

Controlling the Ambiphilic Nature of σ -Arylpalladium Intermediates in Intramolecular Cyclization Reactions

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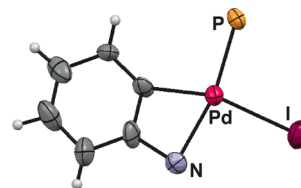
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CONSPECTUS

The reactivity of main group organometallics, such as organolithium compounds (RLi) and Grignard reagents (RMgX), is quite straightforward. In these species the R group usually exhibits nucleophilic reactivity without any possibility of inducing electrophilic character. In contrast, in organopalladium complexes, researchers can switch the reactivity from electrophilic to nucleophilic relatively simply. Although σ -aryl and σ -vinylpalladium complexes are commonly used as electrophiles in C–C bond-forming reactions, recent research has demonstrated that they can also react with carbon–heteroatom multiple bonds in a nucleophilic manner. Nevertheless, researchers have completely ignored the issue of controlling the ambiphilic nature of such species.



One ring to bring them all...

This Account describes our efforts toward selectively promoting the same starting materials toward either electrophilic α -arylation or nucleophilic addition reactions to different carbonyl groups. We could tune the properties of the σ -arylpalladium intermediates derived from amino-tethered aryl halides and carbonyl compounds to achieve chemoselective transformations. Therefore, chemists can control the ambiphilic nature of such intermediates and, consequently, the competition between the alternative reaction pathways by the adequate selection of the reaction conditions and additives (base, presence/absence of phenol, bidentate phosphines). The nature of the carbonyl group (aldehydes, ketones, esters, and amides) and the length of the tether connecting it to the aniline moiety also play an important role in the outcome of these processes.

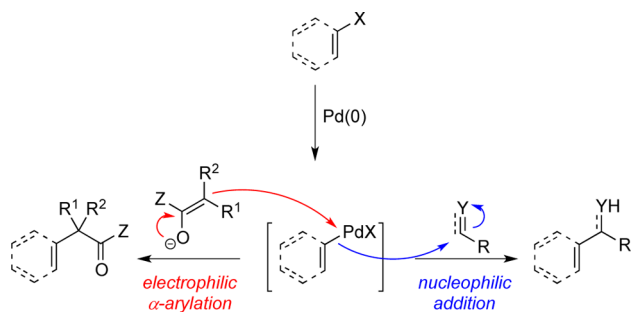
Our joint computational and experimental efforts to elucidate the reaction mechanism of these palladium-catalyzed transformations suggest that beyond the formation of the four-membered azapalladacycle, two major factors help to control the dual character of the palladium(II) intermediates derived from 2-haloanilines. First, their high nucleophilicity strongly modifies the interaction of the metal center with the carbonyl group. Second, the additive phenol exchanges the iodide ligand to give an arylpalladium(II) phenoxide complex, which has a beneficial effect on the arylation. The formation of this transient intermediate not only stabilizes the arylpalladium moiety, thus preventing the nucleophilic attack at the carbonyl group, but also assists the enolization reaction, which takes place in a more favorable intramolecular manner.

The azapalladacycle intermediate is, in the words of J. R. R. Tolkien, “the one ring to bring them all and in the darkness to bind them.” With this intermediate, we can easily achieve the synthesis of a variety of heterocyclic systems by selectively promoting electrophilic α -arylation or nucleophilic addition reactions from the same precursors.

Introduction

While the nucleophilic addition of main group organometallics to carbonyl compounds is a very common and useful reaction, the addition of organopalladiums to carbonyl derivatives represents an uncommon transformation. Indeed, the intermediacy of σ -aryl and σ -vinylpalladium species in C–C bond-forming processes is usually based on their electrophilic nature. Among the palladium-catalyzed annulation

processes, the α -arylation of carbonyl compounds has emerged as an extremely powerful methodology for the synthesis of heterocyclic systems. Recent research, however, has demonstrated that in organopalladium complexes, switching the usual reactivity from electrophilic to nucleophilic is relatively simple since the same palladium intermediates can also react with carbon–heteroatom multiple bonds in a nucleophilic manner (Scheme 1). Although these

SCHEME 1. Ambiphilic Character of σ -Organopalladium Species

addition reactions are still rare, they are growing in popularity because the increased diversity they give to organopalladium compounds is highly beneficial for organic synthesis.¹

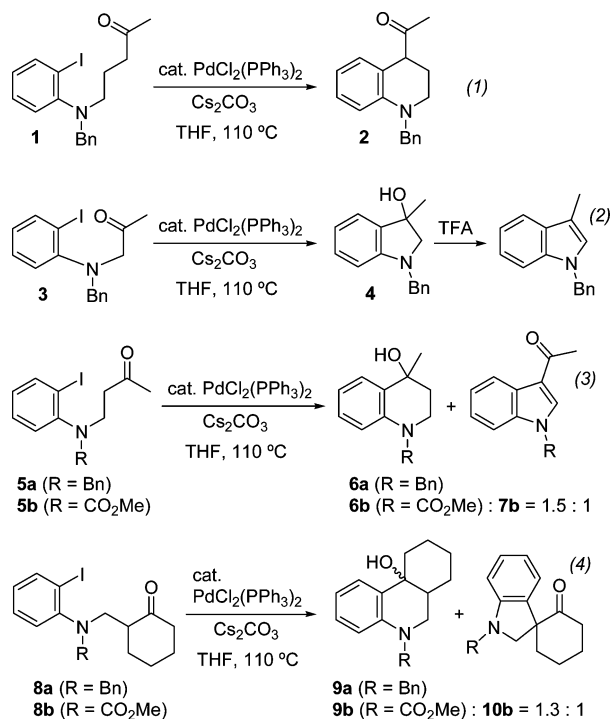
Since the seminal report by Heck and co-workers describing a single example of palladium-catalyzed annulation of σ -iodobenzaldehyde and alkynes to give indenones,² the number of publications on the intramolecular nucleophilic addition of σ -vinyl and σ -arylpalladium species to aldehydes³ and ketones^{4,5} has steadily increased. Their direct coupling with nitriles,⁶ imines,⁷ and isocyanates⁸ has also led to the development of new reliable catalytic processes. In contrast, the nucleophilic attack of these species on the less electrophilic ester and amide carbonyls has been almost completely ignored.⁹

Moreover, despite the inherent interest of being able to control the potential ambiphilic character of aryl and vinylpalladium intermediates, when we began our work in this field, to our knowledge, no attempts had been made to selectively promote both the electrophilic and nucleophilic reactivity from the same starting material. This Account describes our research on the ambiphilic character of σ -arylpalladium species in intramolecular palladium-catalyzed coupling reactions. Emphasis has been placed on a deeper understanding of the reaction mechanisms involved in these processes by using a combination of experimental and computational tools. The challenge was sequentially addressed through the following steps.

