ORGANOMETALLICS
Article
Cite This: Organometallics XXXX, XXX, XXX-XXX
pubs.acs.org/Organometallics

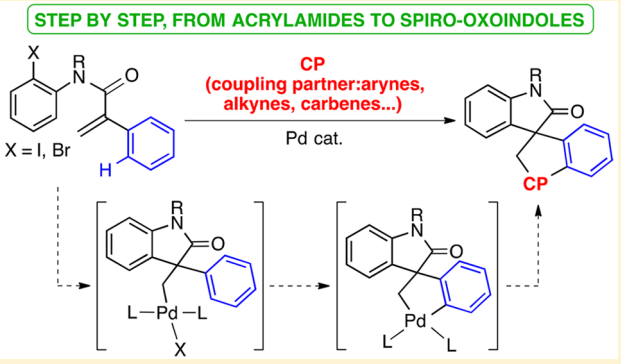
Synthesis and Reactivity of Model Intermediates Proposed for the Pd-Catalyzed Remote C−H Functionalization of *N*-(2-Haloaryl)acrylamides

Marta Pérez-Gómez,[†] Leticia Navarro,[†] Isabel Saura-Llamas,[†] Delia Bautista,[‡] Mark Lautens,*[,§] and José-Antonio García-López*[,†]

[†]Grupo de Química Organometálica. Dpto. Química Inorgánica, Universidad de Murcia, Campus de Espinardo, 30100, Murcia, Spain
[‡]SAI, Universidad de Murcia, 30100, Murcia, Spain
[§]Davenport Research Laboratories, Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada

Supporting Information

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 proposed 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 such as benzyne, alkynes, and isocyanides has been studied in order to gain further insight into 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, and 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.

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 these types of cascade reactions was reported by one of our research groups.[10]

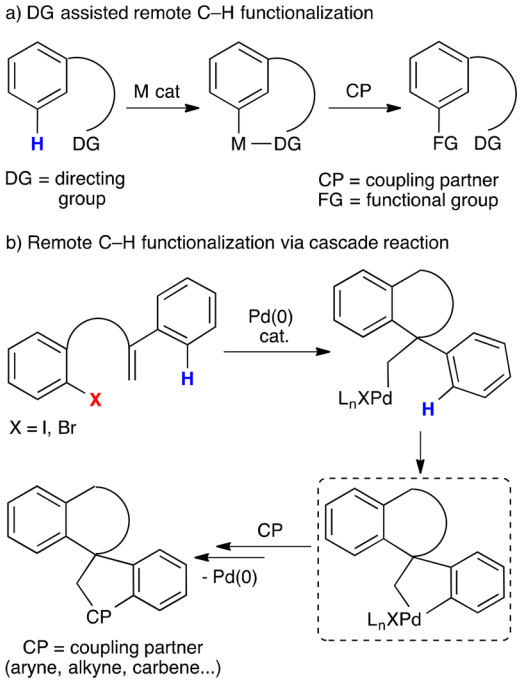
These strategies have been successfully applied to the synthesis of functionalized spiro-oxoindoles, a molecular scaffold that has attracted great interest due to its presence in natural products and pharmaceuticals.[11] We have now studied in detail the synthesis and reactivity of some of the key intermediates 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 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

Received: September 13, 2017

DOI: 10.1021/acs.organomet.7b00702
Organometallics XXXX, XXX, XXX−XXX

Scheme 1. Directing-Group-Assisted and Cascade-Type Remote C−H Functionalizations



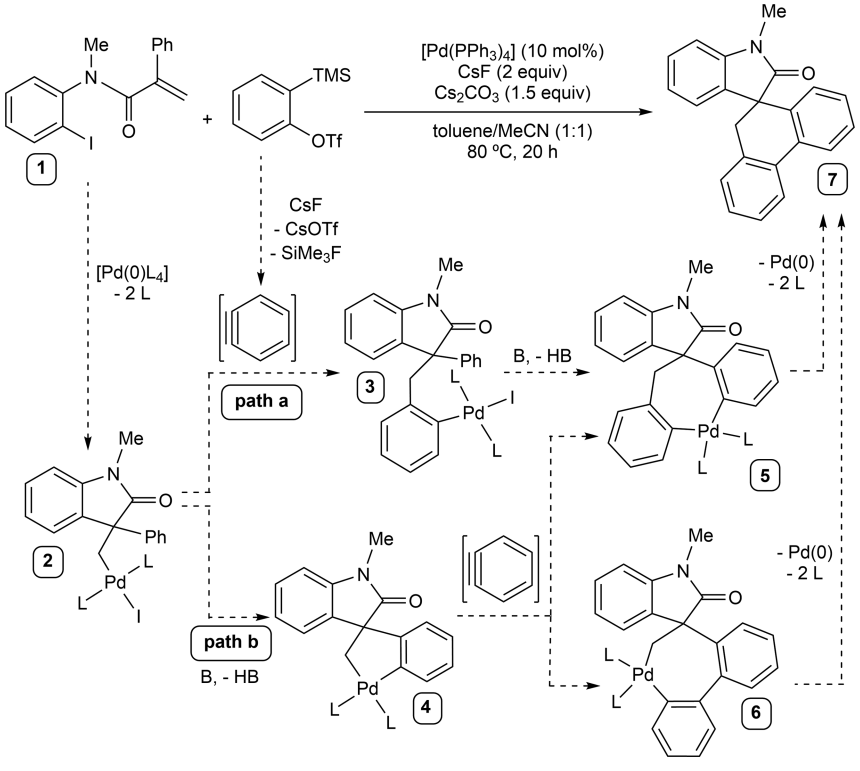
common intermediates. For instance, the oxidative addition of a haloarene to a Pd(0) complex (either preformed or generated in situ from $Pd(OAc)_2$ and PPh_3) would render an aryl-Pd(II) species, which in turn could evolve through the intramolecular carbopalladation of the tethered alkene, generating 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.

