Synthesis and reactivity of model intermediates proposed for the Pd-catalyzed remote C–H functionalization of N-(2-haloaryl)-acrylamides.

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Supporting Information Placeholder

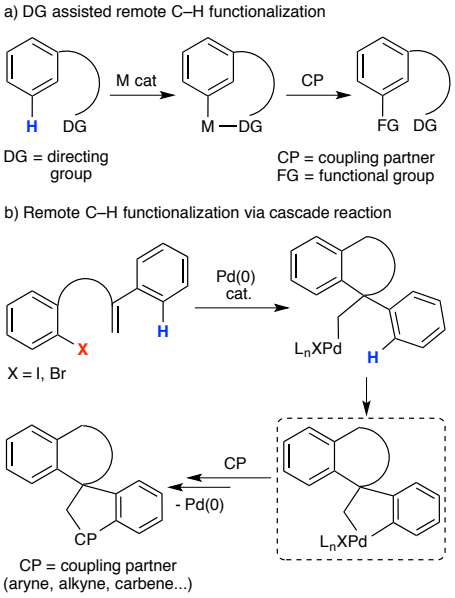
ABSTRACT: We have studied the possible reaction pathways operating in the Pd-catalyzed remote C–H functionalization of *N*-(2-haloaryl)-acrylamides from an organometallic approach. We have isolated and characterized several reaction intermediates, such as σ-alkyl-Pd complexes and spiro *C,C*-palladacycles, and evaluated the role of the base and the auxiliary ligands coordinated to Pd in the remote C–H activation process. In addition, the reactivity of these intermediates toward different unsaturated species like benzyne, alkynes or isocyanides has been studied in order to gain further insight on the reaction mechanism leading to functionalized spiro-oxoindoles.

INTRODUCTION

The functionalization of unreactive remote C–H bonds has become an emerging research topic since this approach opens up new routes and molecular disconnections in organic synthesis.[1,2] These transformations have generally been performed through the installation of suitable directing groups in the core substrate, which guide regioselectively a transition metal toward the desired C–H position, forming a C–metal bond, which can be further functionalized. For instance several synthetic methods involving the use of palladium have been recently developed by introducing coordinating groups, such as 8-aminoquinoline, substituted pyridines or tethered cyanides into the molecular structure of the starting material.[2,3] These protocols allow the functionalization (*i.e.* arylation, alkenylation, acetoxylation, etc.) of C–H positions previously thought inaccessible, such as *meta*-[2b,g] and *para*-[2d] positions in aromatic rings or δ-[2a] and γ-[2e,f] positions in aliphatic chains.

Palladium-catalyzed cascade reactions represent a complementary approach for the functionalization of remote C–H moieties (Scheme 1).[4,5] In these processes, an organopalladium intermediate is able to add regioselectively to a tethered unsaturated moiety, such as an alkene or alkyne, leading to a new organometallic species in which the palladium atom becomes closer to a formerly remote C–H moiety, therefore enabling its activation by the metal and its subsequent functionalization. Those cascade reactions involving the carbopalladation of alkenes are mainly carried out in conveniently designed substrates to avoid *β*-hydrogen elimination.

Scheme 1. Directing-group-assisted and cascade-type remote C–H functionalizations.

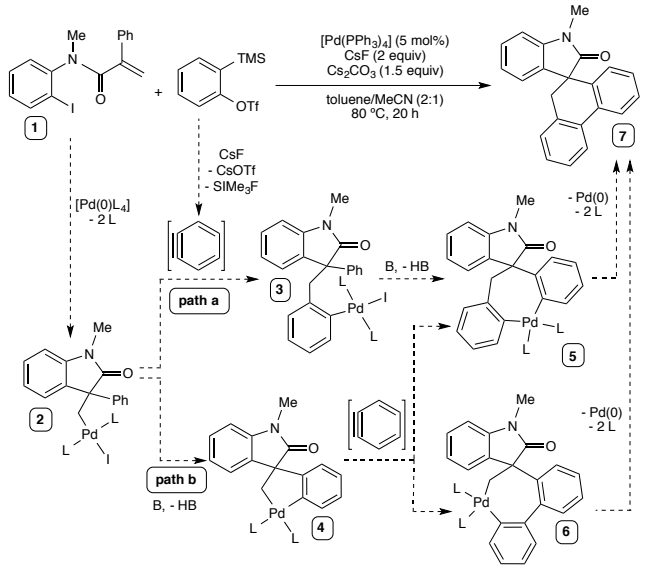


Our research groups[6–8] and others[9] have recently developed new methodologies based on this last approach, such as the synthesis of complex spirocyclic heterocycles in a straightforward manner through the coupling of simple alkenylated building blocks and arynes, alkynes or α-diazocarbonyl compounds. Furthermore, a remote alkylation employing alkyl halides in this type of cascade reactions was reported by one of our research groups.[10]

These strategies have been successfully applied to the synthesis of functionalized spiro-oxoindoles, a molecular scaffold that has attracted great interest due to its presence in natural products and pharmaceuticals.[11] We have now studied in detail the synthesis and reactivity of some of the key intermediates proposed in this new type of remote C–H functionalization in order to gain further insight into the reaction pathway.

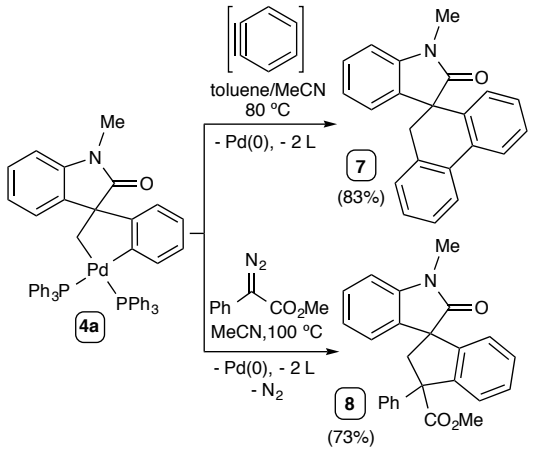
Taking the remote arylation of the *N*-(2-iodophenyl)-acrylamide **1** with benzyne as a representative example of the transformations based on the carbopalladation of tethered alkenes (Scheme 2),[6,7a] two possible reaction pathways can be envisioned for the overall remote C–H functionalization (paths **a** and **b**, depicted in the Scheme 2). Both pathways share some common intermediates. For instance, the oxidative addition of a haloarene to a Pd(0) complex (either pre-formed or generated *in situ* from $Pd(OAc)_2$ and PPh_3) would render an aryl-Pd(II), which in turn could evolve through the intramolecular carbopalladation of the tethered alkene, generating a σ-alkyl Pd(II) intermediate of type **2**.[12] This species could react with the corresponding coupling partner (benzyne in this case) to give a new intermediate **3**, followed by a C–H activation step and a final C–C coupling process (path a, Scheme 2). Alternatively, the intermediate **2** can give a spiro-palladacycle of type **4**, where the insertion of the unsaturated coupling partner would take place, giving rise to the functionalization of both C–Pd bonds.

Scheme 2. Remote arylation of *N*-(2-iodophenyl)-acrylamide with benzyne and its possible reaction pathways. B represents a generic base.



The synthesis of a type **4** complex was recently reported as part of the mechanistic studies in the remote cascade C–H arylation leading to spiro-biaryl scaffolds (Scheme 2).[7a] It was found that complex **4a** could react with benzyne to give the expected spiro-biaryl **7**, upon decomposition of the corresponding carbopalladated species (Scheme 3). A similar assay carried out soon thereafter replacing benzyne by an α-diazocarbonyl compound as the coupling partner also provided the spirocyclic oxoindole **8** (Scheme 3).[8] Both results support the generation of intermediates of the type **4** in the overall catalytic arylation or alkylation, respectively. Nevertheless, the feasibility of the alternative path **a** (Scheme 2), in which the coupling partner reacts first with the σ-alkyl intermediate **2**, has not yet been assessed from an organometallic approach.

Scheme 3. Reported reactivity of the *C,C*-palladacycle 4a with arynes and α-diazocarbonyl compounds.



RESULTS AND DISCUSSION

First, we focused on the stepwise synthesis of both types of intermediates starting from the *N*-(2-iodophenyl)-acrylamide **1**, a model substrate which we have previously functionalized by means of the Pd-catalyzed remote C–H activation protocols: the σ-alkyl Pd(II) complex of type **2** and the *C,C*-spiropalladacycle of type **4**. The *N*-(2-iodophenyl)-acrylamide **1** was reacted with an equimolar amount of $Pd(dba)_2$ in the presence of 2 equivalents of PPh_3 in CH_2Cl_2 at room temperature under inert atmosphere for 2 h (Scheme 4). A pale grey solid could be isolated upon addition of Et_2O to the reaction mixture, which ^{31}P NMR spectra showed a main signal at 33.1 ppm (attributed to the expected complex **2a**), along with two smaller and much broader signals at 40.2 ppm and -4.5 ppm (Figure 1). The chemical equivalence of the phosphine ligands in **2a** indicated their mutual trans disposition, in agreement with the high transphobia for P/C-donor ligands.[13] A solution of this solid in $CDCl_3$ was monitored by ^1H NMR at rt for 14 h. We found that two new singlets appeared at 37.7 and 29.3 ppm and gained intensity at the expenses of the three former signals (40.2, 33.1 and -4.5 ppm, Figure 1). A plausible explanation for this behaviour could rely on the dissociation of one of the phosphine ligands caused by a high steric hindrance around the metallic center, giving rise to a complex such as **9** (broad signal at 40.2 ppm, Figure 1) and free PPh_3 (broad signal at -4.5 ppm).

