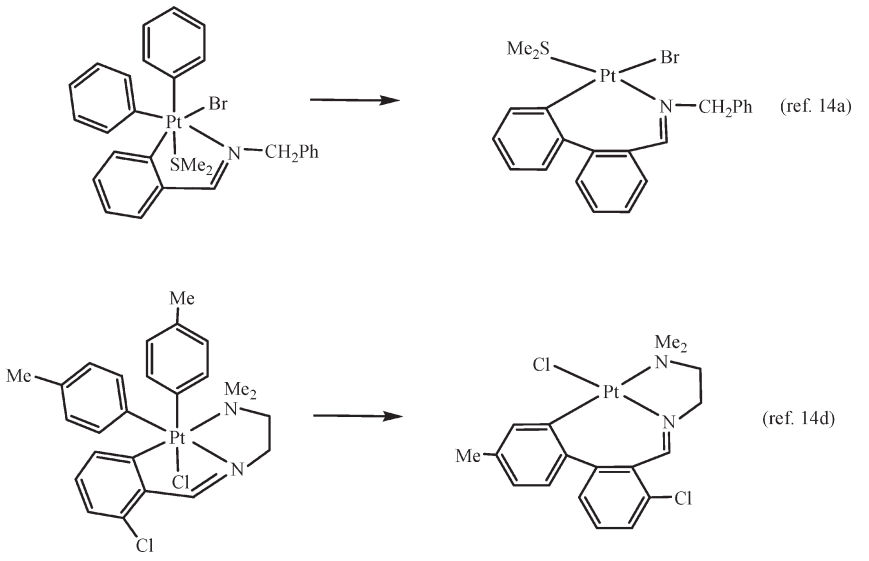
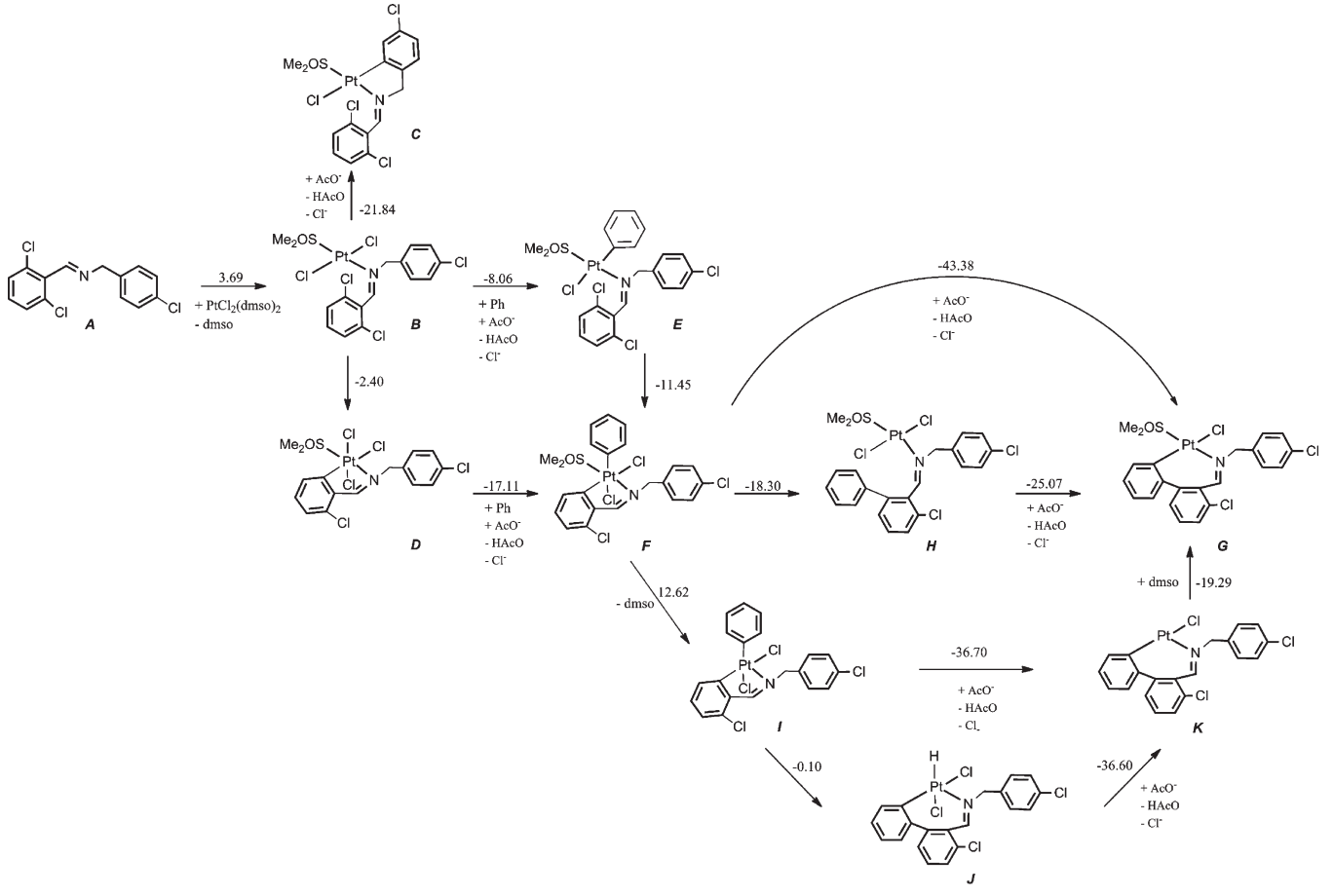
Scheme 4. Formation of Seven-Membered Platinacycles from Platinum(IV) Precursors