The synthesis of a type **4** complex was recently reported as part of the mechanistic studies in 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 where benzyne was replaced 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 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.

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 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 equiv of PPh_3 in CH_2Cl_2 at room temperature under an inert

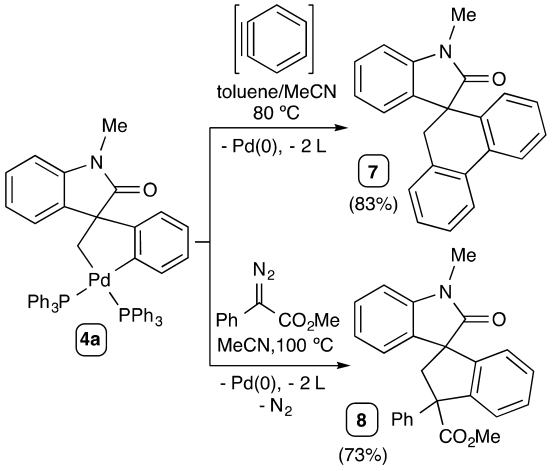
Scheme 2. Remote Arylation of *N*-(2-Iodophenyl)acrylamide with Benzyne and Its Possible Reaction Pathways[a]



[a]B represents a generic base.

DOI: 10.1021/acs.organomet.7b00702
Organometallics XXXX, XXX, XXX−XXX

Scheme 3. Reported Reactivity of the *C,C*-Palladacycle 4a with Arynes and *α*-Diazocarbonyl Compounds

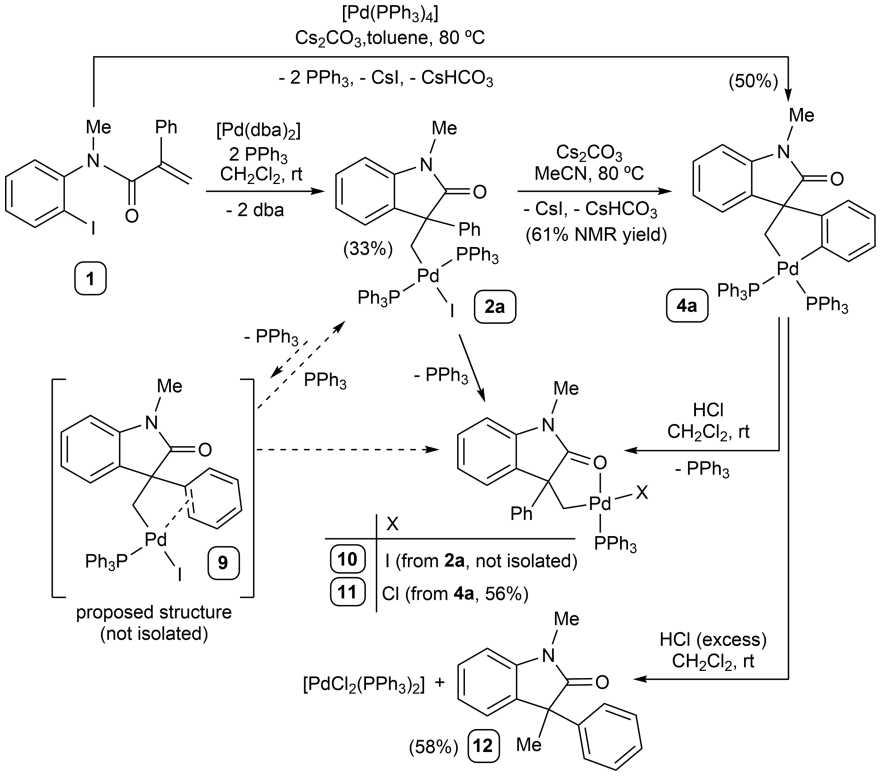


atmosphere for 2 h (Scheme 4). A pale gray solid could be isolated upon addition of Et_2O to the reaction mixture, whose ^{31}P NMR spectrum showed a main signal at 33.1 ppm (attributed to the expected complex **2a**), along with two smaller and much broader signals at 40.2 and −4.5 ppm (Figure 1). The chemical equivalence of the phosphine ligands in **2a** indicated their mutually 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 room temperature 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 first three signals (40.2, 33.1, and −4.5 ppm, Figure 1). A plausible explanation for this behavior 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 time.

According to path b, depicted in the Scheme 2 for the catalytic reaction, complex **2a** should be able to generate the *C,C*-palladated intermediate **4a** under the right conditions. When complex **2a** was heated in toluene at 80 °C for 4 h, 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, complex **4a** was the main product of the crude

Scheme 4. Synthesis of the *σ*-Alkyl Pd Complex 2a and Its Evolution under Different Conditions: Protonolysis of the Complex 4a



DOI: 10.1021/acs.organomet.7b00702
Organometallics XXXX, XXX, XXX−XXX

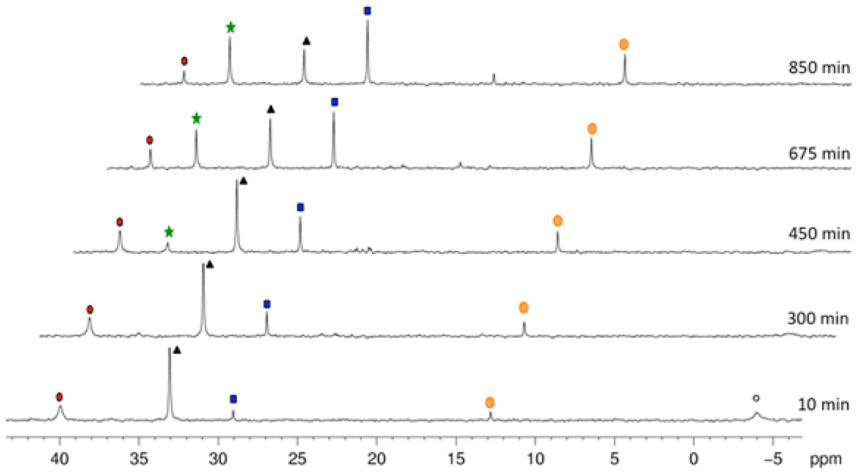


Figure 1. Stacking of the ^{1}H NMR spectra of a $CDCl_3$ solution of complex **2a** at 25 °C at increasing times. The different species are marked as follows: **9**, red circles (40.2 ppm); **10**, green stars (37.7 ppm); **2a**, black triangles (33.1 ppm); $OPPh_3$, blue squares (29.3 ppm); $[PdI_2(PPh_3)_2]$,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