The Pd center present in the proposed complex **9** could interact with the nearby aryl group to complete its coordination sphere. A similar σ-alkyl complex where the Pd atom coordinates to the phenyl ring was fully characterized and crystallized by Cámpora et al.[14a] Nevertheless, the species **9** could evolve to give a new intermediate **10** where a more stable *C,O*-palladacycle was generated (signal at 37.7 ppm). Finally, the oxidation of the free phosphine would produce $OPPh_3$ (signal at 29.3 ppm). An additional peak at 12.4 ppm was attributed to $[PdI_2(PPh_3)_2]$, arising from further decomposition processes, and it gained in intensity over the time.

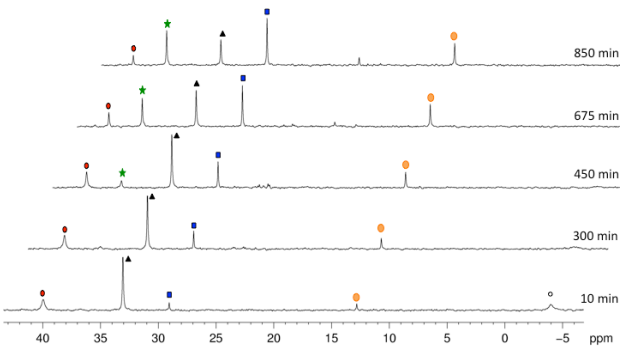
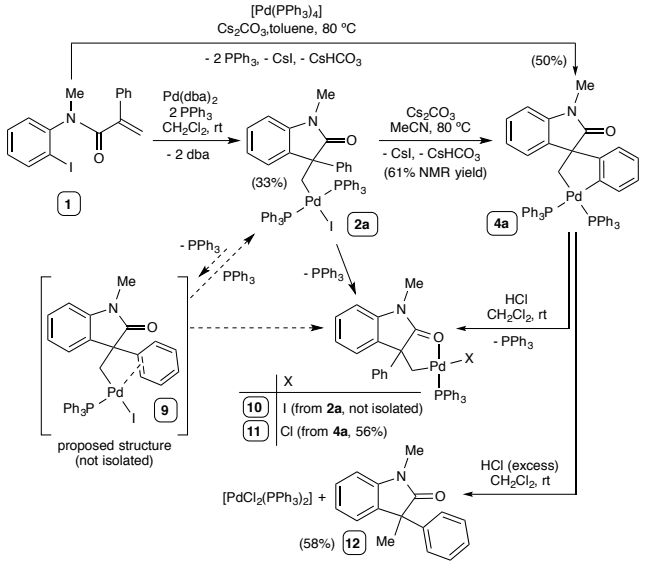


Figure 1. Stacking of the ^{1}H NMR spectra of a $CDCl_3$ solution of the complex **2a** at 25 °C at increasing times. The different species are marked as follows: **9**, red circles (40.2 ppm); **10**, green stars (37.7 ppm); **2a**, black triangles (33.1 ppm); $OPPh_3$, blue squares (29.3 ppm); $[PdI_2(PPh_3)_2]$, orange circles (12.4 ppm); PPh_3, white circle (–4.5 ppm).

According to path **b**, depicted in the Scheme 2 for the catalytic reaction, the complex **2a** should be able to generate the *C,C*-palladated intermediate **4a** under the right conditions. When the complex **2a** was heated in toluene at 80 °C for 4 h, only traces of **4a** could hardly be detected in the ^{31}P NMR spectrum of the crude reaction mixture. Nevertheless, when the same experiment was run in MeCN, we observed the consumption of the starting material and the formation of a mixture of products containing the palladacycle **4a**, which could be easily identified by ^{31}P NMR, since its spectrum shows two characteristic doublets at 25.6 and 24.8 ppm (corresponding to the two distinct phosphine ligands). Likely, the generation of **4a** from **2a** under base-free conditions might be related to the generation of ill-defined side decomposition products that can act as bases to remove the HI formed upon the C–H activation step. Moreover, the complex **4a** was the main product of the crude mixture when an analogous reaction was carried out in MeCN in the presence of Cs_2CO_3 (61%, NMR yield). Therefore, the addition of Cs_2CO_3 was not essential for the C–H activation to proceed in MeCN, but its presence was beneficial for the overall process. The intermediate **4a** could be better prepared in good yield and in a single step by reacting **1** with one equivalent of $[Pd(PPh_3)_4]$ in toluene at 80 °C and in the presence of Cs_2CO_3 (Scheme 4), as reported previously by one of us.[7a]

Scheme 4. Synthesis of the σ-alkyl Pd complex 2a and its evolution under different conditions. Protonolysis of the complex 4a.



In an attempt to isolate an analogous complex to **10**, we carried out the partial protonolysis of the Csp^2–Pd bond[15] (present in intermediate **4a**) by adding carefully a small amount of a saturated solution of HCl in CH_2Cl_2 to a solution of **4a** in CH_2Cl_2 at rt (Scheme 4). Via this method, we could isolate the complex **11**, whose ^{31}P NMR spectrum showed a singlet at 37.8 ppm, very close to that of the complex **10**. The X-ray crystal structure of **11**·CH_2Cl_2 could be successfully determined, confirming the nature of the *C,O*-palladacycle (Figure 2). The palladium atom was in a slightly distorted square-planar environment, with a mean deviation of the Pd(II)-coordination plane of 0.066 Å and a dihedral angle of 6.5° between the planes Cl(1)–Pd(1)–P(1) and O(1)–Pd(1)–C(1). The *C,O*-chelated ligand formed a five-membered metallacycle, with an envelope conformation.

The addition of an excess of HCl to a solution of **4a** provoked the protonolysis of both C–Pd bonds, affording the oxoindole **12** (Scheme 4).

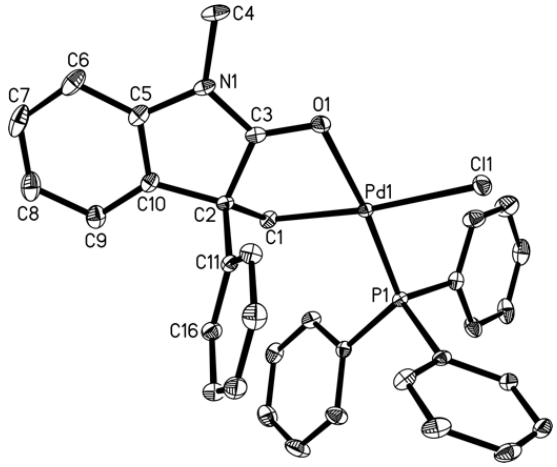


Figure 2. Thermal ellipsoid plot (50% probability) of **11** along with the labelling scheme. Hydrogen atoms have been omitted for clarity.

Next, we attempted the synthesis of intermediates of type **2** easier to handle and study, by switching the ligand from PPh_3 to *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) or 4,4'-di-*t*-butyl-2,2'-bipyridyl (t-bipy). The oxidative addition of the *N*-(2-

iodophenyl)-acrylamide **1** to $Pd(dba)_2$ in the presence of either of these nitrogen ligands afforded the corresponding σ-alkyl Pd(II) complexes **2b** and **2c** in good yields (Scheme 5). These complexes were sufficiently stable to be fully characterized and in the case of **2b** conveniently crystallized to study its crystal structure by X-ray diffraction (Figure 3). The palladium atom was in an almost perfect square-planar environment, with a mean deviation of the Pd(II)-coordination plane of 0.003 Å and a dihedral angle of 0.7° between the planes N(1)–Pd(1)–N(2) and C(1)–Pd(1)–I(1). The N(1)–Pd(1)–N(2) angle is 77.94(7)°, quite smaller than the standard value of 90° for an ideal square planar complex, due to the steric constraints imposed by the bite angle of the bipyridine ligand.