Scheme 5. Possible Paths in the Formation of the Benzene Inserted Cyclometalated Complex[a]



[a] Energy values are expressed in kcal/mol.

reductive elimination from six-coordinate platinum(IV) compounds. Such five-coordinate intermediates have also being postulated in the proposed mechanisms for the formation of analogous seven-membered metallacycles[14c] either through a fully concerted transition state (**K**) or via the intermediate formation of a hydride complex (**J**).

In conclusion, the "formal insertion" of benzene, toluene, and *ortho*-, *meta*-, and *para*-xylene, typical "innocent" solvents, into platinum−carbon bonds is produced in the reaction of *cis*-[$PtCl_2(SOMe_2)_2$] with different imines. Therefore, the process can be considered a general procedure for intermolecular C−H activation leading to C−C coupling to produce metalated biaryls.

Our results suggest that both the steric hindrance arising from the methyl substituents of the arene and the basicity of the nitrogen atom determine the stability of the obtained seven-membered metallacycles. On the other hand, the presence of C−Cl bonds in the *ortho* positions of the imine plays a crucial role in the process that takes place through a platinum(IV) intermediate. This result can be related to the Shilov mechanism for platinum(II)-mediated C−H bond activation, which requires oxidation of platinum(II) to platinum(IV), and indeed a recent review[10] pointed out that cyclometalated compounds could be promising candidates for developing intermolecular C−H activation chemistry of platinum. Moreover, the key role of acetate disclosed for these reactions through computational studies is consistent with base-assisted inter- and intramolecular C−H activation processes recently reviewed.[19]

Experimental Section

General Procedures. All reactants and arene solvents (ACS grade) were used as received from commercial sources. Silica gel (70−230 mesh) was used for chromatography columns.

IR spectra were recorded with a Nicolet 5700 spectrophotometer, using KBr pellets.

NMR spectra were performed at the Unitat de RMN d'Alt Camp de la Universitat de Barcelona. ^{1}H, ^{19}F, and ^{195}Pt NMR spectra were recorded by using Bruker DRX-250 (^{195}Pt, 54 MHz), Varian 300 (^{19}F, 282.0 MHz), Mercury-400 (^{1}H, 400 MHz; ^{1}H−^{1}H-NOESY; ^{195}Pt, 86 MHz), and Bruker DMX-500 (^{1}H, 500 MHz; ^{1}H−^{1}H-COSY) spectrometers and referenced to $SiMe_4$ (^{1}H), $CFCl_3$ (^{19}F), and H_2PtCl_6 in D_2O (^{195}Pt). δ values are given in ppm and J values in Hz. Abbreviations used: s = singlet; d = doublet; t = triplet; m = multiplet; b = broad; NMR labels as shown in Schemes 2 and 3.

Mass spectra were obtained by the Servei d'Espectrometria de Masses de la Universitat de Barcelona. FAB mass spectra were obtained with a VG-Quattro (with a 3-nitrobenzyl alcohol matrix), MALDI mass spectra with a Voyager DE-RP (with a dithranol matrix), electrospray ESI(+) mass spectra with a LC/MSD-TOF spectrometer using H_2O−CH_3CN (1:1) to introduce the sample, and CI mass spectra (with NH_3 as reactive gas) with a ThermoFinnigan TRACE DSQ spectrometer.

