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Intramolecular Pd(0)-Catalyzed Reactions of (2-Iodoanilino)-aldehydes: A Joint Experimental–Computational Study

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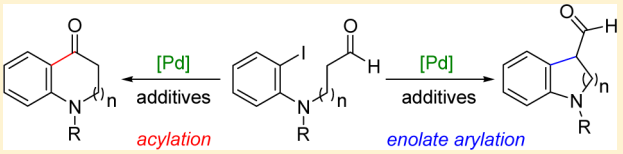
Supporting Information

ABSTRACT: An extensive joint experimental–computational density functional theory (DFT) study has been carried out to gain insight into the factors that control the chemoselectivity (i.e., acylation vs α-arylation reaction) of palladium-catalyzed cyclizations of (2-iodoanilino)-aldehydes. To this end, the nature of the tethers joining the aniline nitrogen and the aldehyde moiety, different palladium precatalysts and reaction conditions (base and temperature), as well as different additives (mono- and bidendate ligands) has been explored. The adequate selection of these variables allows for the control of the selectivity of the process. Thus, (2-iodoanilino)-aldehydes generally lead to the formation of nucleophilic addition derived products when Cs_2CO_3/Et_3N is used as base. In contrast, the use of stronger bases like K^{t}OBu (in the presence of PhOH) mainly forms α-arylation reaction products. The different reaction pathways leading to the experimentally observed reaction products have been studied by means of computational tools.

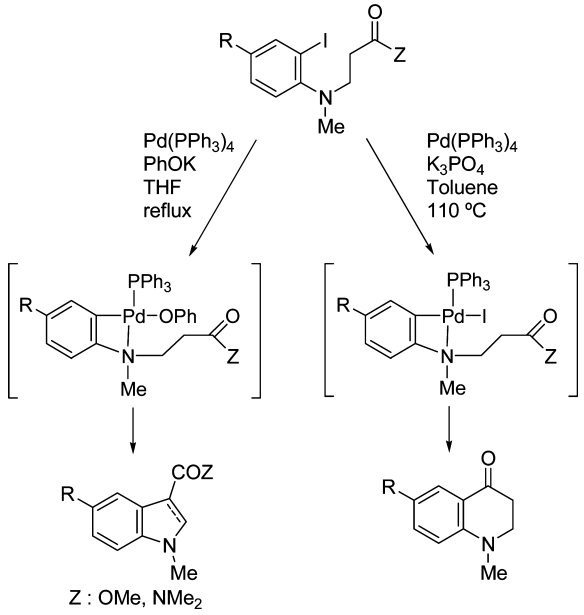


INTRODUCTION

During the past years, a myriad of metal-catalyzed reactions have considerably expanded the organic chemists' arsenal, leading to the development of highly efficient and reliable synthetic methodologies.[1] Paramount among these strategies are those allowing the generation of different compounds from common building blocks as a result of subtle modifications of either the active catalysts or reaction conditions.[2]

In this context, the palladium-catalyzed intramolecular coupling reactions between aryl halides and carbonyl compounds offer a challenging field because of the potential ambiphilic character of the transient σ-arylpalladium intermediates.[1b] Thus, the α-arylation of carbonyl compounds, which exploits the electrophilic character of the Pd(II) species, has emerged as an extremely powerful synthetic methodology.[3] On the other hand, the palladium-catalyzed nucleophilic addition of aryl halides to electrophilic carbon-heteroatom multiple bonds has also been explored, and now encompasses the couplings with aldehydes,[4] ketones,[5] esters,[4f,6] amides,[7] imines,[8] nitriles,[9] and isocyanates.[10] Despite the inherent interest of being able to control the ambiphilic character of the σ-arylpalladium intermediates involved in these reactions, little effort has been focused on selectively promoting either their electrophilic or nucleophilic reactivity from the same starting material.[11] As part of our ongoing studies on the palladium-catalyzed intramolecular coupling reactions of amino-tethered aryl halides and carbonyl compounds, we have recently reported that starting from β-(2-iodoanilino) esters,[6,12] amides,[7] or ketones[5d,13] both the enolate arylation and the nucleophilic attack on the carbonyl group can be selectively promoted (Schemes 1 and 2). In these processes, the formation of a transient four-membered azapalladacycle intermediate, which strongly modifies the interaction of the metal center with the carbonyl moiety, allows the control of the ambiphilic character of the palladium(II) species by slight modifications of the reaction conditions.