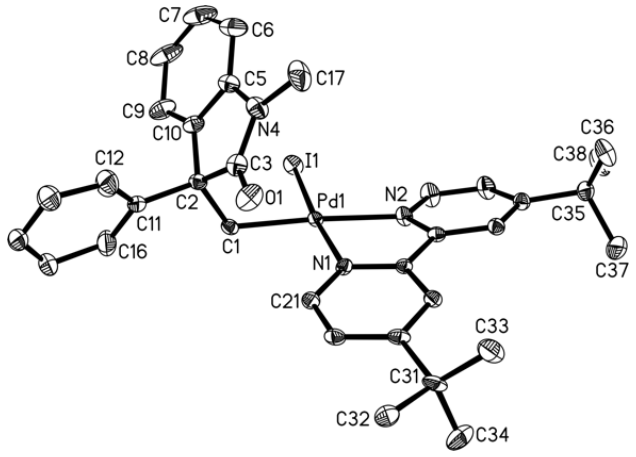
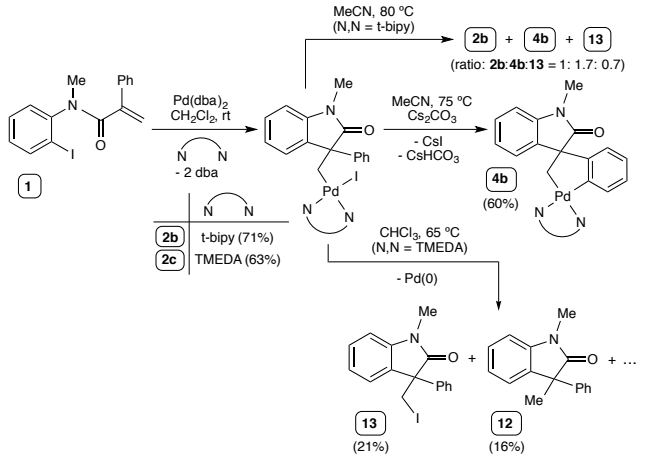


Figure 3. Thermal ellipsoid plot (50% probability) of **2b** along with the labelling scheme. Hydrogen atoms have been omitted for clarity.

Scheme 5. Synthesis of complexes 2b and 2c and their evolution in different conditions.



We can conclude that the first two steps of the catalytic cycle operating in the remote C–H functionalization reactions (Scheme 1) i.e., the oxidative addition of the C–I bond to Pd(0) and the intramolecular carbopalladation of the tethered olefin, took place smoothly at room temperature regardless of the nature of the ligand (PPh_3 or *N,N*-chelating donors).

At this point we explored the thermal evolution of the σ-alkyl Pd(II) complex bearing *N,N*-chelating ligands. When a solution of the complex **2b** in MeCN was heated at 80 °C for 8 h, a mixture of the starting material **2b**, the *C,C*-palladacycle **4b** (arising from the C–H activation) and the organic product **13** (ratio **2b**:**4b**:**13** 1:1.7:0.7) was obtained (Scheme 5). The product **13** arises from a C–I coupling process in the σ-alkyl Pd(II) complex, and represents formally a carboiodination of the initial double bond present in the *N*-(2-iodophenyl)-acrylamide **1**.[5e,16] The palladacycle **4b** was isolated in good yield when we performed the reaction in the presence of Cs_2CO_3.

The crystal structure of complex **4b**·C_3H_6O was solved by X-ray diffraction studies (Figure 4). The palladium atom was in a distorted square-planar environment, with a mean deviation of the Pd(II)-coordination plane of 0.064 Å and a dihedral angle of 6.8° between the planes N(1)–Pd(1)–N(2) and C(1)–Pd(1)–C(11). The palladium atom is simultaneously coordinated to two chelated ligands: a *N,N*- and a *C,C*-moieties. The angles N(1)–Pd(1)–N(2) and C(1)–Pd–C(11) are far from the optimal value of 90° (79.98(7) and 77.20(5)°, respectively) due to the steric constraints imposed by the bite angles of both chelated ligands. The Pd(1)–N bond lengths are not significatively different (Pd(1)–N(1), trans to $C_{sp}2$ = 2.1107(14) Å; Pd(1)–N(2), *trans* to $C_{sp}3$ = 2.1190(14) Å), indicating in this case a similar trans influence of both the $C(sp^2)$ and the $C(sp^3)$-donor atoms. The discrete molecules of **4b**·C_3H_6O are associated through C–H···O hydrogen bonds, giving *zigzag* chains along the *b* axis (details, including symmetry operations, are given in the Supporting Information). The crystal structure of **4b**·C_3H_6O resembles the structural features of that previously reported for **4a**.[7a]

Once again, the addition of Cs_2CO_3 suppressed the generation of the secondary by-products (**12** and **13**, Scheme 5). Noteworthy, the product **13**, arising from the C–I coupling process, was only observed in the decomposition process of complexes **2b,c** (containing *N,N*-chelating ligands), and not in the case of **2a** (containing PPh_3). This observation might be closely related to the fact that the *N,N*-chelating ligands force a *cis* geometry of the iodide and the alkyl moiety around the Pd atom.

In $CHCl_3$ solution at 65 °C, the complex **2c** evolved to give a mixture of the products **12** and **13** (Scheme 5). The oxoindole **12** is the result of an alternative reaction pathway which presumably involves the protonolysis of the Csp^3–Pd bond. Likely, the absence of a base in the reaction mixture allows the protonolysis of the Csp^3–Pd bond to proceed.

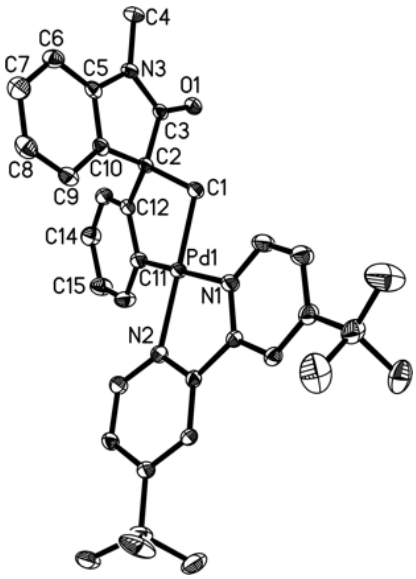
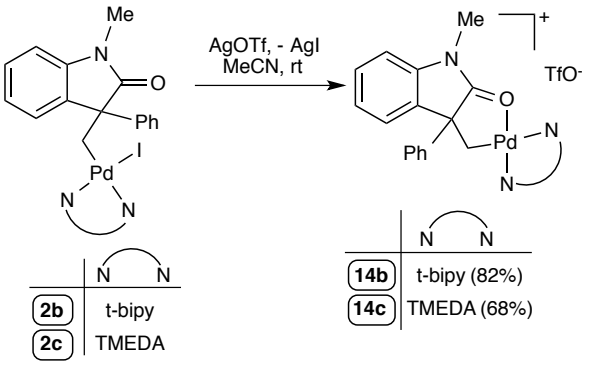


Figure 4. Thermal ellipsoid plot (50% probability) of **4b** along with the labeling scheme. Hydrogen atoms have been omitted for clarity.

The Cs_2CO_3 assists the palladation reaction, and it can operate through different mechanisms: i) removing the iodo ligand from the coordination sphere of palladium, hence avoiding the C–I bond formation, and ii) providing a base to facilitate the abstraction of the proton either intra- or intermolecularly.[17] To further evaluate the role of Cs_2CO_3 in the remote C–H activation process, we synthesized the complexes **14b** and **14c** by reacting the σ-alkyl Pd(II) complexes **2b** and **2c** with AgOTf in MeCN at rt (Scheme 6). We intended to replace the iodine moiety by a far less coordinating ligand, such as the triflate anion. The cationic complexes **14b** and **14c** were obtained. The crystal structure of complex **14c** was determined by X-ray diffraction (Figure 5), and showed the intramolecular chelation of the oxygen atom from the amide moiety to Pd(II). The palladium atom was in a slightly distorted square-planar environment, with a mean deviation of the Pd(II)-coordination plane of 0.041 Å, and a dihedral angle of 7.5º between the planes N(1)–Pd(1)–N(2) and C(1)–Pd(1)–O(1). The palladium atom is simultaneously coordinated to two chelated ligands: the TMEDA (angle N(1)–Pd(1)–N(2) = 85.22(12)º), and the anionic *C,O*-moiety (angle O(1)–Pd(1)–C(1) = 84.48(11)º). The Pd(1)–N(1) bond length (2.167(3) Å) is significatively longer than the Pd(1)–N(2) (2.054(3) Å), reflecting the greater *trans* influence of the C-donor atom. The organic cation is associated with the triflate anion through a C–H···O hydrogen bond (details, including symmetry operations, are given in the Supporting Information). The cationic nature of complexes complexes **14b** and **14c** in solution was confirmed by measuring the values of their molar conductivity in acetone.

Scheme 6. Synthesis of cationic complexes 14b and 14c.



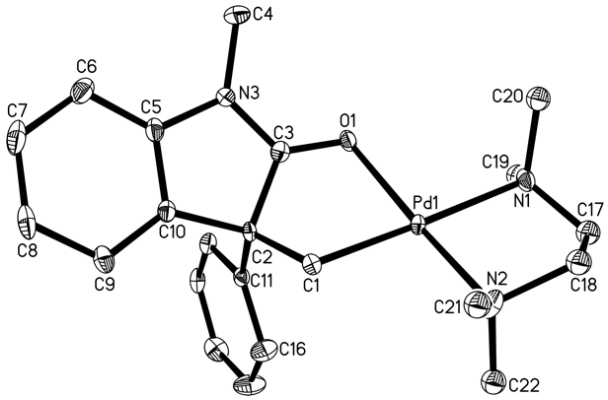
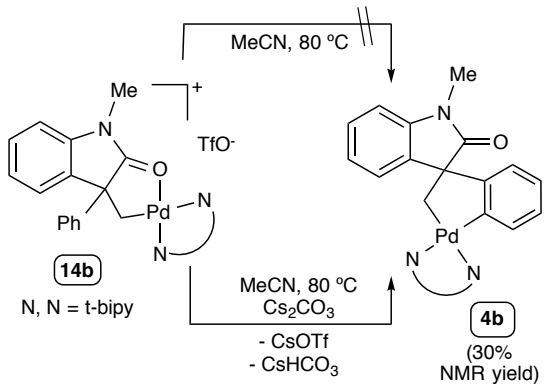


Figure 5. Thermal ellipsoid plot (50% probability) of **14c** along with the labeling scheme. Hydrogen atoms and the triflate anion have been omitted for clarity.