Intramolecular Pd-Catalyzed Reactions of Amino-Tethered Aryl Halides and Ketones

More than 10 years ago, we decided to explore the intramolecular palladium-catalyzed coupling of aryl halides and ketones¹⁰ as a methodology for the synthesis of aza-heterocycles. Our initial efforts were focused on developing an optimum set of reaction conditions for the intramolecular coupling of (2-haloanilino)ketones.¹¹ We observed that these substrates show remarkable structure-dependent behavior when undergoing palladium-catalyzed cyclization.¹²

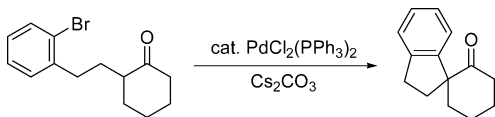
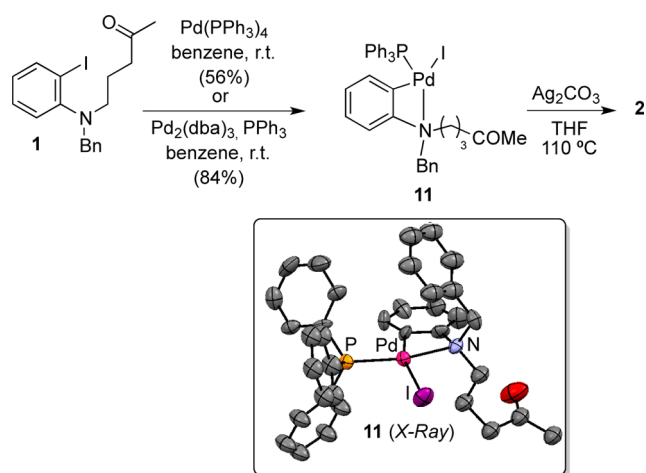
SCHEME 2. Pd(0)-Catalyzed Reactions of (2-Haloanilino)ketones



Thus, treatment of γ -(anilino)ketone **1** with $\text{PdCl}_2(\text{PPh}_3)_2$ and Cs_2CO_3 afforded the α -arylation compound **2** (Scheme 2, eq 1). In contrast, under the same reaction conditions, α -(anilino)ketone **3** and β -(anilino)ketone **5a** exclusively afforded alcohols **4** and **6a**, respectively, as a result of the addition of the palladium intermediate to the ketone carbonyl group (Scheme 2, eqs 2 and 3). In the case of β -(anilino)ketones, changing the substituent at the nitrogen from alkyl to alkoxy carbonyl resulted in a competition between the nucleophilic addition to the carbonyl and the α -arylation, regardless of the substrate structure (Scheme 2, eqs 3 and 4).¹³

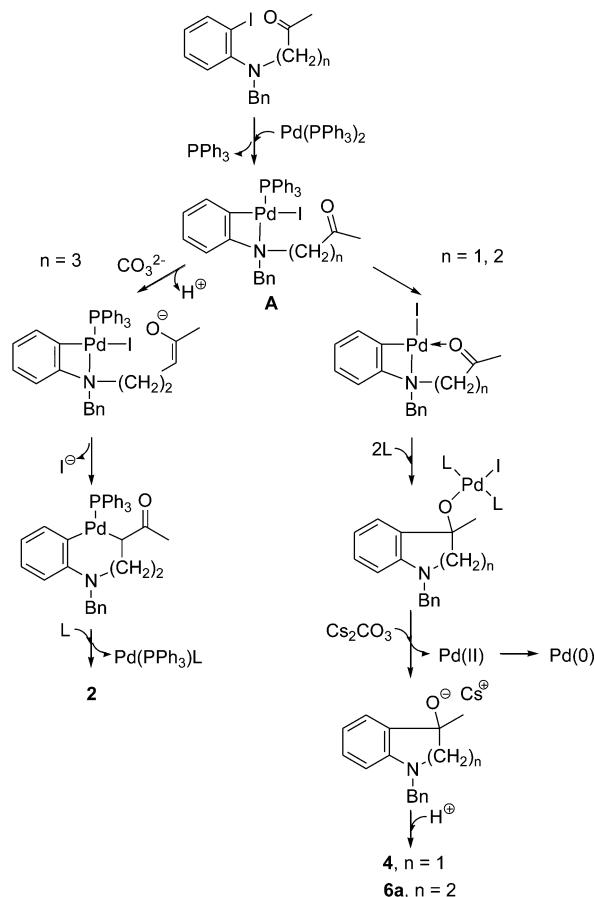
Interestingly, both the intramolecular enolate arylation¹⁴ and addition of aryl halides to ketones catalyzed by $\text{Pd}(0)$ ^{5a} had been previously reported in the carbocyclic series. However, these two reactions seemed to operate quite independently of each other, and no competition between the two processes had been observed.¹⁵ It proved illuminating to compare the results obtained in our work with β -(anilino)ketones (Scheme 2, eq 4) with those reported by Muratake and co-workers in the carbocyclic series (Scheme 3).¹⁴ It was immediately obvious that the change in the reaction pathway was strongly related to the presence of the nitrogen atom in our substrates.

To gain more insight into the above palladium-catalyzed cyclizations, we attempted the isolation of the σ -arylpalladium complexes, the purported intermediates in these

SCHEME 3. Pd(0)-Catalyzed α -Arylation of Carbocyclic Ketones**SCHEME 4.** Synthesis of the Four-Membered Palladacycle **11** and Its α -Arylation Reaction

reactions. Interestingly, γ -(2-iodoanilino)ketone **1** reacted with equimolar amounts of zerovalent palladium sources in the presence of PPh_3 to give the four-membered palladacycle **11**, whose structure was unambiguously confirmed by X-ray crystallography (Scheme 4). The intermediacy of azapalladacycle **11** in the α -arylation of ketone **1** was confirmed when the cyclization was promoted by treatment with Ag_2CO_3 in THF at high temperature.¹³ Similar reactions were observed starting from other γ -(anilino)ketones. In contrast, when both α - and β -(anilino)ketones were treated with zerovalent palladium sources to obtain the corresponding azapalladacycles, their behavior was completely different. In both cases, the alcohols resulting from the nucleophilic addition to the carbonyl were directly obtained, while the corresponding four-membered azapalladacycles were never isolated.

On the basis of these results, the reaction pathway dichotomy (namely, the enolate arylation vs the attack at the carbonyl group) in the palladium-catalyzed reactions of (2-haloanilino)ketones was initially rationalized by the intermediacy of the four-membered azapalladacycles (**A**), in which the interaction of the metal center with the carbonyl group is chain-length dependent (Scheme 5). While shorter carbon tethers ($n = 1, 2$) would favor the nucleophilic attack of the arylpalladium metallacycle **A** at the carbonyl group, longer carbon tethers ($n = 3$) would allow the electrophilic attack of the enolate at the palladium center. The easy

SCHEME 5. Initially Proposed Mechanisms for the Intramolecular Pd(0)-Catalyzed α -Arylation and Ketone Carbonyl Addition of (2-Haloanilino)ketones

addition to the carbonyl group in β - and α -(anilino)ketones ($n = 2$ and $n = 1$, respectively) would be a consequence of the coordination of the amino group to the palladium atom, which brings the carbonyl group in close proximity to the metal. This would facilitate the formation of a transient $\text{C}=\text{O}$ chelated intermediate, which would afford a Pd(II) alkoxide via carbopalladation. On the contrary, for γ -(anilino)ketones ($n = 3$), the formation of the $\text{C}=\text{O}$ chelated intermediate would be more difficult (i.e., a larger ring is created), allowing the corresponding four-membered azapalladacycle to undergo the α -arylation reaction.