Microanalyses were performed by the Servei de Recursos Científics i Tècnics de la Universitat Rovira i Virgili de Tarragona with a Carlo Erba 1106 or an Eager 1108 microanalyzer.

Preparation of the Compounds. *cis*-$[PtCl_2(SOMe_2)_2]$[20] and imine **1h**[21] were prepared as reported elsewhere. $[Pt(OAc)_2(SOMe_2)_2]$ was prepared from 200 mg (0.47 mmol) of *cis*-$[PtCl_2(SOMe_2)_2]$ and 158 mg (0.95 mmol) of Ag(OAc), which were allowed to react protected from the light in a mixture of dichloromethane (20 mL) and methanol (20 mL) with vigorous stirring during 24 h. The AgCl was filtered off and the solvent was removed in vacuo to yield a white solid. Yield: 180 mg (81.6%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.41 [s, ^{3}J(Pt−H) = 15.0, 12H, $SOMe_2$], 2.02 [s, 6H, AcO]. FAB-MS, m/z: 409.0 $[M - AcO]^+$, 350.0 $[M - 2AcO]^+$. The synthesis and characterization of compounds **2a**−**e**, **3**, **4a**, and **4b** have been previously reported.[8,9]

Preparation of Imines. Imine **1f** was prepared from 1.001 g (5.7 mmol) of 2,6-dichlorobenzaldehyde and 818 mg (5.7 mmol) of 2,6-difluorobenzylamine, which were allowed to react in refluxing dichloromethane (25 mL) in the presence of Na_2SO_4 for two hours. The mixture was filtered, and the solvent was removed to produce a white solid. Yield: 0.952 g (88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (t, 1H, $^{4}J(H_4-H_3)$ = 1.2, H_4), 7.17−7.39 (m, 4H, $H_{2,5,6}$), 6.92 (t, 2H, $^{3}J(H_1-F) = {}^{3}J(H_1-H_2)$ = 7.5, H_1), 4.97 (d, 2H, $^{4}J(H_6-H_3)$ = 1.5, H_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.4 (t, $^{3}J(F-H_1)$ = 6.5). MS-CI{NH_3} (m/z): 300.0 $[M + H]^+$.

Imine **1g** was prepared using an analogous procedure from 1.511 g (8.67 mmol) of 2,6-dichlorobenzaldehyde and 1.106 g (8.67 mmol) of 4-chloroaniline. Yield: 2.020 g (82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H, H_3), 7.41 (d, 2H, $^{3}J(H_4-H_5)$ = 7.3, H_4), 7.39 (d, 2H, $^{3}J(H_1-H_2)$ = 8.8, H_1), 7.28 (m, 1H, H_5), 7.20 (d, 2H, $^{3}J(H_1-H_2)$ = 8.9, H_2). MS-CI{NH_3} (m/z): 284.2 $[M + H]^+$.

Preparation of Platinum Compounds. [PtCl$_2${(2,6-Cl$_2$C$_6$H$_3$)-CHNCH$_2$CH$_2$NMe$_2$] (1h). This was obtained from 0.208 g (0.50 mmol) of *cis*-$[PtCl_2(SOMe_2)_2]$, 0.120 g (0.50 mmol) of imine **1h**, and 82 mg (1 mmol) of sodium acetate (dissolved in 1 mL of methanol), which were allowed to react in refluxing toluene (30 mL) for 72 h. A white solid was filtered. Yield: 221 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (d, 1H, ^{3}J(H−Pt) = 54.3, ^{4}J(H−H) = 1.9, H_1), 7.42 (m, 3H, H_5, H_6), 3.62 (td, 2H, ^{3}J(H−H) = 5.9, ^{4}J(H−H) = 1.7, H_2), 3.12 (t, 6H, ^{3}J(H−Pt) = 29.4, H_4), 2.69 (t, 2H, ^{3}J(H−H) = 6.1, H^3). ESI-MS (m/z): 528.2 $[M + H_2O]^+$. Anal. Found (calcd for $C_{11}H_{14}Cl_4N_2Pt$): C: 25.4 (25.85); H: 2.8 (2.76); N: 5.0 (5.48).