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 1 equiv of $[Pd(PPh_3)_4]$ in toluene at 80 °C in the presence of Cs_2CO_3 (Scheme 4), as reported previously by one of us.[7a]

In an attempt to isolate an analogous complex to **10**, we carried out the partial protonolysis of the C(sp^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 room temperature (Scheme 4). Via this method, we could isolate 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

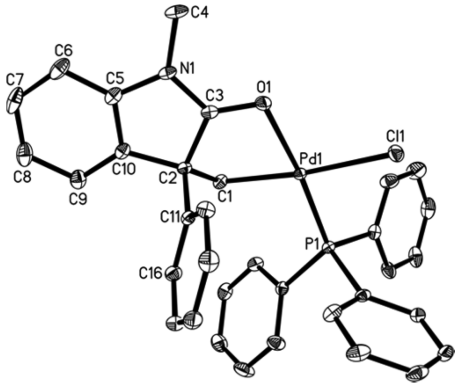


Figure 2. Thermal ellipsoid plot (50% probability) of **11** along with the labeling scheme. Hydrogen atoms have been omitted for clarity.

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).

Next, we attempted the synthesis of intermediates of type **2** that were easier to handle and study, by switching the ligand from PPh_3 to *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) or 4,4′-di-*tert*-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,c** in good yields (Scheme 5). These complexes were sufficiently stable to be fully characterized, and **2b** could be 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.

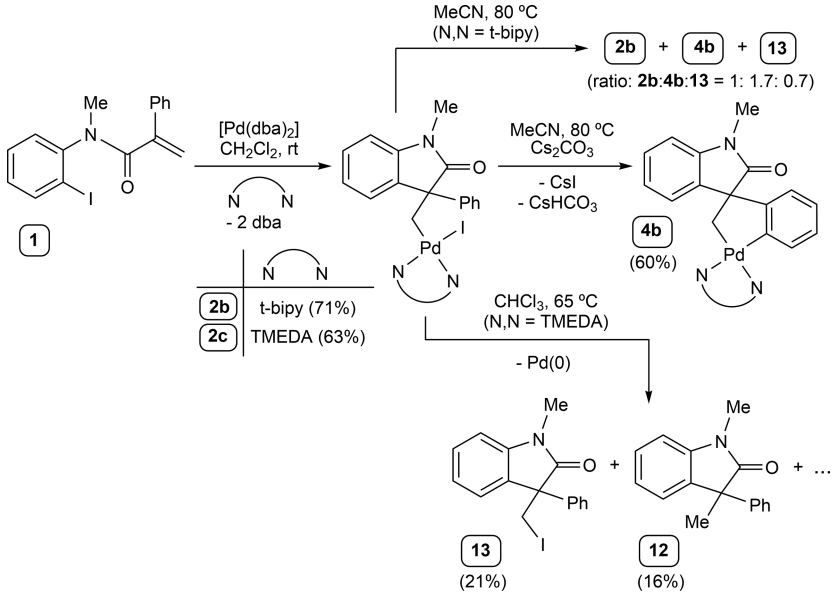
We can conclude that the first two steps of the catalytic cycle operating in the remote C−H functionalization reactions (Scheme 1), i.e., the oxidative addition of the C−I bond to Pd(0) and the intramolecular carbopalladation of the tethered olefin, took place smoothly at room temperature regardless 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 complex **2b** in MeCN was heated to 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** (**2b**:**4b**:**13** ratio 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

DOI: 10.1021/acs.organomet.7b00702
Organometallics XXXX, XXX, XXX−XXX

Scheme 5. Synthesis of Complexes 2b,c and Their Evolution under Different Conditions



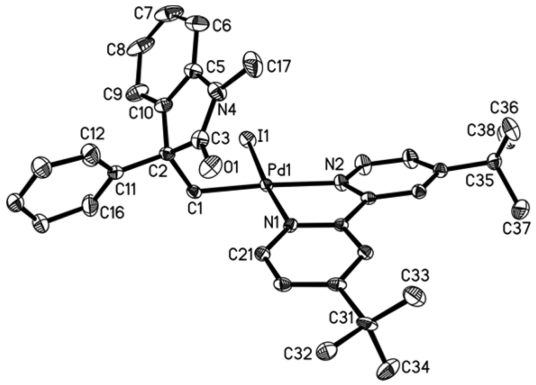


Figure 3. Thermal ellipsoid plot (50% probability) of **2b** along with the labeling scheme. Hydrogen atoms have been omitted for clarity.

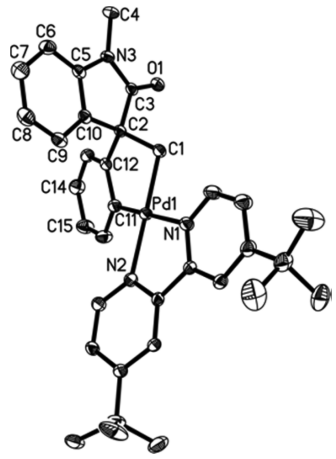


Figure 4. Thermal ellipsoid plot (50% probability) of **4b** along with the labeling scheme. Hydrogen atoms have been omitted for clarity.