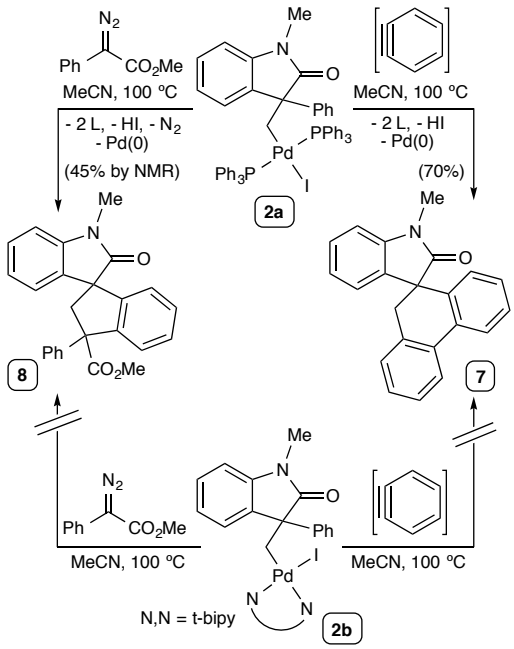
We hypothesized that the exchange of the iodo by a triflate ligand would lead to an enhancement of the electrophilic character of Pd(II), promoting the C–H activation step.[17a,18] Nevertheless, the complexes **14b** and **14c** were very stable in solution, and did not evolve to give the corresponding palladacycles **4b** and **4c**, respectively, when heated at 80 °C in MeCN for 16 h (Scheme 7). This behavior contrasts to that observed for the neutral complexes **2a** and **2b**, which did undergo partially the cyclometalation in MeCN, even in the absence of an external base (Scheme 5). These results might indicate that the C–H activation is facilitated by the generation of a coordination vacancy, upon ligand dissociation from Pd(II), to afford species such as **9** (Scheme 4). This dissociation would take place more easily from a neutral complex; otherwise, for cationic precursors, the formation of a stable *C,O*-chelated intermediate, such as **14b** or **14c**, could take place, precluding the rotation of the alkyl-Pd moiety, the placement of the metal in a conveniently close position to the neighbouring phenyl ring, and therefore the metalation. The neutral precursor could bear either the initial iodide or a carbonate ligand. Furthermore, when the complex **14b** was heated in MeCN at 80 °C in the presence of Cs_2CO_3 (Scheme 7), the formation of the palladacycle **4b** was observed (30%, NMR yield).

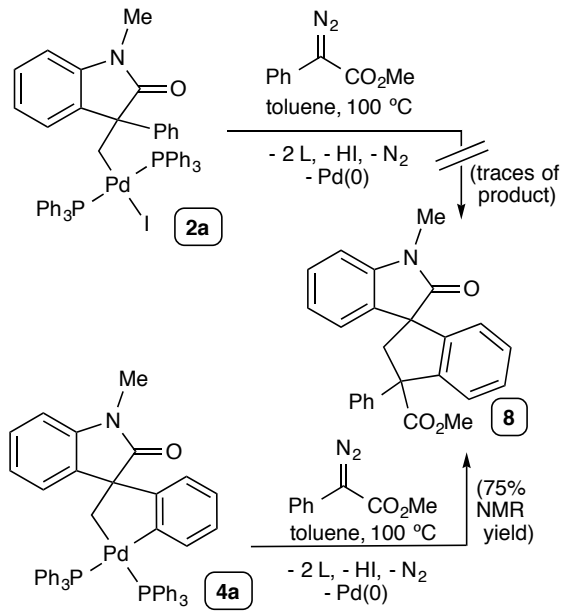
Scheme 7. Formation of 4b from 14b.



Once we had assessed the synthesis of the intermediates of type **2** and their evolution to give **4** with different ligands, we continued our study by exploring their behaviour toward unsaturated species. We carried out the reactions of the σ-alkyl Pd(II) complexes **2a** and **2b** with two different coupling partners: a) *in situ* generated benzyne and b) an α-diazocarbonyl compound (Scheme 8). The intermediate **2a** gave the corresponding organic products **7** and **8** in moderate yields. However, when using **2b** as starting material a complex mixture of products was obtained, where **7** and **8** could not be detected either by ^{1}H NMR or HPLC-MS (Scheme 8). The outcome of these reactions indicates that the nature of the ligands on the Pd coordination sphere plays a key role in the overall transformation: the strongly chelating bipyridine ligand blocks the process while a more labile ligand such as PPh_3 allows the reaction to proceed.

Scheme 8. Reactivity of the complexes 2a and 2b with different coupling partners.





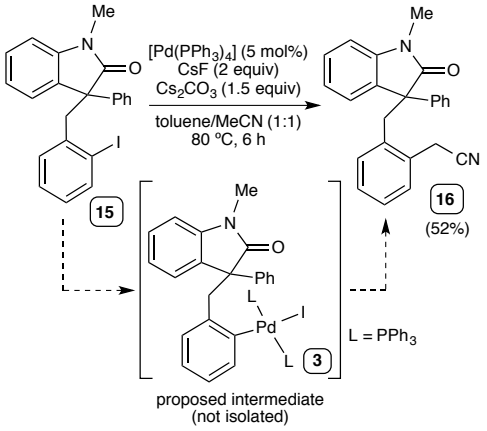
None of the results, at this stage, can be used to discard either of the two possible reaction pathways for the intermediate **2a** (paths **a** and **b**, Scheme 2), since, as discussed above, the remote metalation of **2a** to give **4a** can take place in MeCN. When the reaction of **2a** and the α-diazocarbonyl compound was performed in toluene in the absence of Cs_2CO_3 (conditions that disfavored the formation of **4a**, *vide supra*), a complex mixture of products was observed where only traces of **8** were present (Scheme 9). This result does not exclude completely the possibility of generating **8** from a hypothetical alkyl-Pd(II) intermediate arising from the insertion of the α-diazocarbonyl compound into **2a** (since there is no presence of an external base to assist the subsequent C–H activation). However, we know that: 1) **2a** reacts with the α-diazocarbonyl compound in MeCN, under base-free conditions, to give **8** (Scheme 8), but the same reaction does not happen in toluene; and 2) **4a** reacts with the α-diazocarbonyl compound in toluene in the absence of an external base to afford **8** (75%, NMR yield; Scheme 9). Hence, the overall transformation seems to proceed via the generation of the key *C,C*-spiropalladacycle **4a** from **2a**, and its subsequent reaction with the coupling partner (path b, Scheme 2), rather than the alternative direct reaction from the σ-alkyl Pd(II) **2a** (path a, Scheme 2).

Scheme 9. Reactivity of the complexes 2a and 4a toward the α-diazocarbonyl coupling partner.

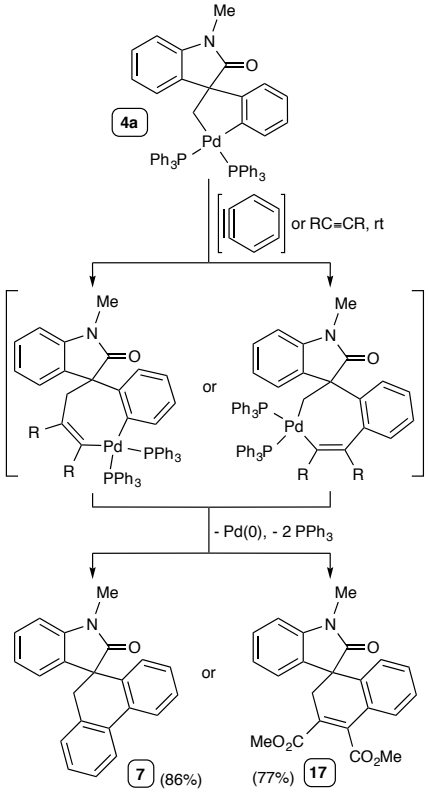
Complementarily to the stoichiometric studies we report in this manuscript, one of our research groups designed a different approach to check the feasibility of the reaction path **a** (Scheme 2).[7a] The oxidative addition of the model substrate **15** to Pd(0) (Scheme 10) would provide a similar intermediate to **3** (path **a**, Scheme 2), arising from the benzyne insertion into the σ-alkyl Pd(II) **2a**. Nevertheless, the submission of the substrate **15** to the Pd(0) catalysis did not provide the expected spiro-biaryl scaffold **7**, but the product **16** arising from the coupling with MeCN. It is noteworthy that the formation of this last product was not observed in the catalytic reaction.