[PtCl{(CD$_3$C$_6$D$_3$)(2-ClC$_6$H$_3$)CHNCH$_2$(4-ClC$_6$H$_4$)}{SOMe$_2$}] (d_6-4b). This was obtained from 0.150 g (0.32 mmol) of $[Pt(OAc)_2(SOMe_2)_2]$ and 0.095 g (0.32 mmol) of imine **1b**, which were allowed to react in deuterated toluene (5 mL) at 90 °C for 48 h under N_2. The mixture was filtered, the solvent was removed under vacuum, and the residue was eluted with silica column chromatography using ethyl acetate−hexane (100:80) as eluent; d_6-**4b** was obtained from the last fraction. Yield: 42 mg (30%). ^{1}H NMR (250 MHz, $CDCl_3$): major isomer δ 8.59 (s, ^{3}J(Pt−H) = 116.0, 1H, H_4), 7.46−7.34 (m, 3H), {7.24 (d, ^{3}J(H−H) = 8.0, 2H), 7.12 (d, ^{3}J(H−H) = 8.0, 2H), H_1, H_2}, 5.48 (dd, ^{2}J(H−H) = 13.0, ^{4}J(H−H) = 1.6, 1H, H_3), 4.90 (d, ^{2}J(H−H) = 13.0, 1H, $H_{3'}$), 3.29 (s, ^{3}J(Pt−H) = 21.6, 3H, SOMe), 2.82 (s, ^{3}J(Pt−H) = 30.0, 3H, SOMe); minor isomer δ 8.52 (s, ^{3}J(Pt−H) = 104.0, 1H, H_4), {7.24 (d, ^{3}J(H−H) = 8.0, 2H), 7.13 (d, ^{3}J(H−H) = 8.0, 2H), H_1, H_2}, 5.40 (dd, ^{2}J(H−H) = 13.6, ^{4}J(H−H) = 1.7, 1H, H_3), 5.03 (d, ^{2}J(H−H) = 14.2, 1H, $H_{3'}$), 3.30 (s, 3H, SOMe), 2.85 (s, ^{3}J(Pt−H) = 30.0, 3H, SOMe). MALDI-MS, m/z: 632.0 $[M - Cl]^+$, 554.0 $[M - Cl - SOMe_2]^+$, 359.0 $[M - Cl - SOMe_2 - Pt]^+$.

[PtCl{(MeC$_6$H$_3$)(2-ClC$_6$H$_3$)CHNCH$_2$(2,6-F$_2$C$_6$H$_3$)}SOMe$_2$] (4f). This was obtained from 0.202 g (0.48 mmol) of *cis*-$[PtCl_2(SOMe_2)_2]$, 0.142 g (0.47 mmol) of imine **1f**, and 76 mg (0.93 mmol) of sodium acetate (dissolved in 2 mL of methanol), which were allowed to react in toluene at 90 °C (25 mL) for 48 h. The mixture was filtered, the solvent was removed under vacuum, and the residue was extracted with dichloromethane. Upon removal of the solvent under vacuum, the oily residue was crystallized in acetone at low temperature. Yield: 45 mg (14%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (s, 1H, ^{3}J(H−Pt) = 109.3, H_4), 7.46 (t, 1H, ^{3}J(H−H) = 7.8, H_6), 7.41 (dd, 1H, ^{3}J(H−H) = 8.0, ^{4}J(H−H) = 1, H_5), 7.35 (dd, 1H, ^{3}J(H−H) = 7.5, ^{4}J(H−H) = 1.2, H_7), 7.30 (t, 1H, ^{3}J(H−H) = 7.4, H_1), 6.82 (d, 1H, ^{3}J(H−H) = 7.7, H_8), 6.78 (t, 2H, ^{3}J(H−H) = 8.1, H_2), 6.71 (d, 1H, ^{3}J(H−H) = 7.7, H_9), 6.47 (s, 1H, ^{3}J(H−Pt) = 51.8, H_{10}), 5.76 (dd, 1H, $^{2}J(H_3-H_{3'})$ = 12.8, $^{4}J(H_3-H_4)$ = 1.5, H_3), 4.86 (d, 1H, $^{2}J(H_3-H_{3'})$ = 12.8, $H_{3'}$), 3.35 (s 3H, SOMe), 2.90 (s, 3H, SOMe), 2.05 (s, 3H, Me). ^{19}F NMR (282.0 MHz, $CDCl_3$): δ −113.69 (t, J = 13.1) . ESI-MS (m/z): 627.1 $[M - Cl]^+$. Anal. Found (calcd for $C_{23}H_{21}Cl_2F_2NOPtS$): C: 41.5 (41.64); H: 3.0 (3.19); N: 2.0 (2.11); S: 4.6 (4.83).