To support our hypotheses, the competition between the α -arylation and the nucleophilic addition reaction pathways of (2-haloanilino)ketones was explored by means of density functional theory (DFT) calculations.¹⁶ Figure 1 gathers the corresponding reaction profiles starting from complex **1M**. This intermediate is initially formed from a model β -(2-iodoanilino)ketone, in which the benzyl group has been replaced by a hydrogen atom, after the corresponding oxidative addition process. Our calculations suggest that

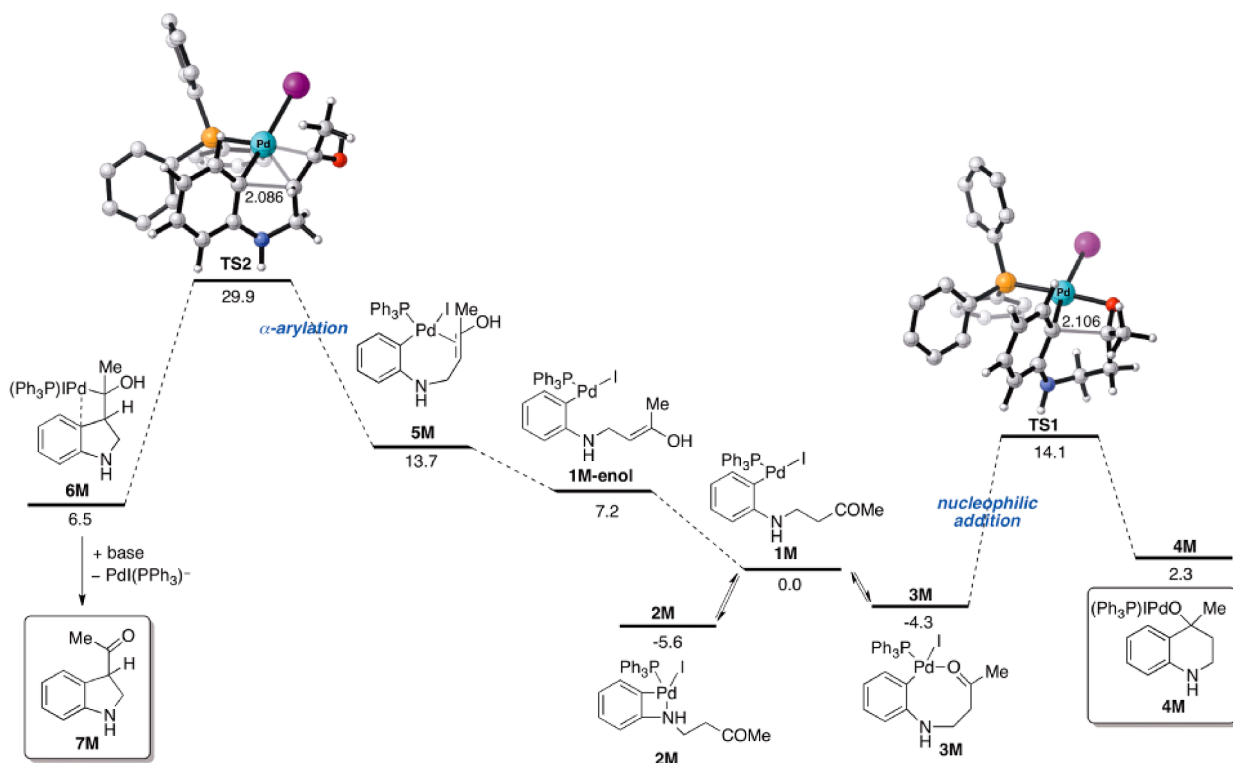


FIGURE 1. Computed reaction profiles for model ketone **1M**. Free energies (ΔG_{298}) are given in kcal/mol and bond distances in angstroms. Hydrogen atoms at the PPh_3 ligand were omitted for clarity. All data have been computed at the PCM(tetrahydrofuran)-B3LYP/def2-SVP level.

1M may evolve to the metallacyclobutane intermediate **2M** by coordination of the amino group to the palladium center or, alternatively, it can be easily transformed into complex **3M**, where the oxygen atom of the carbonyl moiety is coordinated to the transition metal. These species are in equilibrium in view of the computed low interconversion barriers (<8 kcal/mol).¹⁶ From complex **3M**, the nucleophilic addition reaction to the carbonyl group occurs through the transition state **TS1** (activation barrier of $\Delta G_{298}^{\ddagger} = 18.4$ kcal/mol), producing the tetrahydroquinoline **4M**. The latter intermediate would be easily converted into the corresponding alcohol, the analogue of the experimentally observed product **6a**, by protonolysis of the O–Pd bond.

Alternatively, the enolic species **1M-enol**, formed from **1M** in an endergonic process ($\Delta G_{298} = 7.2$ kcal/mol), can coordinate the transition metal through its double bond to form the π -complex **5M**. This species evolves to the five-membered ring complex **6M** through the transition state **TS2** (activation barrier of $\Delta G_{298}^{\ddagger} = 16.2$ kcal/mol), which is associated with the α -arylation process, in an exergonic transformation ($\Delta G_{298} = -7.2$ kcal/mol). Complex **6M** would then be transformed into **7M** (the analogue of the α -arylation product) via a base-mediated process. Furthermore, the α -arylation reaction may also occur through the

corresponding enolate complex **8M** formed from **1M-enol**. In this case, **7M** is produced through **TS3** with an activation barrier of 18.6 kcal/mol (Figure 2).

Our calculations suggest that although the metallacyclobutane intermediate is formed under the reaction conditions, it does not directly lead to either of the two competitive processes. Moreover, from the computed data, one would expect the exclusive formation of the nucleophilic addition product, as we experimentally observed in the reaction of **5a** (Scheme 2, eq 3). The high chemoselectivity of this reaction is mainly due to the energetic cost associated with the endergonic enolization process that hampers the pathways leading to the corresponding α -arylation product (via **TS2** or **TS3**). In contrast, the α -arylation products are also formed in the reactions of substrates bearing a CO_2Me group at the aniline nitrogen atom (Scheme 2). This is a consequence of the electron-withdrawing effect of this group, which avoids the π -delocalization of the lone pair of the nitrogen atom into the aryl ring. As a result, the nucleophilicity of the reactive aryl carbon atom is dramatically reduced, making the addition reaction (via **TS1**) far more difficult (i.e., with a higher activation barrier). Under these conditions, the α -arylation is now competitive, and a mixture of reaction products is observed.