Scheme 1



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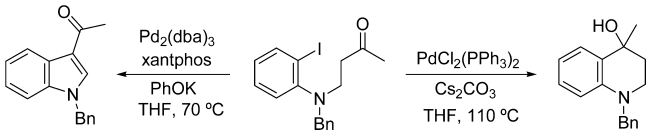
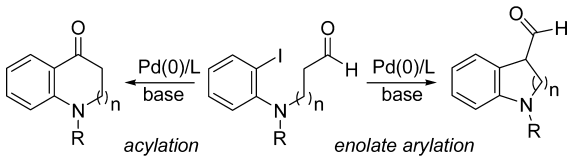
Scheme 2



We herein expand our previous findings to aldehyde containing compounds and report that the dual character of the corresponding σ-arylpalladium(II) intermediates can indeed be efficiently controlled in the intramolecular reactions of amino-tethered aryl halides and aldehydes (Scheme 3). It

Scheme 3



should be noted that even if the Pd(0) catalyzed intramolecular enolate arylation[14] and acylation of aryl halides by aldehydes[4f,g,15] have been previously reported in the carbocyclic series, these processes have not been extensively studied. More importantly, the switch from one reaction mode to the other starting from the same precursor has not been explored so far.

RESULTS AND DISCUSSION

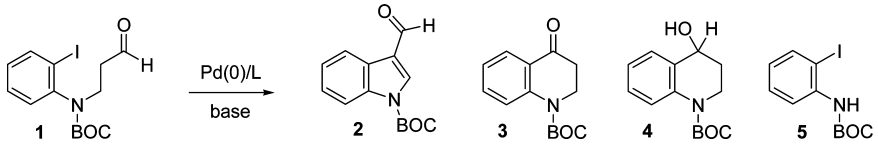
The reactivity of aldehyde **1** with several Pd precatalysts, ligands, bases, solvents and temperatures was studied first. Table 1 gathers the results obtained in the different experiments conducted.

Submission of iodo-aniline **1** to $Pd(PPh_3)_4$ in the presence of Cs_2CO_3 as the base in toluene at 110 °C, a combination that was effective in promoting the nucleophilic addition in β-(2-iodoanilino)ketones,[5d] led to the formation of a 1:1.3 mixture of aldehyde **2** and ketone **3** (entry 1). The use of lower reaction temperatures resulted in the formation of major amounts of carbamate **5**, arising from the retro-Michael degradation of the β-amino aldehyde moiety (not shown in the table). Changing the base from Cs_2CO_3 to K_3PO_4 resulted in an increase in the formation of the acylation product **3** (entry 2). A similar nucleophilic addition-to-α-arylation ratio was observed when K_3PO_4 was used as the base in the presence of a catalytic amount of phenol[13,16] in toluene, since a 1:3.8:0.2 mixture of aldehyde **2**, ketone **3** and alcohol **4** was obtained (entry 3). The use of the K_3PO_4/phenol couple either in THF or in DMF, as well as the combination of KO^{t}Bu/phenol resulted in the total decomposition of the material (entries 4−6). On the other hand, when K_2CO_3 was used as the base in THF (entry 7), alcohol **4** (26%) was obtained together with ketone **3** (31%) and aldehyde **2** (11%).

Different ligands were next tested to modify the α-arylation-to-nucleophilic addition ratio. From the plethora of ligands currently used in palladium-catalyzed reactions, three phosphine families were chosen: bulky monodentate phosphines, biaryl monodentate phosphines, and bidentate phosphine ligands (Figure 1).