Focusing on the generation of the diverse spirocyclic organic products from the intermediate **4a**, we attempted to determine which of its two distinct Pd–C bonds was functionalized in first instance, to get a detailed picture of the complete reaction from the *N*-(2-iodophenyl)-acrylamide **1** to the final organic product. Our goal was the isolation of any of the organometallic intermediates arising from the insertion of unsaturated coupling partners, such as benzyne, alkynes, carbon monoxide or isocyanides, into either of the two Pd–C bonds present in **4a**. Vicente's group have reported the isolation of several aryl-Pd complexes arising from the insertion of benzyne into the Pd–C bond of six-membered palladacycles.[19] Following a similar method, we set the reaction of **4a** with benzyne generated *in situ* at rt, but, even under these mild conditions the organic product **7** (arising from the C–C coupling) was detected, that is, the plausible organometallic intermediate arising from the insertion of the aryne decomposed rapidly (Scheme 11). A similar behaviour was found when a reactive alkyne such as dimethylacetylene dicarboxylate (DMAD) was used instead of benzyne (Scheme 11). This reaction was monitored by ^{1}H NMR, which confirmed the finding that the concentration of possible insertion species was quite low, and only starting materials or the organic product **17** arising from the decomposition could be detected. Other alkynes such as diphenylacetylene or 3-hexyne proved to be unreactive. Related insertion reactions of alkynes into five-membered Csp^2,Csp^3-palladacycles and nickelacycles have been reported in the literature.[14b-d] Similarly to our case, no seven-membered metalacyclic intermediates arising from the insertion of the alkyne into the Pd–C bond could be isolated from the reaction mixtures.

Scheme 10. Reported catalytic reaction from substrate 15.

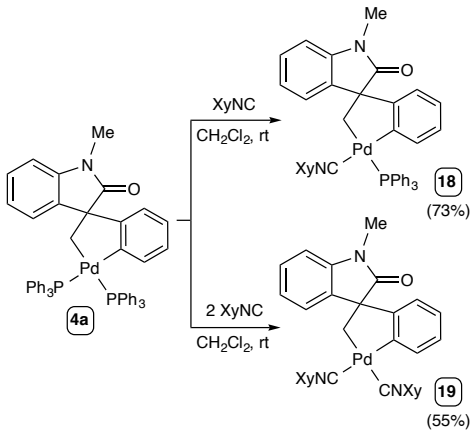


Scheme 11. Attempts to isolate organometallic intermediates arising from the insertion of benzyne and DMAD.



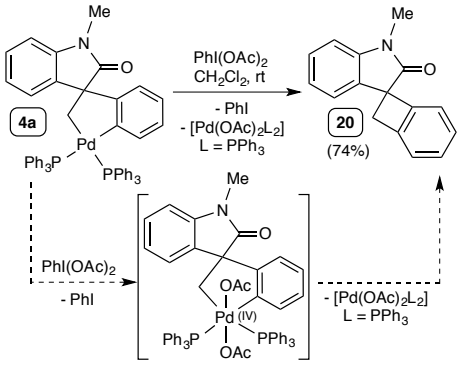
There are numerous examples in the literature regarding the insertion of carbon monoxide or isocyanides into the Pd–C bond of palladated arenes, which render isolable acyl or iminoacyl complexes.[13c,15b,19c,20] Nevertheless, the palladacycle **4a** was quite robust toward CO insertion, since no reaction was observed after 16 h under CO atmosphere (1.5 atm) either at rt or 90 °C. The reaction of **4a** with xylylisocyanide (XyNC) at rt afforded the complexes **18** and **19**, arising from the displacement of one or two of the phosphine ligands from the coordination sphere, depending on the stoichiometry of the reaction (Scheme 12).[21] No iminoacyl derivatives from the insertion of the isocynide were observed. Forcing the reaction conditions with an excess of XyNC (3 equiv) at 100 °C lead to a complex mixture of products. Noteworthy, the products **18** and **19** contain a palladium centre bonded simultaneously to sp, sp^2 and sp^3 hybridized C-donors. For the complex **18** we propose that the XyNC ligand is coordinated trans to the aryl group, similarly to other Pd(II) complexes containing a Csp^2-donor, PPh_3 and an isocyanide.[13d]

Scheme 12. Reactions of complex 4a with XyNC.



In addition to the reactivity of the intermediate **4a** toward unsaturated species, we investigated the behaviour of this complex toward an oxidant such as $PhI(OAc)_2$. The reaction of **4a** with $PhI(OAc)_2$ at rt gave rise to the strained [4,5]-spirocyclic **20** (Scheme 13). Very likely, the oxidant promoted the formation of a Pd(IV) intermediate in the course of the reaction, which evolved through an oxidative C–C coupling process to afford **20**, rather than undergoing a C–O coupling event. The catalytic synthesis of similar [4,5]-spirocyclic scaffolds was reported to occur via a Pd(0)/Pd(II) cycle when a bulky phosphine such as $P(^tBu)_3$ was used as ligand.[9]

Scheme 13. Oxidative C–C coupling promoted by $PhI(OAc)_2$.



CONCLUSION

In conclusion, we have synthesized several of the organometallic intermediates operating in the Pd-catalyzed cascade remote C–H functionalization of *N*-(2-halophenyl)acrylamides. According to the results presented in this study, these type of catalytic reactions proceed successfully when the σ-alkyl Pd(II) complex generated upon the intramolecular carbopalladation is prone to undergo a C–H activation on the formerly remote phenyl moiety of the substrate. The feasibility of the palladation step is affected by the auxiliary ligands present on the coordination sphere of the metal, the solvent of choice and the presence of a base. Labile ligands such as PPh_3, in MeCN as the solvent, and in the presence of Cs_2CO_3 favour the formation of the key *C,C*-spiropalladacycle intermediate,

which in turn reacts with a coupling partner to render the corresponding spirocyclic organic skeletons. When the reaction conditions hamper the C–H metalation (and subsequently the formation of the spiropalladacycle intermediate), the overall remote functionalization is blocked. These results indicate that an alternative reaction pathway in which the σ-alkyl Pd(II) complex reacts with the unsaturated species in first instance is unlikely to happen in the catalytic transformations. Furthermore, the final steps of the catalytic remote arylation cycle (i.e., insertion of the aryne or activated alkyne into the Pd–C bond of the *C,C*-spiropalladacycle intermediate and subsequent C–C bond fomation leading to the spirooxoindole scaffold) are not the rate-limiting steps of the cycle since they take place rapidly at rt.

EXPERIMENTAL SECTION

Infrared spectra were recorded on a Perkin-Elmer spectrum 100 spectrophotometer. High-resolution ESI mass spectra were recorded on an Agilent 6220 Accurate Mass TOF LC/MS spectrometer. Melting points were determined using a Reichert apparatus and are uncorrected. Nuclear Magnetic Resonance (NMR) spectra were recorded on a 300 or 400 MHz Bruker NMR spectrometers in $CDCl_3$ at 298 K (unless stated otherwise). All chemical shift values are reported in parts per million (ppm) with coupling constant (*J*) values reported in Hz. All spectra were referenced to TMS for ^1H NMR and the $CDCl_3$ solvent peak for $^{13}C\{^1H\}$ NMR. Anhydrous MeCN was purchased from commercial sources and used as received. TLC tests were run on TLC Alugram® Sil G plates and visualized under UV light at 254 nm. Chromatography: Separations were carried out on silica gel.

Synthesis of complex 2a. $Pd(dba)_2$ (240 mg, 0.41 mmol) and PPh_3 (220 mg, 0.83 mmol) were added to a solution of *N*-(2-iodophenyl)acrylamide **1** (150 mg, 0.41 mmol) in dry CH_2Cl_2 (30 mL) in a Carius tube under nitrogen atmosphere. The tube was sealed, and the mixture was stirred at room temperature for 2.5 h. The resulting solution was filtered over a Celite pad. The solvent of the filtrate was partially removed from to ca. 4 mL, and Et_2O (20 mL) was added. The resulting suspension was filtered, and the solid was washed with Et_2O (2 x 2 mL) and air-dried to give compound **2a** as a grey solid. Yield: 137 mg, 0.14 mmol, 33%. The complex **2a** is not stable in solution and gives rise to other species such us **9**, **10** and PPh_3, for this reason only the representative ^1H NMR signals are described. ^1H NMR (400.9 MHz, $CDCl_3$): δ = 6.99–6.93 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.36 (s, 3H), 2.03 (d, *J* = 9.3 Hz, 1H), 1.55 (br dd, *J* = 9.3, 5.4 Hz, 1H). ^{31}P NMR (121.50 MHz, $CDCl_3$) δ = 33.1 (s). HR-MS (+ESI) *m*/z calcd for $C_{52}H_{44}NOP_2Pd$ $[M–I]^+$ 866.1933, found 866.1941. We could not obtain adequate elemental analysis of the complex **2a**, probably due to the precipitation of small amounts of **9**, **10** and/or PPh_3 along with **2a**.