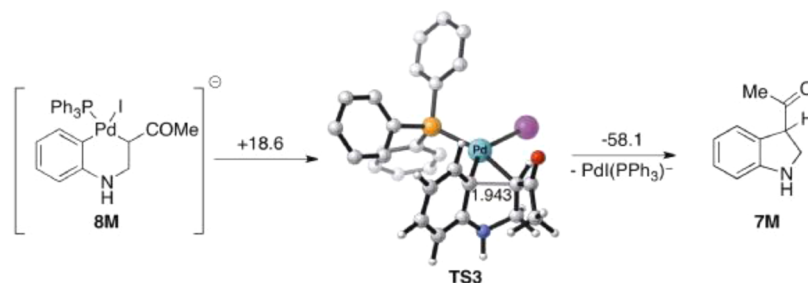


FIGURE 2. α -Arylation from complex **8M**. See caption for Figure 1 for additional details.

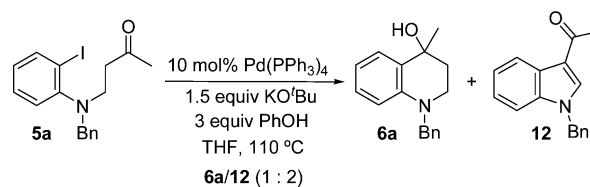
Finally, our calculations also confirm that the length of the tether joining the amino and carbonyl groups is decisive for the outcome of the process. Thus, for the analogous γ -(anilino)ketone ($n = 3$) the nucleophilic addition barrier via **TS1** becomes much higher ($\Delta G_{298}^\ddagger = 21.7$ kcal/mol), making this process kinetically more difficult.¹⁶

Continuing our research on this chemistry, we hypothesized that if we were able to stabilize the arylpalladium(II) moiety and also significantly increase the enolization of the ketone, we could overcome the nucleophilic attack at the carbonyl and favor the α -arylation reaction. Interestingly, we had observed the effectiveness of potassium phenoxide¹⁷ as the base for promoting the palladium-catalyzed intramolecular coupling of amino-tethered vinyl or aryl halides with enolate-type nucleophiles.¹⁸ So, we aimed to capitalize on the beneficial effect of the phenoxide anion to force the α -arylation reaction from β -(2-iodoanilino)-ketone **5a**, a substrate that exclusively undergoes the nucleophilic addition to the carbonyl.

We found that annulation reactions of **5a** using $\text{Pd}(\text{PPh}_3)_4$ as the catalyst in the presence of phenol invariably afforded mixtures of alcohol **6a** and indole **12**, the latter arising from the palladium-catalyzed dehydrogenation of the initially formed indoline. The best ratio of arylation/nucleophilic addition products (2:1) was obtained with KO^tBu as the base in the presence of an excess of phenol in THF (Scheme 6).¹⁹

This result indicates that a different α -arylation reaction mechanism, which efficiently competes with the nucleophilic addition, must occur in the presence of phenol. Indeed, DFT calculations show that the enolization process from **1M-OPh**, formed by the exergonic phenoxy-iodide ligand exchange in **1M**, becomes much more favorable ($\Delta\Delta G_{298} = -9.7$ kcal/mol, Figure 3). From the enolic species **1M-OPh-enol**, the α -arylation reaction occurs through **TS2-OPh** to produce **6M-OPh**, which would be transformed into indoline **7M**, the precursor of the experimentally observed indole, via a base-mediated process. Nevertheless, we located an alternative and more favorable pathway from

SCHEME 6. Pd(0)-Catalyzed α -Arylation of Ketone **5a**



1M-OPh-enol on the potential energy surface. Thus, an intramolecular proton transfer from the OH moiety of **1M-OPh-enol** to the phenoxy ligand leads to intermediate **9M**. As a consequence of the low donor ability of the PhOH ligand, the Pd–O interaction in **9M** is relatively weak (computed Wiberg bond index of only 0.15), which permits the easy dissociation ($\Delta G_{298} = -8.4$ kcal/mol) of PhOH to form intermediate **10M**. This species finally evolves to indoline **7M** via the transition state **TS4**.

Once the role of the phenoxy additive was established, further exploration showed that a complete reversal in chemoselectivity to favor the α -arylation reaction from ketone **5a** could be achieved by simply changing the ligand on palladium. When PPh_3 was replaced by xantphos, ketone **12** was obtained in 80% yield in a highly chemoselective transformation (i.e., **6a/12** = 1:14.5). Similarly, the use of binap also favored the α -arylation product (**6a/12** = 1:3.9).¹⁹

Interestingly, the competition between α -arylation and the nucleophilic attack on the ketone carbonyl was also observed in the palladium-catalyzed cyclization of α -amino-ketone **13a** (Table 1).²⁰

Thus, the use of binap for the cyclization of iodindole **13a** resulted in the formation of a nearly equimolar mixture of ketone **14a** and alcohol **15**. Although we were unable to increase the ratio of the α -arylation product, the nucleophilic addition to the carbonyl became the only apparent reaction when using dppe as the ligand. As mentioned above, in 2-iodoanilines the delocalization of the nitrogen lone pair in the aryl π -system increases the nucleophilicity of the reactive carbon atom, thus favoring the attack at the carbonyl