When the reaction was performed in the presence of bulky monodentate phosphines, the acylation process was, in all cases tested, the preferred reaction pathway. A direct correlation between the phosphine cone angle and the observed chemo-

Table 1. Pd(0)-Catalyzed Reactions of Aldehyde 1



entry	catalyst[a]	base/additives[a]	solvent/temp (°C)	time (h)	^{1}H NMR ratio	yield (%)[b]
1	$Pd(PPh_3)_4$ (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]	**2** + **3** (1:1.3)	
2	$PdCl_2(PPh_3)_2$ (0.1)	K_3PO_4 (3), Et_3N (10)	toluene/110	24[c]	**2** + **3** (1:4)	
3	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3), phenol (0.3)	toluene/110	24[c]	**2** + **3** + **4** (1:3.8:0.2)	
4	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3), phenol (3)	THF/110	24[c]	[d]	
5	$PdCl_2(PPh_3)_2$ (0.1)	K_3PO_4 (3), phenol (0.3)	DMF/90	24	[d]	
6	$Pd(PPh_3)_4$ (0.1)	KO^{t}Bu (2.5), phenol (2.75)	THF/reflux	24	[d]	
7	$PdCl_2(PPh_3)_2$ (0.2)	K_2CO_3 (3), Et_3N (3)	THF/110	24[c]		**2** (11), **3** (31), **4** (26)
8	$Pd_2(dba)_3$ (0.05) PCy_3 (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]	**2** + **3** (1:2.3)	
9	$Pd_2(dba)_3$ (0.05) (^{t}Bu)$_3$PH·BF_4 (0.11)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]	**2** + **3** (1:9.1)	**2** (4), **3** (30)
10	$Pd_2(dba)_3$ (0.05) (*o*-tolyl)$_3$P (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]	**2** + **3** (1:11.5)	**2** (5), **3** (52)
11	$Pd_2(dba)_3$ (0.05) L_1 (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]	**2** + **3** (1:4.1)	
12	$Pd_2(dba)_3$ (0.05) L_2 (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]		**5** (not quantified)[e]
13	$Pd_2(dba)_3$ (0.05) L_3 (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]	**2** + **3** + **5** (1:10:30)	
14	$Pd_2(dba)_3$ (0.05) BINAP (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]	**2** + **3** (1:1.2)	
15	$Pd_2(dba)_3$ (0.05) xantphos (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]	**2** + **3** (1:0.9)	
16	$Pd_2(dba)_3$ (0.05) ^{t}Bu-xantphos (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]		**5** (not quantified)[e]
17	$Pd_2(dba)_3$ (0.05) dppf (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]	**2** + **3** (1:4.3)	
18	$Pd_2(dba)_3$ (0.05) dtpf (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]	**2** + **3** (1:26)	**3** (65)

[a]Equivalents in parentheses. [b]Yields refer to pure products isolated by flash chromatography. [c]The reaction was carried out in a sealed tube. [d]Complex reaction mixtures were obtained, from which no identifiable product was isolated. [e]Traces of **3** were also observed.

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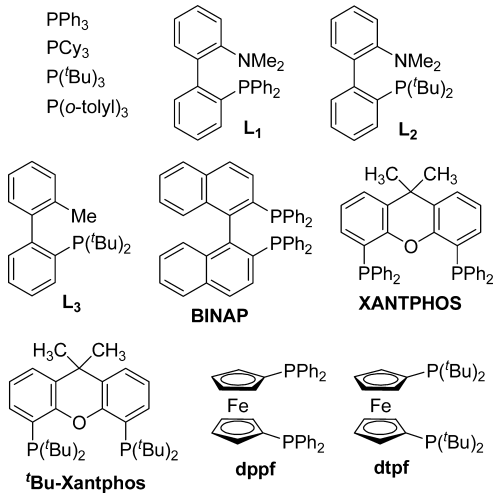


Figure 1. Ligands used in the Pd-catalyzed cyclization reactions.