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: an *N,N*- and a *C,C*-moiety. 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 significantly 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 previously reported for **4a**.[7a]

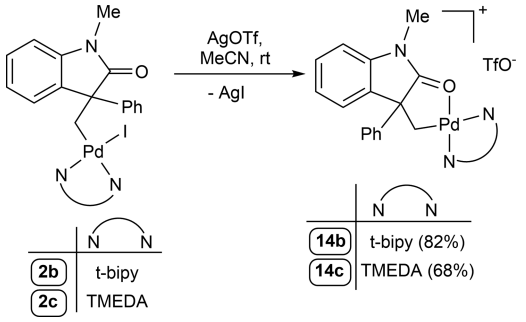
Once again, the addition of Cs_2CO_3 suppressed the generation of the secondary byproducts (**12** and **13**, Scheme 5). It is worth noting that the product **13**, arising from the C−I coupling process, was only observed in the decomposition process of complexes **2b,c** (containing *N,N*-chelating 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 C_{sp^3}−Pd bond. Likely, the absence of a base in the reaction mixture allows the protonolysis of the C_{sp^3}−Pd bond to proceed.

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 complexes **14b,c** by reacting the σ-alkyl Pd(II) complexes **2b,c** with AgOTf in MeCN at room temperature (Scheme 6). We intended to replace the iodine moiety by a far less coordinating ligand, such as the triflate anion. The cationic complexes **14b,c** were obtained. The crystal structure of complex **14c** was

DOI: 10.1021/acs.organomet.7b00702
Organometallics XXXX, XXX, XXX−XXX

Scheme 6. Synthesis of Cationic Complexes 14b,c



determined by X-ray diffraction (Figure 5) and showed the intramolecular chelation of the oxygen atom from the amide

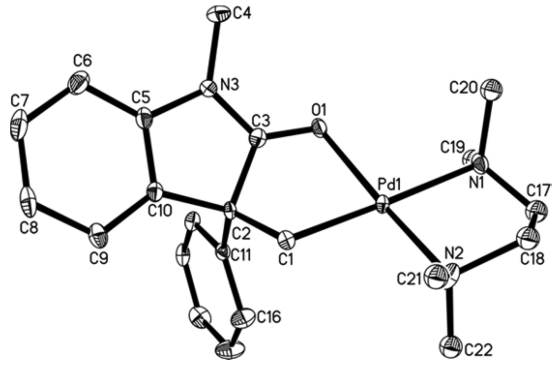
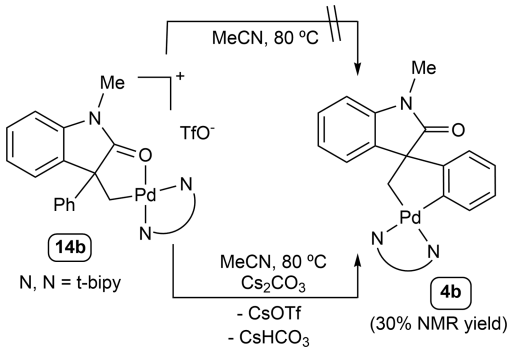


Figure 5. Thermal ellipsoid plot (50% probability) of **14c** along with the labeling scheme. Hydrogen atoms and the triflate anion have been omitted for clarity.

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 7.5° 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)°) and the anionic *C,O*-moiety (angle O(1)−Pd(1)−C(1) = 84.48(11)°). The Pd(1)−N(1) bond length (2.167(3) Å) is significantly longer than the Pd(1)−N(2) bond length (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 **14b,c** in solution was confirmed by measuring the values of their molar conductivity in acetone.

We hypothesized that the exchange of the iodo by a triflate ligand would lead to an enhancement in the electrophilic character of Pd(II), promoting the C−H activation step.[17a,18] Nevertheless, complexes **14b,c** were very stable in solution and did not evolve to give the corresponding palladacycles **4b,c**, respectively, when they were heated at 80 °C in MeCN for 16 h (Scheme 7). This behavior is in contrast with that observed for the neutral complexes **2a,b**, 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

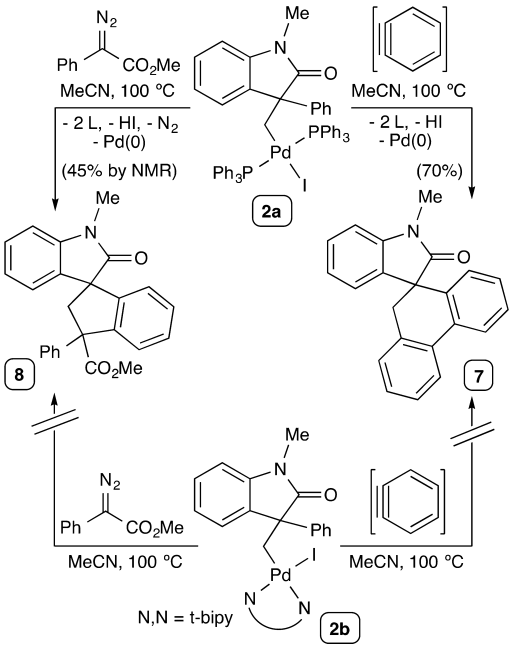
Scheme 7. Formation of 4b from 14b



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 neighboring phenyl ring, and therefore the metalation. The neutral precursor could bear either the initial iodide or a carbonate ligand. Furthermore, when 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).

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 behavior toward unsaturated species. We carried out the reactions of the *σ*-alkyl Pd(II) complexes **2a,b** 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 **2b** was used as the starting material, a complex mixture of products was obtained, where **7** and **8** could not be detected by either ^{1}H NMR or HPLC-MS (Scheme 8). The outcome of these reactions indicates that the nature of the ligands in the Pd coordination sphere plays a key

Scheme 8. Reactivity of the Complexes 2a,b with Different Coupling Partners

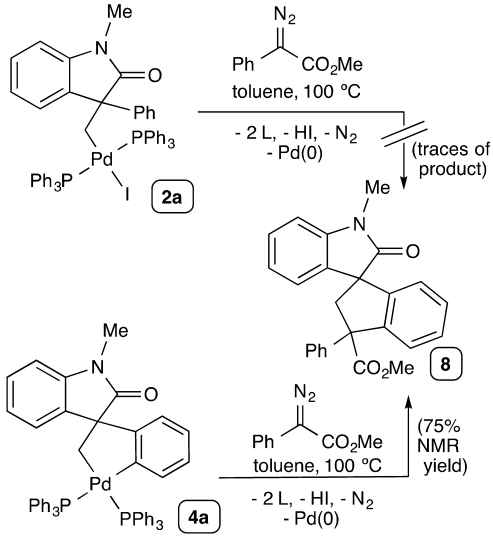


DOI: 10.1021/acs.organomet.7b00702
Organometallics XXXX, XXX, XXX−XXX

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.