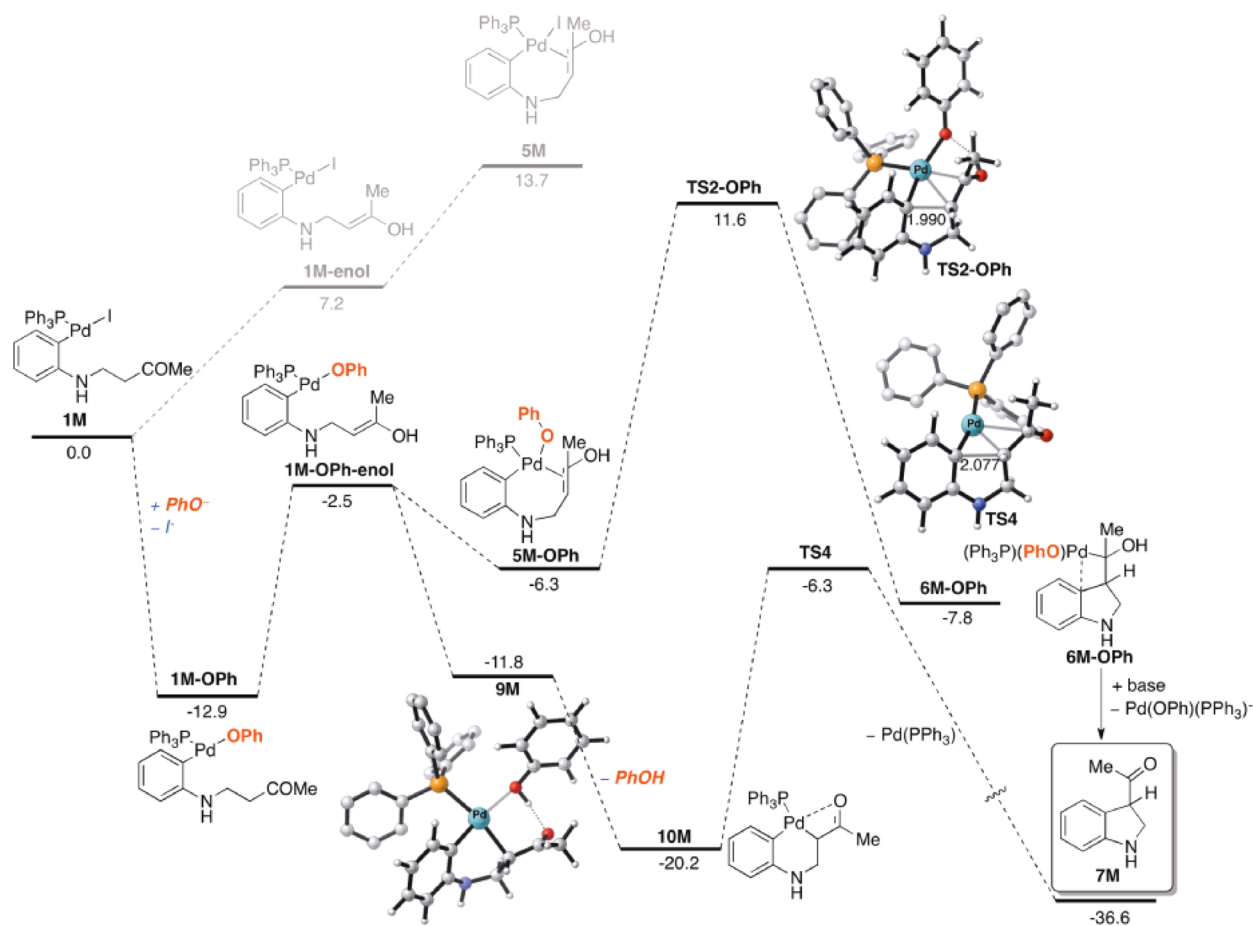


FIGURE 3. Computed reaction profiles for model ketone **1M** in the presence of PhO^- . See caption for Figure 1 for additional details.

TABLE 1. Pd(0)-Catalyzed Reactions of Ketones **13a,b**

13a (R: Me)
 $\text{13b (R: SO}_2\text{Ph)}$

14a (R: Me)
 $\text{14b (R: SO}_2\text{Ph)}$

15

ketone	catalyst	ligand	products (yield)
13a	$\text{Pd}_2(\text{dba})_3$	 binap	14a (31%), 15 (35%)
13a	$\text{Pd}(\text{OAc})_2$	 dppe	15 (48%)
13b	$\text{Pd}_2(\text{dba})_3$	binap	14b (58%)

group.¹⁶ As a similar delocalization operates in 3-haloindoles, we realized that by significantly decreasing the nucleophilicity

of the indole C-3 position, the α -arylation process could be favored instead. Indeed, the nucleophilic addition to the

ketone carbonyl was not observed in the reactions of *N*-phenylsulfonylindole **13b**, which exclusively afforded **14b** (Table 1).

Pd-Catalyzed Reactions of (2-Iodoanilino) Aldehydes

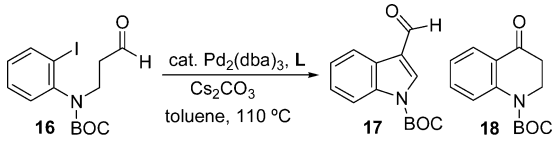
We expanded our work on the ambiphilic character of σ -arylpalladium species by exploring the reactions of amino-tethered aryl halides and aldehydes. Both the intramolecular palladium-catalyzed α -arylation of aldehydes²¹ and acylation of aryl halides by aldehydes²² had also been previously reported in the carbocyclic series. However, although one example of competition between the two processes had been reported,^{21a} the switch from one reaction mode to the other starting from the same precursor had not been explored prior our report.²³

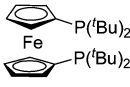
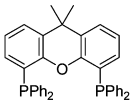
In these palladium-catalyzed cyclization reactions, we chose β -(anilino)aldehyde **16** as a model for investigating the control over chemoselectivity. It was found that the acylation process was the preferred reaction pathway in the presence of bulky monodentate phosphines, with a direct correlation between the phosphine cone angle and the observed chemoselectivity (Table 2).²³ Interestingly, the best acylation-to- α -arylation ratio was obtained with dtpf, which afforded ketone **18** in 65% yield in a highly chemoselective transformation. Although it contains two phosphorus donors, dtpf is probably ligated to the metal in a κ^1 -fashion, thus also acting as a sterically hindered monophosphine.²⁴

While we found that the palladium-catalyzed nucleophilic addition of aryl halides to ketones was quite sensitive to the length of the tether connecting the nitrogen atom and carbonyl group, the acylation reaction with aldehydes was successfully promoted starting from α -, β -, or γ -(anilino)-aldehydes (Figure 4). As expected, the aminoaldehydes without hydrogen atoms α to the carbonyl group smoothly underwent acylation to give the corresponding ketones in high yields.

Based on these results, a reasonable mechanism was proposed for the palladium-catalyzed intramolecular acylation with aldehydes (Scheme 7). A carbopalladation reaction between the σ -arylpalladium(II) moiety and the carbonyl group would give a Pd(II) alkoxide.²⁵ β -Hydride elimination from the latter would afford ketone **18** and regenerate the Pd(0) catalyst (pathway A). The nucleophilic addition mechanism is supported by the formation of minor amounts of alcohol **19** in some of the cyclization reactions of aldehyde **16**. This alcohol would be formed by the competitive

TABLE 2. Pd(0)-Catalyzed Reactions of β -(anilino)aldehyde **16**



L	cone angle	products (ratio)	yield
(Cy) ₃ P	170°	17 + 18 (1:2.3)	---
(^t Bu) ₃ P	182°	17 + 18 (1:9.1)	18 (30%)
(<i>o</i> -tolyl) ₃ P	194°	17 + 18 (1:11.5)	18 (52%)
	---	17 + 18 (1:26)	18 (65%)
dtpf	---	17 + 18 (1:0.9)	---
	---	17 + 18 (1:0.9)	---
xantphos	---	---	---