[PtCl{(MeC$_6$H$_3$)(2-ClC$_6$H$_3$)CHN(4-ClC$_6$H$_4$)}SOMe$_2$] (4g). This was obtained under analogous conditions from 0.201 g (0.48 mmol) of *cis*-$[PtCl_2(SOMe_2)_2]$, 0.134 g (0.47 mmol) of imine **1g**, and 76 mg (0.93 mmol) of sodium acetate. Yield: 41 mg (14%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 (s, 1H, ^{3}J(H−Pt) = 106.7, H_4), 7.60−7.30 (m, 6H, H_{Ar}), 7.01 (d, 2H, ^{3}J(H−H) = 7.7, H_1),

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6.92 (d, 2H, ^3J(H−H) = 7.7, H_2), 3.33 (s 3H, ^3J(H−Pt) = 23.4, SOMe), 2.89 (s, 3H, ^3J(H−Pt) = 32.9, SOMe), 2.36 (s, 3H, Me). ^{195}Pt NMR (86 MHz, $CDCl_3$): δ −3802.4 (s). ESI-MS (*m*/*z*): 611.04 $[M - Cl]^+$. Anal. Found (calcd for $C_{22}H_{20}Cl_3NOPtS$): C: 41.1 (40.78); H: 3.2 (3.11); N: 2.2 (2.16); S: 4.6 (4.95).

[PtCl{(C_6H_4)(2-ClC_6H_3)CHNCH$_2$(4′-ClC_6H_4)}SOMe$_2$] (5b). This was obtained from 0.150 g (0.36 mmol) of *cis*-[$PtCl_2$(SOMe$_2$)$_2$], 0.106 g (0.36 mmol) of imine **1b**, and 58 mg (0.71 mmol) of sodium acetate (dissolved in 1 mL of methanol), which were allowed to react in refluxing benzene (30 mL) for 48 h. The mixture was filtered, the solvent was removed under vacuum, and the residue was eluted in a chromatography silica column using $CHCl_3$ as eluent. From the latest fraction collected **5b** was obtained as a brownish solid. Yield: 57 mg (25%).

Compounds **6b**, **7b**/**7b′**, and **8b** were obtained under analogous conditions from 141, 167, and 188 mg of *cis*-[Pt(Cl_2-(SOMe$_2$)$_2$], in *ortho*-, *meta*-, and *para*-xylene, respectively, and using molar ratios [Pt]:[imine]:[NaAcO] = 1:1:2 and a reaction temperature of 90 °C. For compounds **1d**/**1d′** and **1e**, the middle fractions contained a mixture of the expected products and the *exo*-derivative; a second chromatography column using $CHCl_3$−MeOH (100:2) as eluent allowed the separation of these products. Compounds **6b**, **7b**/**7b′**, and **8b** were obtained as off-white solids with 25%, 22%, and 28% yields, respectively.

[PtCl{(C_6H_4)(2-ClC_6H_3)CHNCH$_2$(4′-ClC_6H_4)}SOMe$_2$] (5b). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H, ^3J(H−Pt) = 111.0, H_4), 7.49 (t, 1H, ^3J(H−H) = 7.8, H_6), 7.43 (dd, 1H, ^3J(H−H) = 8.0, J(H−H) = 1.4, H_5), 7.37 (dd, 1H, ^3J(H−H) = 8.9, J(H−H) = 1.3, H_7), 7.23 (d, 2H, ^3J(H−H) = 8.5, H_1), 7.12 (d, 2H, ^3J(H−H) = 8.4, H_2), 7.00−6.85 (m, 4H, H_8−H_{11}), 5.43 (dd, 1H, $^2J(H_3-H_{3'})$ = 13.5, $^4J(H_3-H_4)$ = 1.9, H_3), 4.93 (d, 1H, $^2J(H_3-H_{3'})$ = 13.6, $H_{3'}$), 3.31 (s 3H, ^3J(H−Pt) = 19.4, SOMe), 2.84 (s, 3H, ^3J(H−Pt) = 27.7, SOMe). ^{195}Pt NMR (54 MHz, $CDCl_3$): δ −3796.2 (s). IR (cm^{-1}): ν(C═N) = 1635, ν(S═O) = 1127. MALDI-MS (*m*/*z*): 669.8 $[M + Na]^+$, 611.9 $[M - Cl]^+$, 595.9 $[M + Na - SOMe_2]^+$, 337.9 $[M - Cl - SOMe_2 - Pt]^+$. Anal. Found (calcd for $C_{22}H_{20}Cl_3NOPtS$): C: 40.6 (40.78); H: 3.0 (3.11); N: 1.9 (2.16); S: 4.5 (4.95).