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

Scheme 9. Reactivity of the Complexes 2a and 4a toward the α-Diazocarbonyl Coupling Partner

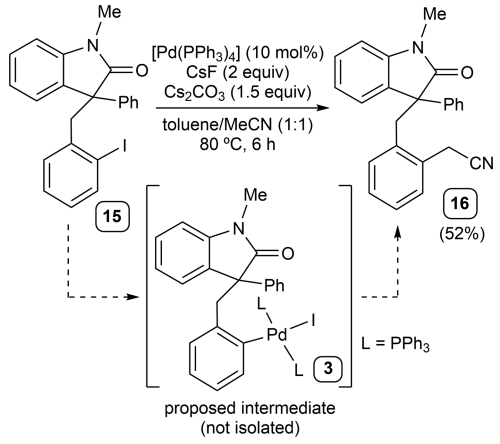


completely the possibility of generating **8** from a hypothetical alkyl-Pd(II) intermediate arising from the insertion of the α-diazocarbonyl compound into **2a** (since there is no presence of an external base to assist the subsequent C−H activation). However, we know that (1) **2a** reacts with the 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).

Complementarily to the stoichiometric studies we report in this paper, 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

Scheme 10. Reported Catalytic Reaction from Substrate 15

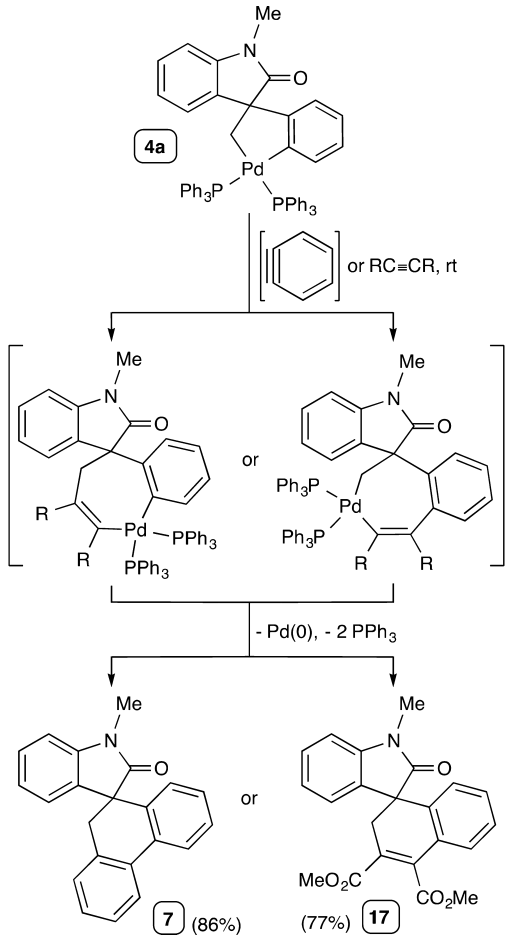


which of its two distinct Pd−C bonds was functionalized at first, to get a detailed picture of the complete reaction from the *N*-(2-iodophenyl)acrylamide **1** to the final organic product. Our goal was the isolation of any of the organometallic intermediates arising from the insertion of unsaturated coupling partners, such as benzyne, alkynes, carbon monoxide, and isocyanides, into either of the two Pd−C bonds present in **4a**. Vicente's group 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 room temperature, 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 behavior was found when a reactive alkyne such as dimethyl acetylenedicarboxylate (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 and 3-hexyne proved to be unreactive. Related insertion reactions of alkynes into five-membered C_{sp^2},C_{sp^3}-palladacycles and -nickelacycles have been reported in the literature.[14b−d] Similarly to our case, no seven-membered metallacyclic intermediates arising from the insertion of the alkyne into the Pd−C bond could be isolated from the reaction mixtures.

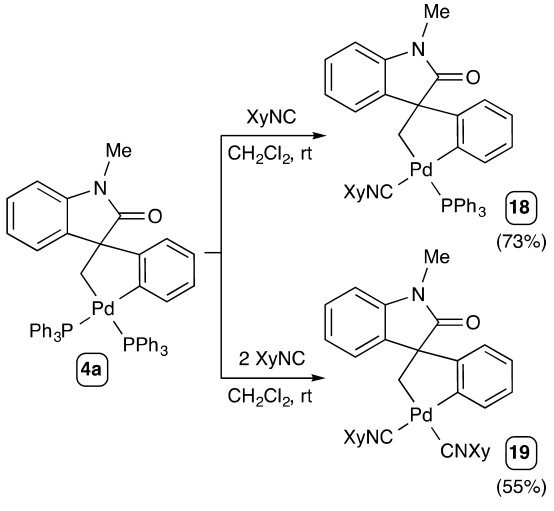
There are numerous examples in the literature regarding the insertion of carbon monoxide or isocyanides into the Pd−C bond of palladated arenes, which render isolable acyl or iminoacyl complexes.[13c,15b,19c,20] Nevertheless, the palladacycle **4a** was quite robust toward CO insertion, since no reaction was observed after 16 h under CO atmosphere (1.5 atm) at either room temperature or 90 °C. The reaction of **4a** with xylyl isocyanide (XyNC) at room temperature afforded 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 led to a complex mixture of products. It is worth noting that the products **18** and **19** contain a palladium center bonded simultaneously to sp-, sp^2-, and sp^3-hybridized