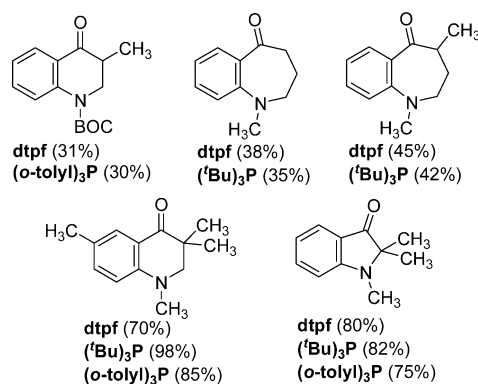
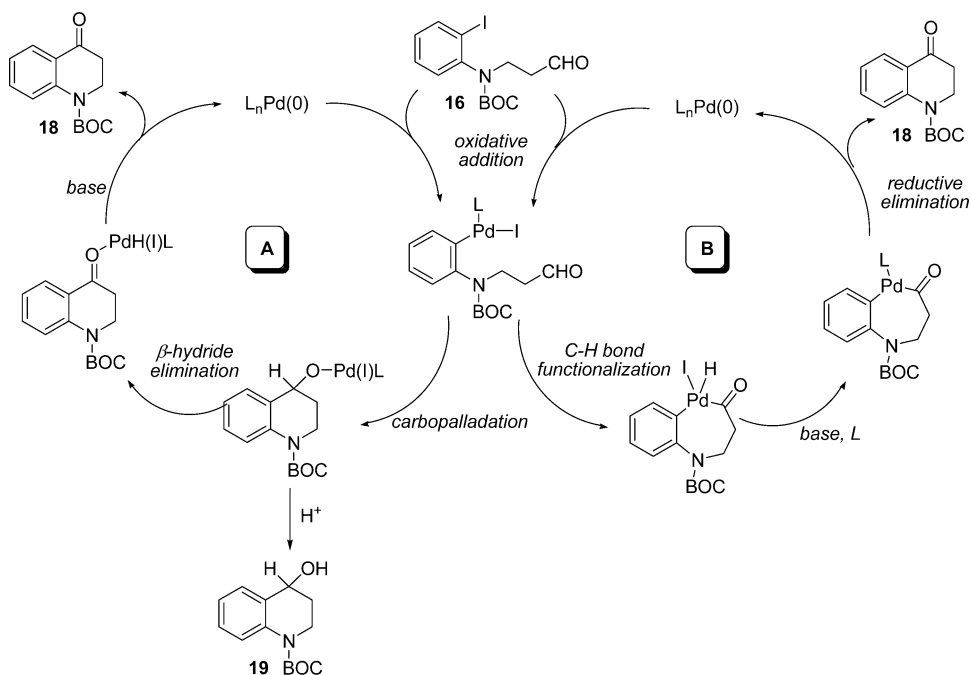


FIGURE 4. Scope of the intramolecular Pd(0)-catalyzed acylation with aldehydes.

protonation of the palladium(II) alkoxide intermediate. The alternative mechanism for the acylation involving the insertion of the σ -aryl palladium(II) species into the formyl C–H bond (pathway B), which has been suggested to explain some related processes,^{22,26} does not appear to be operative in this case (see below).

Similar to the reaction profiles depicted in Figure 1, our calculations suggest that the nucleophilic addition reaction is favored over the corresponding pathways leading to the α -arylation products.²³ Again, this is ascribed to the computed lower barrier for the acylation and to the energetic cost associated with the endergonic enolization process. Moreover, the competition between the nucleophilic

SCHEME 7. Proposed Catalytic Cycle for the Intramolecular Pd(0)-Catalyzed Acylation of Aldehyde **16**

addition and the alternative C–H insertion was also computed starting from the palladacycle **11M**, which lacks hydrogen atoms placed at the α -position to the carbonyl group and is therefore unable to undergo α -arylation. As clearly seen in Figure 5, the nucleophilic addition reaction is kinetically and thermodynamically favored over the insertion of the σ -arylpalladium(II) species **15M** into the formyl C–H bond. Once complex **13M** is formed via **TS5**, it evolves to the corresponding alcohol by protonolysis of the O–Pd bond or alternatively it can undergo a β -hydride elimination process to produce complex **14M** via **TS6**. The latter reaction pathway is very likely to occur in view of the very low barrier energy ($\Delta G_{298}^\ddagger = 0.7$ kcal/mol) and high exergonicity ($\Delta G_{298} = -19.8$ kcal/mol) computed for this process. Complex **14M** will be finally converted into the corresponding ketone by the simple decoordination of the carbonyl group regenerating the palladium catalyst.

While we were able to efficiently effect the acylation from aldehydes, the possibility of selectively promoting the enolate arylation proved to be a more challenging task. To date, starting from aldehyde **16**, we have only managed to obtain equimolar amounts of **17** and **18** using xantphos as the ligand (Table 2). The use of strong bases like KO^tBu or PhOK , which could favor the α -arylation reaction, is completely hampered by the retro-Michael degradation of the β -amino aldehyde moiety. In contrast, the α -arylation was the only reaction pathway observed in the cyclizations

of aldehydes **20** and **21** when using xantphos and PhOK . Interestingly, aldehyde **22** was not isolated because it was directly transformed into ketone **24** under the reaction conditions (Scheme 8).

Pd-Catalyzed Reactions of β -(2-Iodoanilino)-esters and β -(2-Iodoanilino)carboxamides

The ester and carboxamido groups have been traditionally considered inert toward organopalladium reagents. The scarcely reported palladium-catalyzed reactions resulting in the modification of an ester functionality do not involve the carbopalladation of the carbonyl group but the attack of the oxygen atom at the carbon–palladium bond.^{2,27} In this context, we thought that we could take advantage of the high nucleophilicity of the palladium(II) species derived from 2-haloanilines to force the nucleophilic attack at the low electrophilic ester and amide carbonyl groups, therefore manipulating their dual reactivity.

After some optimization studies, we found that the substitution reaction at the alkoxy carbonyl group on ester **25** can be successfully promoted by using $\text{Pd}(\text{PPh}_3)_4$ and K_3PO_4 in toluene at high temperature (Scheme 9).²⁸

A range of differently substituted dihydroquinolin-4-ones was synthesized under the optimized reaction conditions. In general, the acylation was largely unaffected by the aromatic ring substituents, whose electronic properties do not influence the nucleophilicity of the aryl palladium species.