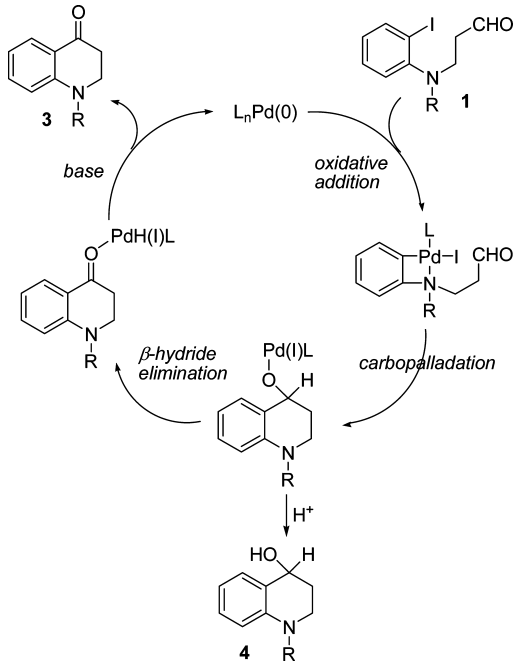
selectivity was found (entries 8−10). Thus, the best result was obtained using P(*o*-tolyl)$_3$ (cone angle of 194°) as the ligand, which afforded ketone **3** in 52% yield, while PCy_3 (cone angle of 170°) afforded the worst chemoselectivity.

Although the use of biaryl monodentate phosphines (entries 11−13) resulted in some cases in acceptable acylation-to-*α*-arylation ratios, the copious formation of the retro-Michael product **5** warns against their use in the acylation reaction. Finally, among the bidentate phosphine ligands, BINAP (entry 14) and xantphos (entry 15) afforded nearly equimolecular mixtures of indole **2** and ketone **3**, whereas ^{t}Bu-xantphos (entry 16) resulted in the degradation of the material. In this family of ligands, the best acylation-to-*α*-arylation ratios were obtained with dppf (entry 17) and dtpf (entry 18), the latter affording ketone **3** in 65% yield in a high chemoselective transformation (26:1 ratio). It should be noted that the sense of the selectivity is the same than that obtained with monodentated phosphines.

Data in Table 1 show that while the acylation reaction from *β*-amino aldehyde **1** can be efficiently effected, the enolate arylation process remains elusive. It should be noted that the use of strong bases (e.g., KO^{t}Bu), which could favor the *α*-arylation reaction as reported for related esters and amides,[12] is hampered by the retro-Michael degradation of the *β*-amino aldehyde moiety.

The mechanism proposed for the Pd-catalyzed intramolecular acylation is shown in Scheme 4. A carbopalladation reaction between the *σ*-aryl palladium(II) moiety and the C═O would give a Pd(II) alkoxide. *β*-Hydride elimination from the latter would afford ketone **3** and regenerate the Pd(0) catalyst. The nucleophilic addition mechanism is experimentally supported by the formation of minor amounts of alcohol **4** in some of the cyclization reactions of aldehyde **1**. This alcohol would be formed by the competitive protonation of the corresponding palladium(II) alkoxide intermediate. Moreover, when alcohol **4** was treated with $PdCl_2(PPh_3)_2$, K_2CO_3 and Et_3N in THF at 110 °C for 48 h, a 4:1 mixture of alcohol **4** and ketone **3** was obtained.[17] The low conversion observed in this reaction could be due to the difficulty of the formation of the palladium(II) alkoxide starting from the corresponding alcohol. It should be noted that this palladium intermediate is directly obtained in the cyclization reaction by the nucleophilic attack of the *σ*-aryl palladium(II) moiety to the carbonyl group.

Scheme 4. Proposed Catalytic Cycle



Density functional theory (DFT) calculations[18] have been carried out to gain more insight into the competence between the *α*-arylation and nucleophilic addition reaction pathways of aldehyde **1**. We have selected the same combination of methods/basis set (see the Computational Details) used by us to study the substrate-dependent reactivity of related (2-iodoanilino)-ketones[19] and carboxylic esters[13] for comparison reasons. Thus, Figures 2−4 gather the corresponding PCM-(toluene)-B3LYP/def2-SVP computed reaction profiles starting from the model intermediate **1M** (using PPh_3 as a ligand and also the less computationally demanding model PH_3), which is initially formed after the corresponding oxidative addition process.[13,19]