DOI: 10.1021/acs.organomet.7b00702
Organometallics XXXX, XXX, XXX−XXX

Scheme 11. Attempts To Isolate Organometallic Intermediates Arising from the Insertion of Benzyne and DMAD



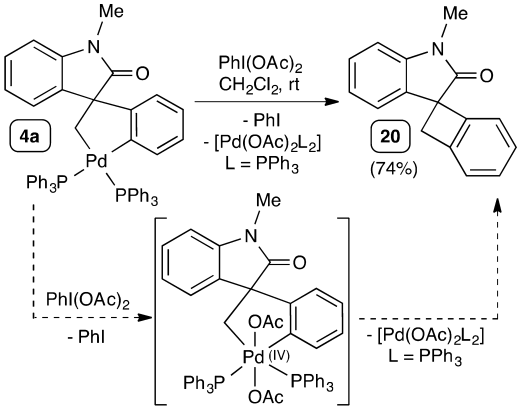
Scheme 12. Reactions of Complex 4a with XyNC



C-donors. For complex **18** we propose that the XyNC ligand is coordinated trans to the aryl group, similarly to other Pd(II) complexes containing a C_{sp^2}-donor, PPh_3, and an isocyanide.[13d]

In addition to the reactivity of the intermediate **4a** toward unsaturated species, we investigated the behavior of this complex toward an oxidant such as $PhI(OAc)_2$. The reaction of **4a** with $PhI(OAc)_2$ at room temperature gave rise to the strained [4,5]-spirocycle **20** (Scheme 13). Very likely, the oxidant promoted the formation of a Pd(IV) intermediate in

Scheme 13. Oxidative C−C Coupling Promoted by $PhI(OAc)_2$



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]

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 types 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, favor 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 at first 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 spiro-oxoindole scaffold) are not the rate-limiting steps of the cycle, since they take place rapidly at room temperature.

EXPERIMENTAL SECTION

Infrared spectra were recorded on a PerkinElmer 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 spectrometer in

DOI: 10.1021/acs.organomet.7b00702
Organometallics XXXX, XXX, XXX−XXX

$CDCl_3$ 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. Chromatographic 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 a 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 to leave ca. 4 mL, and Et_2O (20 mL) was added. The resulting suspension was filtered, and the solid was washed with Et_2O (2 × 2 mL) and air-dried to give compound **2a** as a gray 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 an 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′-*tert*-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 a 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 × 5 mL) and air-dried to give compound **2b** as a yellow solid. Yield: 877 mg, 1.19 mmol, 71%. Mp: 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). Anal. 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·1/2H₂O. $Pd(dba)_2$ (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 a 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 × 5 mL) and air-dried to give compound **2c**·1/2H_2O as an orange solid. Yield: 341 mg, 0.573 mmol, 63%. Mp: 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). Anal. 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 a 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 the tube was cooled, the crude product 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 min. A yellow solid precipitated slowly. The suspension was filtered, and the solid was washed with ether (2 × 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). Anal. 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 crystals 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 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 × 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 crystals 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 ^1H, ^{13}C, and ^{31}P NMR, and the 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 × 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 product was purified by preparative TLC (silica gel, petroleum ether/EtOAc (10/1)) to give compound **12** as a pale yellow oil. Yield: 8.3 mg, 0.04 mmol, 58%. ^1H NMR (300.1 MHz, $CDCl_3$): δ 7.35 (dd, J = 7.8, 1.6 Hz, 1H), 7.30−

DOI: 10.1021/acs.organomet.7b00702
Organometallics XXXX, XXX, XXX−XXX

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 a 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** are as follows. 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, and the 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 × 5 mL) and air-dried to give complex **14b**·1/2MeCN as an off-white solid. Yield: 44 mg, 0.056 mmol, 82%. Mp: 155 °C dec. Λ_M = 117.0 Ω^{-1} cm^2 mol^{-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). Anal. 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 × 5 mL) and air-dried to give **14c**·1/4CH_2Cl_2. Yield: 92 mg, 0.151 mmol, 68%. Mp: 151 °C dec. Λ_M = 124.3 Ω^{-1} cm^2 mol^{-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, crystallization 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). Anal. 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 acetylenedicarboxylate (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. Mp: 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, and the 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 min. The suspension was filtered, and the solid was washed with Et_2O (2 × 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). Anal. 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 leave 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 × 5 mL) and air-dried to give **19** as a yellow solid. Yield: 20 mg, 0.03 mmol, 55%. Mp: 164−166 °C. ^{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,

DOI: 10.1021/acs.organomet.7b00702
Organometallics XXXX, XXX, XXX−XXX

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). Anal. 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 °C. ^1H 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 at DOI: 10.1021/acs.organomet.7b00702.

^1H, ^{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)

Accession Codes

CCDC 1574286−1574289 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail for M.L.: mlautens@chem.utoronto.ca.
*E-mail for J.-A.G.-L.: joangalo@um.es.

ORCID

Isabel Saura-Llamas: 0000-0001-8335-6747
José-Antonio García-López: 0000-0002-8143-7081

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from MINECO (grant CTQ2015-69568-P) and Fundación Séneca (grant 19890/GERM/15) is gratefully acknowledged. M.L. thanks NSERC Canada, Alphora Inc., and the University of Toronto for financial support. We thank Prof. Vicente Soler, Dr. Ivan Franzoni, and Mr. Hyung Yoon for useful comments and discussion.

■ REFERENCES

(1) For reviews on C−H activation see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (c) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468−3517. (d) Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 2−24. (e) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900−2936. (f) Della Ca, N.; Fontana, M.; Motti, E.; Catellani, M. *Acc. Chem. Res.* **2016**, *49*, 1389−1400. (g) Hartwig, J. F.; Larsen, M. A. *ACS Cent. Sci.* **2016**, *2*, 281−292. (h) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *117*, 8754−8786.