[PtCl{(*ortho*-$Me_2C_6H_2$)(2-ClC_6H_3)CHNCH$_2$(4′-ClC_6H_4)}SOMe$_2$] (6b). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H, ^3J(H−Pt) = 114.2, $^4J(H_3-H_4)$ = 1.5, H_4), 7.33−7.50 (m, 3H, H_5, H_6, H_7), 7.22 (d, 2H, ^3J(H−H) = 8.5, H_1), 7.13 (d, 2H, ^3J(H−H) = 8.4, H_2), 6.74 (s, 1H, H_8), 6.52 (s 1H, ^3J(H−Pt) = 50.1, H_9), 5.45 (dd, 1H, $^2J(H_3-H_{3'})$ = 13.2, $^4J(H_3-H_4)$ = 1.9, H_3), 4.94 (d, 1H, $^2J(H_3-H_{3'})$ = 13.3, $H_{3'}$), 3.29 (s, 3H, ^3J(H−Pt) = 19.8, SOMe), 2.83 (s, 3H, ^3J(H−Pt) = 32.6, SOMe), 2.14 (s, 3H, Me^1), 2.10 (s, 3H, Me^2). ^{195}Pt NMR (54 MHz, $CDCl_3$): δ −3813.3 (s). IR (cm^{-1}): ν(C═N) = 1629, ν(S═O) = 1014. MALDI-MS (*m*/*z*): 639.8 $[M - Cl]^+$, 561.9 $[M - Cl - SOMe_2]^+$, 365.9 $[M - Cl - SOMe_2 - Pt]^+$.

[PtCl{(*meta*-$Me_2C_6H_2$)(2-ClC_6H_3)CHNCH$_2$(4′-ClC_6H_4)}SOMe$_2$] (7b/7b′). ^{1}H NMR (400 MHz, $CDCl_3$): major isomer, δ 8.50 (s, 1H, ^3J(H−Pt) = 110.1, H_4), 7.35−7.53 (m, 3H, H_5, H_6, H_7), 7.23 (d, 2H, ^3J(H−H) = 8.4, H_1), 6.97 (d, 2H, ^3J(H−H) = 8.4, H_2), 6.70 (s, 1H, H_9), 6.63 (s, 1H, H_8), 5.31 (dd, 1H, $^2J(H_3-H_{3'})$ = 14.3, $^4J(H_3-H_4)$ = 2.0, H_3), 5.09 (d, 1H, $^2J(H_3-H_{3'})$ = 14.3, $H_{3'}$), 3.31 (br s, 3H, SOMe), 2.87 (br s, 3H, SOMe), 2.24 (s, 3H, Me_1), 2.10 (s, 3H, Me_2). ^{195}Pt NMR (54 MHz, $CDCl_3$): δ −3768.7 (s); minor isomer, δ 8.57 (s, 1H, ^3J(H−Pt) = 108.2, H_4), 7.35−7.53 (m, 3H, H_5, H_6, H_7), 7.2 (m, H_1 overlapped with free *meta*-xylene), 7.07 (d, 2H, ^3J(H−H) = 8.4, H_2), 6.75 (s, 1H, H_8), 6.40 (s, 1H, ^3J(H−Pt) = 51.8, H_9), 5.40 (dd, 1H, $^2J(H_3-H_{3'})$ = 13.2, $^4J(H_3-H_4)$ = 1.9, H_3), 4.89 (d, 1H, $^2J(H_3-H_{3'})$ = 13.2, $H_{3'}$), 3.27 (s, 3H, SOMe), 2.85 (s, 3H, SOMe), 2.12 (s, 3H, Me^1), 1.98 (s, 3H, Me^2). ^{195}Pt NMR (54 MHz, $CDCl_3$): δ −3782.4 (s). IR (cm^{-1}): ν(C═N) = 1645, ν(S═O) = 1014. MALDI-MS (*m*/*z*): 639.8 $[M - Cl]^+$, 561.9 $[M - Cl - SOMe_2]^+$, 365.9 $[M - Cl - SOMe_2 - Pt]^+$. Anal. Found (calcd for $C_{24}H_{24}Cl_3NOPtS$): C: 42.5 (42.64); H: 3.8 (3.58); N: 1.9 (2.07); S: 4.4 (4.74).