Our calculations suggest that **1M** may evolve to the key metallacyclobutane intermediate **2M** by coordination of the amino group to the coordination vacant of the palladium center[20] or, alternatively, can be easily transformed into complex **3M**, where the oxygen atom of the carbonyl moiety is coordinated to the transition metal, through the saddle point **TS1** (computed activation barrier of $\Delta G^{\ddagger}_{298}$ = 8.5 kcal/mol). From the latter species, the nucleophilic addition reaction to the carbonyl group occurs through the transition state **TS2** (computed activation barrier of $\Delta G^{\ddagger}_{298}$ = 14.8 kcal/mol) producing the tetrahydroquinoline **4M**. The latter compound easily evolves to the experimentally observed alcohol **4** by protonolysis of the O−Pd or to the cyclic ketone **3** via a *β*-hydride elimination reaction (vide infra).

Alternatively, the enol species **1M-enol**, formed from **1M** in an endergonic process (ΔG_{298} = +8.4 kcal/mol), can coordinate the transition metal through its double bond moiety to form the *π*-complex **5M**. This species evolves to the five-membered ring complex **6M** through the transition state **TS3** (activation barrier of $\Delta G^{\ddagger}_{298}$ = 15.0 kcal/mol), a saddle point associated to the *α*-arylation process, in an exergonic transformation (ΔG_{298} = −7.4 kcal/mol). Complex **6M** will then be transformed into **7M** (the precursor of the observed indole **2**) via a base-mediated process or alternatively via a palladium-mediated hydrogen elimination.

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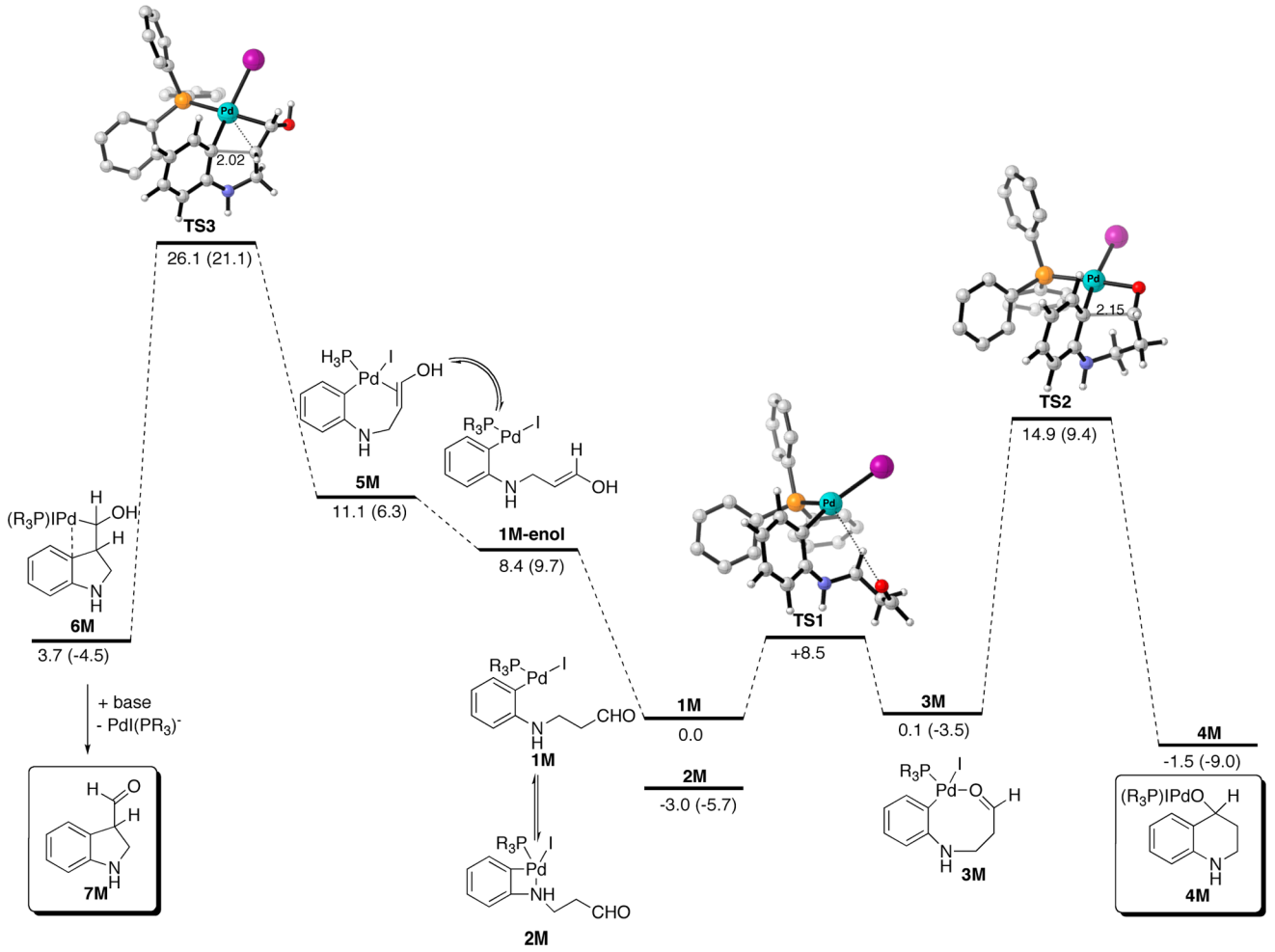