(2) (a) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3−6. (b) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518−522. (c) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053−1064. (d) Patra, T.; Bag, S.; Kancherla, S.; Mondal, A.; Dey, A.; Pimparkar, S.; Agasti, S.; Modak, A.; Maiti, D. *Angew. Chem., Int. Ed.* **2016**, *55*, 7751−7755. (e) Topczewski, J. T.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. *Nature* **2016**, *531*, 220−224. (f) Yada, A.; Liao, W.; Sato, Y.; Murakami, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 1073−1076. (g) Dutta, U.; Modak, A.; Bhaskararao, B.; Bera, M.; Bag, S.; Mondal, A.; Lupton, D. W.; Sunoj, R. B.; Maiti, D. *ACS Catal.* **2017**, *7*, 3162−3168. (h) Zhang, Z.; Tanaka, K.; Yu, J.-Q. *Nature* **2017**, *543*, 538−542.

(3) For examples of transient directing groups used in remote C−H activation see: (a) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. *Science* **2016**, *351*, 252−256. (b) Xu, Y.; Young, M. C.; Wang, C.; Magness, D. M.; Dong, G. *Angew. Chem., Int. Ed.* **2016**, *55*, 9084−9087. (c) Wu, Y.; Chen, Y.-Q.; Liu, T.; Eastgate, M. D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 14554−14557. (d) Liu, Y.; Ge, H. *Nature Chemistry* **2017**, *9*, 26−32. (e) Davis, H. J.; Phipps, R. J. *Chem. Sci.* **2017**, *8*, 864−877. (f) St John-Campbell, S.; White, A. J. P.; Bull, J. A. *Chem. Sci.* **2017**, *8*, 4840−4847.

(4) (a) Grigg, R.; Fretwell, P.; Meerholtz, C.; Sridharan, V. *Tetrahedron* **1994**, *50*, 359−370. (b) *Metal catalyzed cascade reactions*; Müller, J. J. T., Ed.; Springer: Berlin, 2006; Topics in Organometallic Chemistry *19*. (c) Ruck, R. T.; Huffman, M. A.; Kim, M. M.; Shevlin, M.; Kandur, W. V.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4711−4714. (d) Satyanarayana, G.; Maichle-Mossmer, C.; Maier, M. E. *Chem. Commun.* **2009**, 1571−1573. (e) Piou, T.; Neuville, L.; Zhu, J. *Org. Lett.* **2012**, *14*, 3760−3763. (f) Piou, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11561−11565. (g) Piou, T.; Bunescu, A.; Wang, Q.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12385−12389. (h) Mehta, V. P.; García-López, J.−A. *ChemCatChem* **2017**, *9*, 1149−1156.

(5) For recent examples of Pd-catalyzed cascade reactions see: (a) Fan, J.-H.; Wei, W.-T.; Zhou, M.-B.; Song, R.-J.; Li, J.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 6650−6654. (b) Davis, D. C.; Walker, K. L.; Hu, C.; Zare, R. N.; Waymouth, R. M.; Dai, M. *J. Am. Chem. Soc.* **2016**, *138*, 10693−10699. (c) Kong, W.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 9714−9718. Qiu, Y.; Yang, B.; Zhu, C.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2016**, *55*, 6520−6524. (d) Frutos-Pedreño, R.; García-López, J.-A. *Adv. Synth. Catal.* **2016**, *358*, 2692−2700. (e) Petrone, D. A.; Franzoni, I.; Ye, J.; Rodríguez, J. F.; Poblador-Bahamonde, A. I.; Lautens, M. *J. Am. Chem. Soc.* **2017**, *139*, 3546−3557. (f) Qiu, Y.; Yang, B.; Jiang, T.; Zhu, C.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2017**, *56*, 3221−3225.

(6) Pérez-Gómez, M.; García-López, J.-A. *Angew. Chem., Int. Ed.* **2016**, *55*, 14389−14393.

(7) (a) Yoon, H.; Lossouarn, A.; Landau, F.; Lautens, M. *Org. Lett.* **2016**, *18*, 6324−6327. (b) Yoon, H.; Rölz, M.; Landau, F.; Lautens, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 10920.

(8) Pérez-Gómez, M.; Hernández-Ponte, S.; Bautista, D.; García-López, J.-A. *Chem. Commun.* **2017**, *53*, 2842−2845.

(9) (a) Zheng, H.; Zhu, Y.; Shi, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 11280−11284. (b) Shao, C.; Wu, Z.; Ji, X.; Zhou, B.; Zhang, Y. *Chem. Commun.* **2017**, *53*, 10429.

(10) Ye, J.; Shi, Z.; Sperger, T.; Yasukawa, Y.; Kingston, C.; Schoenebeck, F.; Lautens, M. *Nat. Chem.* **2016**, *9*, 361−368.

(11) (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748−8758. (b) Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; Gonzalez-Páez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H.-P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175−1180. (c) Chowdhury, S.; Chafeev, M.; Liu, S.; Sun, J.; Raina, V.; Chui, R.; Young, W.; Kwan, R.; Fu, J.; Cadieux, J. A. *Bioorg. Med.*

DOI: 10.1021/acs.organomet.7b00702
Organometallics XXXX, XXX, XXX−XXX

Chem. Lett. **2011**, *21*, 3676−3681. (d) Wang, S.; Sun, W.; Zhao, Y.; McEachern, D.; Meaux, I.; Barriere, C.; Stuckey, J. A.; Meagher, J. L.; Bai, L.; Liu, L.; Hoffman-Luca, C. G.; Lu, J.; Shangary, S.; Yu, S.; Bernard, D.; Aguilar, A.; Dos-Santos, O.; Besret, L.; Guerif, S.; Pannier, P.; Gorge-Bernat, D.; Debussche, L. *Cancer Res.* **2014**, *74*, 5855−5865. (e) Yu, B.; Yu, D. Q.; Liu, H. M. *Eur. J. Med. Chem.* **2015**, *97*, 673−698.