Synthesis of complex 2b. $Pd(dba)_2$ (914 mg, 1.59 mmol) and 4,4'-t-butyl-2,2'-bipyridine (427 mg, 1.59 mmol) were added to a solution of *N*-(2-iodophenyl)-acrylamide **1** (577 mg, 1.59 mmol) in dry CH_2Cl_2 (30 mL) in a Carius tube, under nitrogen atmosphere. The tube was sealed, and the mixture was stirred at room temperature for 3 h. The resulting solution was filtered over a Celite pad, the filtrate was concentrated to ca. 1 mL, and Et_2O (20 mL) was added. The resulting suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air-dried to give compound **2b** as a yellow solid. Yield: 877 mg, 1.19 mmol, 71%; m.p. 188 °C. ^1H NMR (400.9 MHz, $CDCl_3$): δ = 9.42 (d, *J* = 6.0 Hz, 1H), 8.66 (d, *J* = 6.0 Hz, 1H), 7.86 (dd, *J* = 6.4, 2.0 Hz, 2H), 7.70-7.60 (m, 2H), 7.59 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.38 (dd, *J* = 6.0, 2.0 Hz, 1H), 7.33 (dd, *J* = 6.0, 2.0 Hz, 1H), 7.21–7.17 (m, 2H), 7.13–7.07 (m, 2H), 6.85 (td, *J* = 7.6, 0.8 Hz, 1H), 6.71 (d, *J* = 7.2 Hz, 1H), 3.37 (d, *J* = 8.9 Hz, 1H), 3.12 (s, 3H), 2.61 (d, *J* = 8.9 Hz, 1H), 1.41 (s, 9H), 1.38 (s, 9H). ^{13}C NMR (100.8 MHz, $CDCl_3$): δ = 179.3 (s, C_q), 162.5 (s, C_q), 162.4 (s, C_q), 155.8 (s, C_q), 153.6 (s, C_q), 152.4 (s, CH), 148.7 (s, CH), 143.1 (s, C_q), 142.7 (s, C_q), 135.0 (s, C_q), 127.8 (s, CH), 127.7 (s, CH), 127.5 (s, CH), 126.9 (s, CH), 126.2 (s, CH), 123.4 (s, CH), 122.8 (s, CH), 121.3 (s, CH), 118.2 (s, CH), 117.7 (s, CH), 107.4 (s, CH), 58.8 (s, C_q), 35.4 (s, C_q), 35.3 (s, C_q), 30.3 (s, CH_3), 30.2 (s, CH_3), 26.4 (s, CH_3), 19.3 (s, CH_2). IR (Nujol, cm^{-1}): ν (CO) 1699 (s). Elemental analysis calcd (%) for $C_{34}H_{38}N_3OPdI$: C 55.33, H 5.19, N 5.69; found: C 55.65, H 5.13, N 5.67.

Synthesis of complex 2c•$1/2H_2O$. $Pd(dba)_2$ (524 mg, 0.911 mmol) and TMEDA (136 μL, 0.911 mmol) were added to a solution of *N*-(2-iodophenyl)-acrylamide **1** (331 mg, 0.911 mmol) in dry CH_2Cl_2 (30 mL) in a Carius tube, under nitrogen atmosphere. The tube was sealed and the mixture was stirred at room temperature for 3 h. The resulting solution was filtered over a Celite pad, the filtrate was concentrated to ca. 3 mL, and Et_2O (20 mL) was added. The suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air dried to give compound **2c•**$1/2H_2O$ as an orange solid. Yield: 341 mg, 0.573 mmol, 63%; m.p. 160 °C (dec). ^1H NMR (300.1 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.28–7.14 (m, 5H), 7.10 (td, *J* = 7.5, 0.9 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 3.19 (s, 3H), 2.87 (d, *J* = 8.7 Hz, 1H), 2.67–2.31 (m, 14H), 2.11 (br s, 2H), 1.87 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (100.8 MHz, $CDCl_3$): δ = 180.0 (s, C_q), 143.9 (s, C_q), 143.5 (s, C_q), 135.7 (s, C_q), 127.7 (s, CH), 127.3 (br s, CH), 127.2 (s, CH), 126.3 (s, CH), 121.4 (s, CH), 107.8 (s, CH), 62.0 (br s, CH_2), 61.5 (s, C_q), 57.7 (br s, CH_2), 52.6 (br s, CH_3), 50.4 (br s, CH_3), 49.3 (br s, CH_3), 48.5 (br s, CH_3), 26.6 (s, CH_3), 18.2 (s, CH_2). Some ^{13}C signals are overlapped. IR (Nujol, cm^{-1}): ν(CO) 1692 (s). Elemental analysis calcd (%) for $C_{22}H_{30}IN_3OPd•1/2H_2O$: C 44.42, H 5.25, N 7.06; found: C 44.23, H 5.33, N 6.85.

Synthesis of complex 4b. A Carius tube was charged with the substrate **2b** (300 mg, 0.41 mmol), dry Cs_2CO_3 (199 mg, 0.62 mmol) and a magnetic stirrer. The tube was rapidly set under nitrogen atmosphere and dry CH_3CN was added (12 mL). The tube was sealed, and the mixture was stirred at 75 °C for 16 h. After cooling the tube, the crude was diluted with CH_2Cl_2 (30 mL), and filtered through a Celite plug. The filtrate was concentrated to ca. 1 mL, Et_2O (15 mL) was added, and the mixture was stirred in a cold bath for 30 minutes. A yellow solid precipitated slowly. The suspension was filtered, and the solid was washed with ether (2 x 3 mL) and air-dried to give **4b**·$0.75CH_2Cl_2$ as a yellow solid. Yield: 167 mg, 0.25 mmol, 60%. Mp: 130-132 °C. ^1H NMR (400.9 MHz, $CDCl_3$): δ = 9.20 (d, *J* = 5.6 Hz, 1H), 8.42 (d, *J* = 6 Hz, 1H), 8.01 (dd, *J* = 10.0, 1.6 Hz, 2H), 7.91 (dd, *J* = 7.6 Hz, 0.8, 1H), 7.59 (td, *J* = 5.6, 2 Hz, 2H), 7.33 (dd, *J* = 5.6, 1.6 Hz, 1H), 7.17 (td, *J* = 7.6, 1.2 Hz, 1H), 7.02 (td, *J* = 7.2, 1.2 Hz, 1H), 6.92 (td, *J* = 7.2, 0.8 Hz, 1H), 6.88–6.83 (m, 2H), 6.46 (dd, *J* = 7.6, 1.2 Hz, 1H), 5.30 (crystallization CH_2Cl_2, 1.1H) 3.30 (s, 3H), 2.91 (d, *J* = 8.4 Hz, 1H), 2.20 (d, *J* = 8.4 Hz, 1 H), 1.47 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 181.7 (s, C_q), 162.29 (s, C_q), 162.25 (s, C_q), 161.8 (s, C_q), 161.5 (s, C_q), 155.4 (s, C_q), 155.1 (s, C_q), 150.6 (s, CH), 149.5 (s, CH), 142.9 (s, C_q), 139.5 (s, C_q), 135.2 (s, CH), 126.3 (s, CH), 124.9 (s, CH), 124.4 (s, CH), 123.5 (s, CH), 123.1 (s, CH), 122.7 (s, CH), 122.2 (s, CH), 121.9 (s, CH), 118.2 (s, CH), 118.0 (s, CH), 107.0 (s, CH), 65.4 (s, C_q), 35.4 (s, C_q), 35.3 (s, C_q), 34.4 (s, CH_2), 30.4 (s, CH_3), 30.3 (s, CH_3), 26.2 (s, CH_3). IR (Nujol, cm^{-1}): ν(CO) 1698 (s). Elemental analysis calcd (%) for $C_{34}H_{37}N_3OPd·0.75CH_2Cl_2$: C 61.94, H 5.76, N 6.24; found: C 61.72, H 5.83, N 6.20. Single crystal of **4b**, suitable for an X-ray diffraction study, were obtained by slow diffusion of *n*-pentane into a solution of **4b** in acetone.

Synthesis of complex 11. A saturated solution of HCl in dichloromethane (600 μL), prepared by bubbling HCl gas through dichloromethane, was added to a solution of **4a** (200 mg, 0.23 mmol) in the commercial dichloromethane (30 mL). The resulting mixture was stirred at room temperature for 16 h. The solution was concentrated to ca. 1 mL, and Et_2O (15 mL) was added. The resulting suspension was filtered, and the solid was washed with Et_2O (2 x 3 mL) and air-dried to afford **11** as a yellow solid. Yield: 83 mg, 0.13 mmol, 56%. Mp: 154-156 °C. ^1H NMR (300.1 MHz, $CDCl_3$) δ = 7.57–7.48 (m, 5H), 7.46–7.39 (m, 5H), 7.36–7.30 (m, 9H), 7.23-7.06 (m, 2 H), 6.97-6.95 (m, 2 H), 6.81 (d, *J* = 9.3 Hz, 1 H), 3.39 (s, 3 H). 1.83 (d, *J* = 9.6 Hz, 1H), 1.24 (dd, *J* = 9.6, 6.3 Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 192.0 (s, C_q), 144.1 (s, C_q), 141.7 (s, C_q), 134.5 (d, *J* = 11.7 Hz, CH), 130.6 (d, *J* = 54.9 Hz, C_q), 130.6 (d, *J* = 2.4 Hz, CH), 129.0 (s, CH), 128.4 (s, CH), 128.2 (d, *J* = 11.2 Hz; CH), 127.2 (s, CH), 126.2 (s, CH), 124.2 (s, CH), 123.2 (s, CH), 109.9 (s, CH), 66.4 (s, C_q), 32.0 (s, CH_2), 27.4 (s, CH_3). One C_q signal is overlapped or not

observed. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 37.8 (s). IR (cm^{-1}): 1705 ν(CO) 1704 (s). HR-MS (+ESI) *m*/z: calcd for $C_{34}H_{29}NOPPd$ [M-Cl]$^+$ 604.1022, found 604.1031. Single crystal of **11**, suitable for an X-ray diffraction study, were obtained by slow diffusion of *n*-pentane into a solution of **11** in dichloromethane. No satisfactory elemental analysis could be obtained for this compound, probably due to its tendency to crystallize with variable amounts of solvent. The bulk purity of this compound was assessed by ^{1}H, ^{13}C and ^{31}P NMR, which spectra are provided in the Supporting Information.