[PtCl{(*para*-$Me_2C_6H_2$)(2-ClC_6H_3)CHNCH$_2$(4′-ClC_6H_4)}SOMe$_2$] (8b). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H, ^3J(H−Pt) = 104.7, H_4), 7.45 (t, 1H, ^3J(H−H) = 7.8, H_6), 7.33 (dd, 1H, ^3J(H−H) = 7.5, ^4J(H−H) = 1.2, H_5), 7.40 (dd, 1H, ^3J(H−H) = 8.1, ^4J(H−H) = 1.3, H_7), 7.21 (d, 2H, ^3J(H−H) = 8.5, H_1), 6.86 (d, 2H, ^3J(H−H) = 8.4, H_2), 6.81 (d, 1H, ^3J(H−H) = 7.7, H_8), 6.74 (d, 1H, ^3J(H−H) = 7.6, H_9), 5.22 (dd, 1H, $^2J(H_3-H_{3'})$ = 14.3, $^4J(H_3-H_4)$ = 2.0, H_3), 5.03 (d, 1H, $^2J(H_3-H_{3'})$ = 14.3, $H_{3'}$), 3.31 (s 3H, ^3J(H−Pt) = 25.6, SOMe), 2.88 (s, 3H, ^3J(H−Pt) = 25.8, SOMe), 2.08 (s, 3H, Me^1), 2.01 (s, 3H, Me^2). ^{195}Pt NMR (54 MHz, $CDCl_3$): δ −3758.7 (s). IR (cm^{-1}): ν(C═N) = 1639, ν(S═O) = 1118. MALDI-MS (*m*/*z*): 639.8 $[M - Cl]^+$, 561.9 $[M - Cl - SOMe_2]^+$, 365.9 $[M - Cl - SOMe_2 - Pt]^+$. Anal. Found (calcd for $C_{24}H_{24}Cl_3NOPtS$): C: 42.6 (42.64); H: 3.9 (3.58); N: 1.9 (2.07); S: 4.3 (4.74).

Isotope Effects. The synthesis was carried out in a similar way to that above but using equimolar amounts of *para*-xylene and d_{10}-*para*-xylene. The relative reactivities were determined by isolation of the products followed by analysis using ^{1}H NMR and MALDI mass spectrometry. The integrals corresponding to H_8, H_9, Me^1, and Me^2 were compared to those corresponding to H_2, H_3, and $H_{3'}$, and the isotope ratio of **8b** to d_8-**8b** was determined to be 2.75. Peaks corresponding to **8b** (640.1 $[M - Cl]^+$; 562.0 $[M - Cl - SOMe_2]^+$) and d_8-**8b** (647.9 $[M - Cl]^+$; 569.2 $[M - Cl - SOMe_2]^+$) were observed in the MALDI mass spectra.

Theoretical Calculations. All calculations were carried out with the Gaussian 03[22] package of programs at the B3LYP computational level.[23] The basis set was chosen as follows: For Pt, then the LANL2DZ basis, where an effective core potential was used to replace the 36 innermost electrons,[24] was used. For carbon, hydrogen, chlorine, sulfur, and nitrogen the 6-31G(d,p) basis including polarization functions[25] was used. Geometries have been optimized under vacuum, without including any symmetry constraints. Solvent effects have been included using the CPCM (polarizable conductor calculation) method on the previously optimized species.[26]

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Supporting Information Available: Table S1: Energy (in au) corresponding to all the species shown in Scheme 5, in the presence and absence of solvent. Table S2: Energy increments (in kcal/mol) corresponding to the reactions shown in Scheme 5, in the presence and absence of sodium acetate. Table S3: Optimized atomic coordinates and energies (in the gas phase) for all the species calculated. This material is available free of charge via the Internet at http://pubs.acs.org.

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