(12) The intramolecular 5-exo-trig carbopalladation is favored over the 6-endo-trig cyclization due to steric reasons; hence, the formation of five-membered carbo- or heterocyclic rings has been deeply described in the literature: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. For further examples see the articles of ref 4 in this paper.

(13) For selected references dealing with transphobia see: (a) Oliva-Madrid, M.-J.; García-López, J.-A.; Saura-Llamas, I.; Bautista, D.; Vicente, J. *Organometallics* **2014**, *33*, 33−39. (b) Vicente, J.; Arcas, A.; Gálvez-López, M.-D.; Juliá-Hernández, F.; Bautista, D.; Jones, P. G. *Organometallics* **2008**, *27*, 1582−1590. (c) Vicente, J.; Abad, J. A.; Hernández-Mata, F. S.; Rink, B.; Jones, P. G.; Ramírez de Arellano, M. C. *Organometallics* **2004**, *23*, 1292−1304. (d) Vicente, J.; Abad, J.-A.; López-Serrano, J.; Jones, P. G. *Organometallics* **2004**, *23*, 4711−4722. (e) Vicente, J.; Abad, J. A.; Frankland, A. D.; López-Serrano, J.; Ramírez de Arellano, M. C.; Jones, P. G. *Organometallics* **2002**, *21*, 272−282. (f) Vicente, J.; Arcas, A.; Bautista, D.; Jones, P. G. *Organometallics* **1997**, *16*, 2127−2138.

(14) (a) Cámpora, J.; López, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 147−151. (b) Bennett, M. A.; Macgregor, S.; Wenger, E. *Helv. Chim. Acta* **2001**, *84*, 3084−3104. (c) Cámpora, J.; Llebaría, A.; Moretó, J. M.; Poveda, M. L.; Carmona, E. *Organometallics* **1993**, *12*, 4032−4038. (d) Carmona, E.; Gutiérrez-Puebla, E.; Marín, J. M.; Monge, A.; Paneque, M.; Poveda, M. L.; Ruiz, C. *J. Am. Chem. Soc.* **1989**, *111*, 2883−2891.

(15) (a) Cochran, B. M.; Michael, F. E. *J. Am. Chem. Soc.* **2008**, *130*, 2786−2792. (b) García-López, J.-A.; Oliva-Madrid, M.-J.; Saura-Llamas, I.; Bautista, D.; Vicente, J. *Organometallics* **2012**, *31*, 6351−6364. (c) Ortiz de la Tabla, L.; Matas, I.; Álvarez, E.; Palma, P.; Cámpora, J. *Dalton Trans.* **2012**, *41*, 14524−14539.

(16) For Pd-catalyzed carboiodination of alkenes see: (a) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 1778−1780. (b) Newman, S. G.; Howell, J. K.; Nicolaus, N.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14916−14919. (c) Liu, H.; Li, C.; Qiu, D.; Tong, X. *J. Am. Chem. Soc.* **2011**, *133*, 6187−6193. (d) Liu, H.; Chen, C.; Wang, L.; Tong, X. *Org. Lett.* **2011**, *13*, 5072−5075. (e) Jia, X.; Petrone, D. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9870−9872. (f) Petrone, D. A.; Malik, H. A.; Clemenceau, A.; Lautens, M. *Org. Lett.* **2012**, *14*, 4806−4809. (g) Petrone, D. A.; Lischka, M.; Lautens, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10635−10638. (h) Petrone, D. A.; Yoon, H.; Weinstabl, H.; Lautens, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 7908−7912. (i) Petrone, D. A.; Ye, J.; Lautens, M. *Chem. Rev.* **2016**, *116*, 8003−8104.

(17) (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315−1345. (b) Davies, D. L.; Mcgregor, S. A.; McMullin, C. L. *Chem. Rev.* **2017**, *117*, 8649−8709.

(18) (a) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403−424. (b) Albrecht, M. *Chem. Rev.* **2010**, *110*, 576−623. (c) Vicente, J.; Saura-Llamas, I.; Oliva-Madrid, M.-J.; García-López, J.-A.; Bautista, D. *Organometallics* **2011**, *30*, 4624−4631.

(19) (a) García-López, J.-A.; Oliva-Madrid, M.-J.; Saura-Llamas, I.; Bautista, D.; Vicente, J. *Chem. Commun.* **2012**, *48*, 6744−6746. (b) Oliva-Madrid, M.-J.; Saura-Llamas, I.; Bautista, D.; Vicente, J. *Chem. Commun.* **2013**, *49*, 7997−7999. (c) Oliva-Madrid, M.-J.; García-López, J.-A.; Saura-Llamas, I.; Bautista, D.; Vicente, J. *Organometallics* **2014**, *33*, 6420−6430.

(20) (a) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698−2779. (b) Vicente-Hernández, I.; Chicote, M.-T.; Vicente, J.; Bautista, D. *Organometallics* **2016**, *35*, 1107−1113. (c) Vicente, J.; González-Herrero, P.; Frutos-Pedreño, R.; Chicote, M.-T. *Organometallics* **2011**, *30*, 1079−1093. (d) Sergeev, A. G.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2008**, *130*, 15549−15563.

(21) Similar results where found by Cámpora and co-workers in the reactions of a related five-membered C_{sp^2},C_{sp^3}-palladacycle with CO and RNC: Cámpora, J.; López, J. A.; Palma, P.; del Rio, D.; Carmona, E.; Valerga, P.; Graiff, C.; Tiripicchio, A. *Inorg. Chem.* **2001**, *40*, 4116−4126.

(22) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402−3415.

(23) Katayev, D.; Jia, Y.-X.; Sharma, A. K.; Banerjee, D.; Besnard, C.; Sunoj, R. B.; Kündig, E. P. *Chem. - Eur. J.* **2013**, *19*, 11916−11927.

DOI: 10.1021/acs.organomet.7b00702
Organometallics XXXX, XXX, XXX−XXX