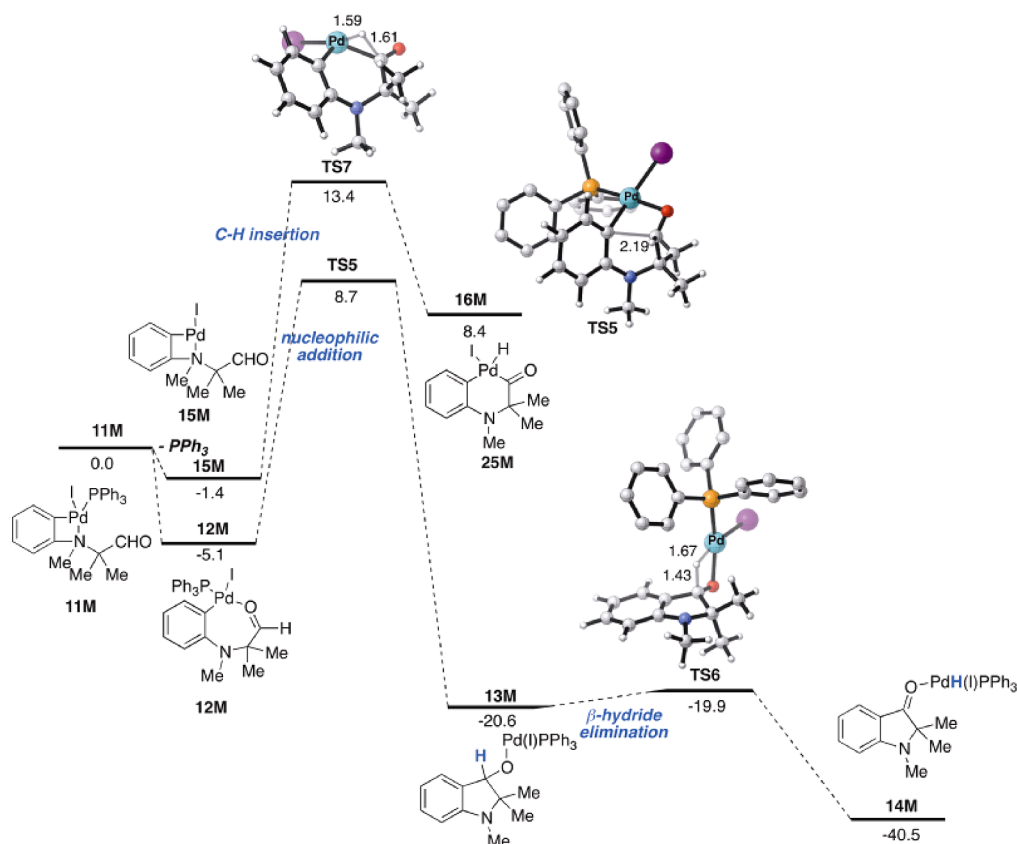
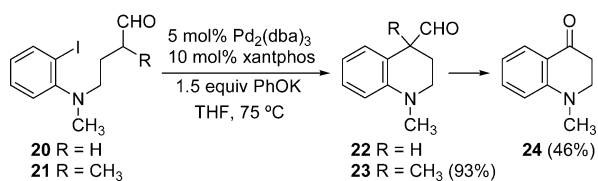


FIGURE 5. Computed reaction profile for complex **11M**. See caption for Figure 1 for additional details. All data have been computed at the PCM(toluene)-B3LYP/def2-SVP level.

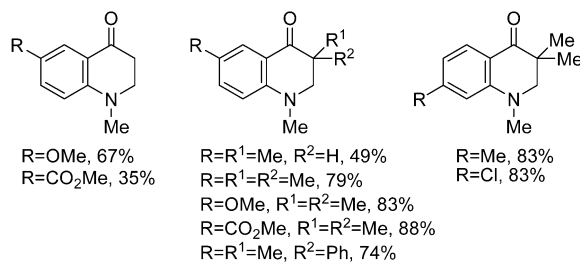
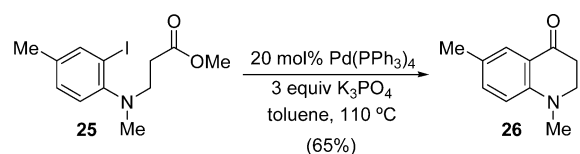
SCHEME 8. Intramolecular Pd(0)-Catalyzed α -Arylation of Aldehydes



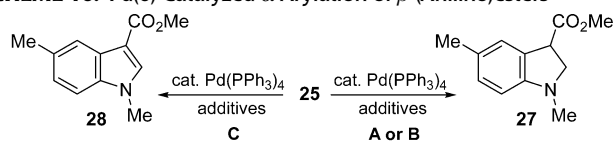
The reaction of amino esters without hydrogen atoms α to the carbonyl group proceeded smoothly to give the corresponding ketones in high yields. Moreover, no competition between the nucleophilic attack at the carbonyl and the α -arylation was observed in the reactions of esters containing hydrogen atoms placed at the α -position to the carbonyl group. Our calculations on model compounds indicate that although the activation barriers for the α -arylation process are feasible, these reaction pathways are not competitive with the nucleophilic addition because of the required highly endergonic (ca. 30 kcal/mol) enolization process.¹⁹

The acylation reaction with esters proceeds through a mechanism involving carbopalladation between the σ -arylpalladium moiety and the alkoxy carbonyl group to give a

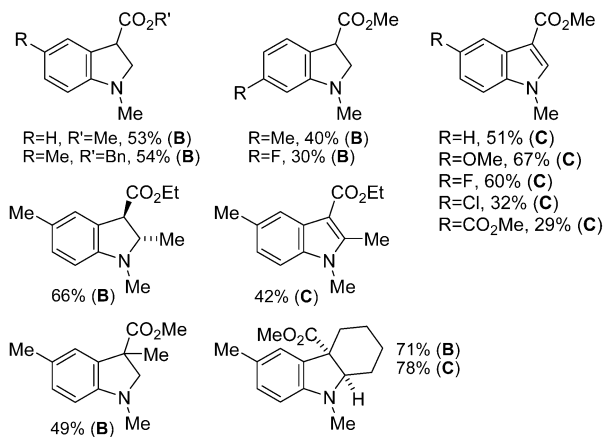
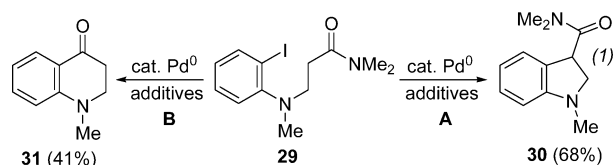
SCHEME 9. Pd(0)-Catalyzed Nucleophilic Substitution at the Alkoxy carbonyl Group



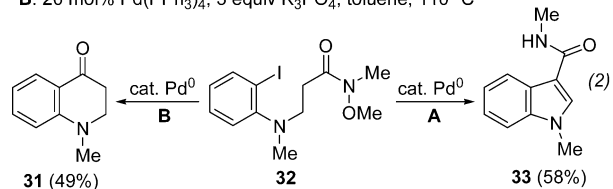
Pd(II) alkoxide, followed by β -alkoxide elimination to give the ketone and a Pd(II) methoxide complex, which would finally undergo β -hydride elimination to regenerate the palladium catalyst with simultaneous loss of formaldehyde. In agreement with our chemical intuition that an ester group is less electrophilic than a ketone, the computed barrier for the nucleophilic addition at the alkoxy carbonyl group is

SCHEME 10. Pd(0)-Catalyzed α -Arylation of β -(Anilino)esters

A: 10 mol% [Pd], 3 equiv K_3PO_4 , 0.3 equiv PhOH, toluene, 90 °C, **25:27** = 1:5
 B: 5 mol% [Pd], 2.25 equiv $KOtBu$, 2.75 equiv PhOH, THF, reflux, **27** (87%)
 C: 10 mol% [Pd], 3 equiv K_3PO_4 , 0.3 equiv PhOH, DMF, 90 °C, **28** (66%)

SCHEME 11. Pd(0)-Catalyzed Reactions of β -(Anilino)carboxamides

A: 5 mol% $Pd(PPh_3)_4$, 2.25 equiv $KOtBu$, 2.75 equiv PhOH, THF, reflux
 B: 20 mol% $Pd(PPh_3)_4$, 3 equiv K_3PO_4 , toluene, 110 °C



higher than at the ketone.¹⁹ It should be noted that the above reaction represents the first example of a palladium-catalyzed acylation of aryl halides by an ester group.