Synthesis of compound 12. An excess of a saturated solution of HCl in dichloromethane (1 mL), prepared by bubbling HCl gas through dichloromethane, was added to a solution of **4a** (50 mg, 0.06 mmol) in commercial dichloromethane (15 mL). The resulting mixture was stirred at room temperature for 16 h, and Et_2O (15 mL) was added. The suspension was filtered, and the solid was washed with Et_2O (2 x 3 mL) and air-dried to give [$PdCl_2(PPh_3)$] (10.5 mg, 0.015 mmol), which was identified by ^{31}P NMR (δ = 23 ppm (s)). The solvent was removed from the filtrate and the crude was purified by preparative TLC (silica gel, Pet.Et/EtOAc (10:1)) to give the compound **12** as a pale yellow oil. Yield: 8.3 mg, 0.04 mmol, 58%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.35 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.30–7.20 (m, 5H), 7.18–7.17 (m, 1H), 7.09 (td, *J* = 7.5, 0.9 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 3.24 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 179.4 (s, C_q), 143.2 (s, C_q), 140.8 (s, C_q), 134.8 (s, C_q), 128.5 (s, CH), 128.1 (s, CH), 127.2 (s, CH), 126.6 (s, CH), 124.2 (s, CH), 122.7 (s, CH), 108.3 (s, CH), 52.1 (s, C_q), 26.5 (s, CH_3), 23.7 (s, CH_3). IR (Nujol, cm^{-1}): 1716 ν(CO) (s). HR-MS (+ESI) *m*/z calcd for $C_{16}H_{15}NO$ [M+H]$^+$ 238.1226, found 238.1234. These data are in agreement with those reported previously in the literature.[22]

Thermal decomposition of complex 2c to give compounds 12 and 13. A solution of complex **2c**•1/2H_2O (180 mg, 0.303 mmol) in $CHCl_3$ (10 mL) was heated for 36 h under nitrogen atmosphere at 70 °C in a sealed Carius tube. The resulting suspension was filtered through a Celite pad, and the solvent was removed from the filtrate. The residue was purified by preparative TLC (silica gel, petroleum ether/Et_2O (11:1)) to give the compounds **12** (12 mg, 0.05 mmol, 16%) and **13** (23 mg, 0.065 mmol, 21%). Data for **13**: pale yellow oil; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.45–7.39 (m, 4H), 7.33–7.27 (m, 3H), 7.19 (td, *J* = 7.5, 0.9 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 4.03 (d, *J* = 9.8 Hz, 1H), 3.77 (d, *J* = 9.8 Hz, 1H), 3.24 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 176.1 (s, C_q), 144.0 (s, C_q), 137.7 (s, C_q), 130.8 (s, C_q), 129.1 (s, CH), 128.8 (s, CH), 128.0 (s, CH), 127.1 (s, CH), 124.9 (s, CH), 122.7 (s, CH), 108.6 (s, CH), 56.6 (s, C_q), 26.5 (s, CH_3), 10.5 (s, CH_2). IR (Nujol, cm^{-1}): ν(CO) 1697 (m). HRMS (+ESI) *m*/z: calcd for $C_{16}H_{15}INO$ [M+H]$^+$ 364.0193, found 364.0183. The bulk purity of the compound **13** was assessed by ^{1}H and ^{13}C NMR, which spectra are provided in the Supporting Information.

Synthesis of complex 14b•1/2MeCN. AgOTf (18 mg, 0.068 mmol) was added to a solution of **2b** (50 mg, 0.068 mmol) in CH_3CN (15 mL). The resulting mixture was stirred in the dark for 12 h. The suspension was filtered through a Celite pad, the filtrate was concentrated to ca. 2 mL, and Et_2O (15 mL) was added. The resulting suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air-dried to give complex **14b**•1/2MeCN as an off-white solid. Yield: 44 mg, 0.056 mmol, 82%; m.p. 155 °C (dec.). Λ_M = 117.0 ($\Omega^{-1}cm^2mol^{-1}$). ^{1}H NMR (400.9 MHz, acetone-d_6): δ = 8.68 (d, *J* = 6.0 Hz, 1H), 8.62 (d, *J* = 1.6 Hz, 2H), 8.55 (d, *J* = 5.6 Hz, 1H), 7.78–7.73 (m, 4H), 7.41–7.34 (m, 4H), 7.32–7.26 (m, 1H), 7.19–7.41 (br m, 2H), 3.51 (br s, 3H), 2.53 (br s, 2H), 2.15 (br s, 1.5H; crystallization MeCN), 1.44 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (100.8 MHz, acetone-d_6): δ = 166.2 (s, C_q), 166.1 (s, C_q), 157.7 (s, C_q), 153.6 (s, C_q), 152.3 (s, CH), 149.2 (s, CH), 145.0 (s, C_q), 142.2 (s, C_q), 129.7 (s, CH), 129.2 (s, CH), 128.4 (s, CH), 127.3 (s, CH), 125.4 (s, CH), 125.3 (s, CH), 122.2 (s, CH), 121.1 (s, CH), 36.6 (s, C_q), 36.5 (s, C_q), 30.3 (s, CH_3), 30.2 (s, CH_3). Some signals are overlapped or not observed. IR (Nujol, cm^{-1}): ν(CO) 1711 (s). Elemental analysis calcd (%) for $C_{35}H_{38}F_3N_3O_4PdS$•1/2MeCN: C 55.39, H 5.06, N 6.27, S 4.10; found: C 55.26, H 4.69, N 6.68, S 4.38.

Synthesis of complex 14c•1/4CH_2Cl_2. AgOTf (56 mg, 0.217 mmol) was added to a solution of **2c**•1/2H_2O (127 mg, 0.213 mmol) in CH_3CN (30 mL). The resulting mixture was stirred in the dark for 12 h. The suspension was filtered through a Celite pad, and the solvent was removed from the filtrate under vacuum. The residue was dissolved in CH_2Cl_2 (2 mL) and Et_2O (10 mL) was added. The resulting suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air-dried to give **14c**•1/4CH_2Cl_2. Yield: 92 mg, 0.151 mmol, 68%. M. p. 151 °C (dec.). Λ_M = 124.3 ($\Omega^{-1}cm^2mol^{-1}$). ^{1}H NMR (400.9 MHz, $CDCl_3$): δ = 7.61–7.59 (m, 2H), 7.46–7.42 (m, 2H), 7.38–7.34 (m, 1H), 7.31 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.27–7.25 (m, 1H), 7.16 (td, *J* = 7.6, 0.8 Hz, 1H), 6.92 (d, *J* = 8 Hz, 1H), 5.30 (s, 0.2H, crystallyzation CH_2Cl_2) 3.35 (s, 3H), 3.02–2.95 (m, 1H), 2.79–2.77 (m, 1H), 2.73-2.2.71 (m partially obscured, 1H) 2.70 (s, 3H), 2.69 (s, 3H), 2.68 (s, 3H), 2.65–2.58 (m, 1H), 2.56 (s, 3H), 1.82 (d, *J* = 8.4 Hz, 1H), 1.71 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ = 194.5 (s, C_q), 143.6 (s, C_q), 141.3 (s, C_q), 134.1 (s, C_q), 129.2 (s, CH), 128.4 (s, CH), 128.0 (s, CH), 125.6 (s, CH), 125.5 (s, CH), 123.5 (s, CH), 110.6 (s, CH), 66.5 (s, C_q), 64.3 (s, CH_2), 57.4 (s, CH_2), 53.4 (s, CH_3), 51.7 (s, CH_3), 48.7 (s, CH_3), 47.3 (s, CH_3), 27.3 (s, CH_3), 21.4 (s, CH_2). IR (Nujol, cm^{-1}): ν(CO) 1600 (s). Elemental analysis calcd (%) for $C_{23}H_{30}F_3N_3O_4PdS$•1/4CH_2Cl_2: C 44.38, H 4.89, N 6.68, S 5.09; found: C 44.28, H 4.93, N 6.65, S 5.07.

Synthesis of compound 17. Dimethyl acetilenedicarboxylate (7.5 μL, 0.06 mmol) was added to a solution of **4a** (50 mg, 0.06 mmol) in dry dichloromethane (15 mL). The mixture was stirred at room temperature for 16 h. The solvent was removed and the residue was purified by preparative TLC chromatography (silica gel, petroleum ether/EtOAc 7:1) to afford compound **17** as a white solid. M.p: 76-78 °C. Yield (17.4 mg, 0.05 mmol, 77%). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.33–7.31 (m, 1H), 7.29–7.22 (m, 4H), 6.96 (td, *J* = 7.8, 1.2 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.87–6.84 (m, 1H), 4.03 (s, 3H), 3.76 (s, 3H), 3.35 (s, 3H), 3.24 (d, *J* = 17.1 Hz, 1H), 2.94 (d, *J* = 17.1 Hz, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 179.3 (s, C_q), 169.5 (s, C_q), 166.7 (s, C_q), 142.6 (s, C_q), 142.2 (s, C_q), 137.2 (s, C_q), 133.5 (s, C_q), 132.3 (s, CH), 130.7 (s, C_q), 129.7 (s, CH), 129.3 (s, CH), 128.2 (s, CH), 127.0 (s, CH), 124.7 (s, CH), 124.3 (s, C_q), 124.2 (s, CH), 109.6 (s, CH), 53.7 (s, CH_3), 53.4 (s, CH_3), 52.7(s, C_q), 33.7(s, CH_2), 27.6 (s, CH_3). IR (Nujol, cm^{-1}): 1722 ν(CO) (br). HRMS (+ESI): *m*/z calcd for $C_{22}H_{20}NO_5$ [M+H]$^+$ 378.1336, found 378.1331. The bulk purity of the compound **17** was assessed by ^{1}H and ^{13}C NMR, which spectra are provided in the Supporting Information.

Synthesis of complex 18·1/2Et_2O. A solution of xylyl isocyanide (30 mg, 0.23 mmol) in dichloromethane (15 mL) was added dropwise to a solution of **4a** (200 mg, 0.23 mmol) in dichloromethane (20 mL), and the mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure, and Et_2O was added (15 mL). The resulting mixture was stirred in a cold bath for 30 minutes. The suspension was filtered, and the solid was washed with Et_2O (2 x 3 mL) and air-dried to give complex **18**·1/2Et_2O as a yellow solid. Yield: 129 mg, 0.17 mmol, 73%. Mp: 118-120 °C. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.82 (td, *J* = 7.3, 1.5 Hz, 1H), 7.71–7.64 (m, 1H), 7.57 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.55–7.46 (m, 6H), 7.30–7.27 (m, 4H), 7.24–7.23 (m, 3H), 7.21–7.20 (m, 1H), 7.17–7.15 (m, 2H), 7.04 (d, *J* = 7.5 Hz, 2H), 6.98 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.95–6.91 (m, 1H), 6.87 (td, *J* = 7.2, 1.2 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.59–6.55 (m, 1H), 3.22 (s, 3H), 2.36 (dd, *J* = 7.2, 1.2 Hz, 1H), 2.14 (s, 6H, Me, Xy), 1.76 ("t", *J* = 10.4 Hz, 1H). ^{13}C NMR (100.8 MHz, $CDCl_3$): δ = 180.9 (s, C_q), 168.5 (s, C_q), 167.4 (s, C_q), 159.8 (s, C_q), 142.3 (s, C_q), 139.2 (s, CH), 138.7 (s, C_q), 134.5 (s, C_q), 133.6 (d, *J* = 13.0 Hz, CH), 132.7 (d, *J* = 34.4 Hz, $C_{q\text{-ipso}}$), 131.6 (d, *J* = 9.9 Hz, CH), 129.4 (s, CH), 128.3 (s, CH), 127.8 (d, *J* = 9.6 Hz, CH), 127.3 (s, CH), 125.8 (s, CH), 124.7 (d, *J* = 8.3 Hz, CH), 123.8 (d, *J* = 7.4 Hz, CH), 122.5 (d, *J* = 3.0 Hz, CH), 121.3 (s, CH), 106.6 (s, CH), 67.9 (d, *J* = 7.6 Hz, C_q), 65.3 (s, CH_2, crystallization Et_2O), 39.8 (d, *J* = 8.2 Hz, CH_2), 25.7 (s, CH_3), 18.1 (s, CH_3), 14.8 (s, CH_3, crystallization Et_2O). ^{31}P NMR (162.3 MHz, $CDCl_3$): δ = 23.3 (s). IR (Nujol, cm^{-1}): ν(CN) 2147 (s), ν(CO) 1708 (s). Elemental analysis calcd (%) for $C_{43}H_{37}N_2OPPd$·1/2Et_2O: C 69.99, H 5.48, N 3.62; found: C 69.80, H 5.33, N 3.37.

Synthesis of complex 19. A solution of xylyl isocyanide (24 mg, 0.18 mmol) in dichloromethane (10 mL) was added dropwise to a solution of **4a** (50 mg, 0.06 mmol) in dichloromethane (15 mL), and the mixture was

stirred at room temperature for 16 h. The solvent was partially removed from the mixture to ca. 2 mL, Et_2O (15 mL) was added, and the suspension was filtered to remove solid impurities. The filtrate was concentrated to ca. 2 mL and *n*-pentane (15 mL) was added. The suspension was filtered, and the solid was washed with *n*-pentane (2 x 5 mL) and air-dried to give **19** as a yellow solid. Yield: 20 mg, 0.03 mmol, 55%. Mp: 164-166 ºC. ^{1}H NMR (400.9 MHz, $CDCl_3$): δ = 7.81 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.54 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.30-7.17 (m, 5H), 7.08 (d, *J* = 7.6 Hz, 2H), 7.01 (td, *J* = 7.6, 0.8 Hz, 1H), 6.94 (td, *J* = 7.2, 1.2 Hz, 1H), 6.87 (td, *J* = 7.2, 1.2 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.51 (dd, *J* = 7.6, 1.2 Hz, 1H). 3.29 (s, 3H), 2.64 (d, *J* = 10.4 Hz, 1H), 2.57 (s, 6H; Me, Xy), 2.36 (s, 6H; Me, Xy), 2.32 (d, *J* = 10.4 Hz, 1H). ^{13}C NMR (100.8 MHz, $CDCl_3$): δ = 181.7 (s, C_q), 165.8 (s, C_q), 160.3 (s, C_q), 142.8 (s, C_q), 140.2 (s, CH), 139.3 (s, C_q), 135.4 (s, CH), 135.1 (s, CH), 132.9 (s, C_q), 129.3 (s, C_q), 129.2 (s, C_q), 128.1 (s, CH), 127.9 (s, CH), 126.6 (s, CH), 125.2 (s, CH), 124.5 (s, CH), 124.2 (s, CH), 122.9 (s, CH), 122.2 (s, CH), 107.2 (s, CH), 67.9 (s, C_q), 34.5 (s, CH_2), 26.3 (s, CH_3), 19.1 (s, CH_3), 18.8 (s, CH_3). Some ^{13}C signals are overlapped. IR (Nujol, cm^{-1}): ν(CN) 2167 (s), 2141, ν(CO) 1698 (s). Elemental analysis calcd (%) for $C_{34}H_{31}N_3OPd$: C 67.60, H 5.17, N 6.95; found: C, 67.64, H 5.27, N 6.82.

Synthesis of compound 20. $PhI(OAc)_2$ (39 mg, 0.12 mmol) was added to a solution of **4a** (100 mg, 0.12 mmol) in dichloromethane (25 mL), and the mixture was stirred at room temperature for 16 h. The solvent was removed, and the residue was purified by preparative TLC chromatography (silica gel, petroleum ether/EtOAc 5:1) to provide compound **20** as a white solid. Yield: 21 mg, 0.09 mmol, 74%. Mp: 124-126 ºC. ^{1}H NMR (300.1 MHz, $CDCl_3$) δ = 7.35–7.28 (m, 2H), 7.26–7.20 (m, 2H), 7.11 (ddd, *J* = 7.2, 1.2, 0.3 Hz, 1 H), 7.02 (td, *J* = 7.5, 0.9 Hz, 1H), 6.91-6.85 (m, 2H), 3.77 (d, *J* = 13.5 Hz, 1H), 3.46 (d, *J* = 13.5 Hz, 1H), 3.29 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 176.9 (s, C_q), 144.3 (s, C_q), 143.9 (s, C_q), 143.8 (s, C_q), 130.6 (s, C_q), 128.8 (s, CH), 128.5 (s, CH), 128.0 (s, CH), 123.2 (s, CH), 123.0 (s, CH), 122.6 (s, CH), 121.6 (s, CH), 108.0 (s, CH), 55.8 (s, C_q), 42.8 (s, CH_2), 26.5 (s, CH_3). IR (Nujol, cm^{-1}): 1717 ν(CO) (s). HR-MS (+ESI) *m/z*: calcd for $C_{16}H_{14}NO$ $[M+H]^+$ 236.107, found 236.1068. These data are in agreement with those reported previously in the literature.[23]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H, ^{31}P and ^{13}C -APT or ^{13}C-NMR spectra of the new compounds, crystallographic data, and details of hydrogen bonds (including symmetry operators) (PDF).

Crystallographic data for compounds **2b**, **4b**·C_3H_6O, **11**·CH_2Cl_2, and **14c**. (CIF).

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Notes

The authors declare no competing financial interest.

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