Further investigation on the palladium-catalyzed reactions of **25** revealed that the addition of a catalytic amount of phenol to otherwise the same reaction conditions previously used for the acylation, avoided the nucleophilic attack at the alkoxy carbonyl group and promoted the α -arylation²⁹ to give indoline **27** (Scheme 10). Indoline **27** was obtained in good yield by using $KOtBu$ in the presence of phenol. We also observed that the use of the couple $K_3PO_4/PhOH$ in DMF resulted in the direct formation of indole **28**.³⁰ This α -arylation reaction was successfully

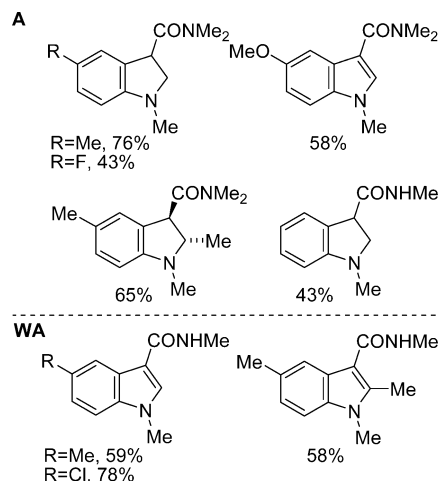


FIGURE 6. Scope of the intramolecular Pd(0)-catalyzed α -arylation of amides (**A**) and Weinreb amides (**WA**).

applied to the preparation of differently substituted indoles and indolines, as shown in Scheme 10. The moderate yields obtained in the synthesis of 3-monosubstituted indolines are mainly due to their high tendency to undergo aerobic oxidation to give the corresponding indoles.

The satisfactory results obtained using esters as initial substrates encouraged us to investigate the palladium-catalyzed reactions of carboxamides. We found that amide **29** can undergo either enolate arylation³¹ to give indoline **30** or acylation to form **31**, using the same reaction conditions employed in the α -arylation or acylation reactions of esters, respectively (Scheme 11, eq 1).³²

Both reactions were extended to Weinreb amides (Scheme 11, eq 2).³² Interestingly, under the reaction conditions of the enolate arylation, Weinreb amide **32** afforded indole **33**, which results from the demethoxylation and aromatization of the initially formed indoline. Following this methodology, a variety of differently substituted indolines and indoles was prepared in acceptable yields (Figure 6).

The acylation with amides also showed a broad substrate scope (Figure 7). This reaction very likely proceeds through a mechanism similar to that proposed for the palladium-catalyzed acylation with esters.¹⁹ Interestingly, Weinreb amides afforded better results than N,N -dimethyl amides in the acylation reaction. This is probably due to the chelation ability of the second oxygen atom, which would both facilitate the carbopalladation step and stabilize the resulting Pd(II) alkoxide intermediate. Notably, this acylation reaction also constitutes the first example of nucleophilic substitution at the carboxamido group by a σ -arylpalladium species.

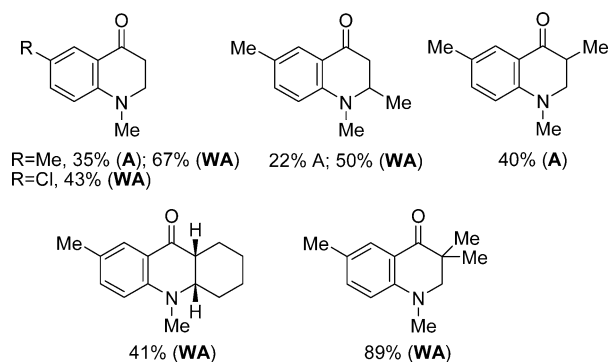


FIGURE 7. Scope of the intramolecular Pd(0)-catalyzed acylation with amides (A) and Weinreb amides (WA).

Summary and Outlook

In this Account, we have summarized our studies on the ambiphilic character of σ -arylpalladium species derived from amino-tethered aryl halides and carbonyl compounds. These palladium intermediates act as electrophiles in α -arylation reactions and as nucleophiles in the transformations that involve a direct attack of the C–Pd bond at the different carbonyl groups. Our joint computational and experimental efforts to elucidate the mechanism of these palladium-catalyzed reactions suggest that two major factors are involved in the control of the dual character of these intermediates: first, the high nucleophilicity of the palladium(II) intermediates derived from 2-haloanilines, which modifies the interaction of the metal center with the carbonyl group, and second, the additive phenol, which has a beneficial effect on the arylation by exchanging the iodide ligand to give an arylpalladium(II) phenoxide complex. The formation of this transient intermediate not only stabilizes the arylpalladium moiety, thus preventing the nucleophilic attack at the carbonyl group, but also assists the enolization reaction, which takes place in a more favorable intramolecular manner. Although the ability to modulate the ambiphilic character of organopalladium species has exciting potential, our study is one of the few reported attempts to switch from one reaction mode to the other starting from the same precursor.^{15,33} We hope that the contents of this Account will motivate further research in the synthetic applications as well as the reaction mechanisms of related processes. In our opinion, this area will experience tremendous growth and activity in the future.

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Supporting Information. Computational details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

BIOGRAPHICAL INFORMATION

Daniel Solé was born in Vielha (Lleida) Spain. He studied Pharmacy at the University of Barcelona, where he received his Ph.D. in 1992 (Honors). After a postdoctoral stay at the Spanish research council (CSIC) with Prof. Josep M. Moretó, he returned to the University of Barcelona, where he became Associate Professor in Organic Chemistry in 1997. His research is centered on the development of synthetic methodologies using transition metals and their application to the synthesis of complex organic molecules.

Israel Fernández (Madrid, 1977) studied Chemistry at the Universidad Complutense of Madrid (UCM). In 2005, he earned his Ph.D. (with honors) at the UCM under the supervision of Prof. Miguel A. Sierra. After that, he joined the Theoretical and Computational Chemistry group of Prof. Gernot Frenking at the Philipps Universität Marburg as a postdoctoral researcher. At the present, I.F. is Profesor Contratado Doctor at the UCM. His current research includes the experimental and computational study of the bonding situations and reaction mechanisms of organic and organometallic compounds with special interest in C–C bond-forming processes.

FOOTNOTES

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The authors declare no competing financial interest.

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