Figure 2. Computed reaction profiles for model aldehyde **1M**. Free energies (ΔG_{298}) are given in kcal/mol (plain values refer to PPh_3, whereas values in parentheses refer to PH_3) and bond distances in angstroms. Hydrogen atoms at the PPh_3 ligand were omitted for clarity. All data have been computed at the PCM(toluene)-B3LYP/def2-SVP level.

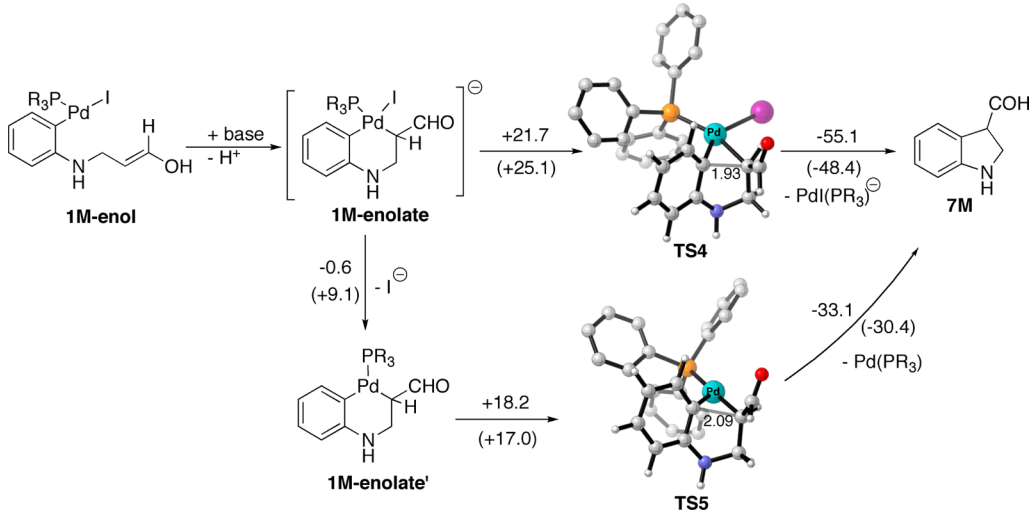

Figure 3. Computed reaction profile starting from **1M-enol**. Free energies (ΔG_{298}) are given in kcal/mol (plain values refer to PPh_3, whereas values in parentheses refer to PH_3) and bond distances in angstroms. Hydrogen atoms at the PPh_3 ligand were omitted for clarity. All data have been computed at the PCM(toluene)-B3LYP/def2-SVP level.

Furthermore, it can be suggested that the α-arylation reaction may also occur through the corresponding enolate complexes **1M-enolate** or **1M-enolate′** formed from **1M-enol** (Figure 3). However, the higher computed activation barriers of the respective transformations via **TS4** or **TS5** ($\Delta G^{\ddagger}_{298}$ = 21.7 and 18.2 kcal/mol, respectively) indicates that the α-arylation

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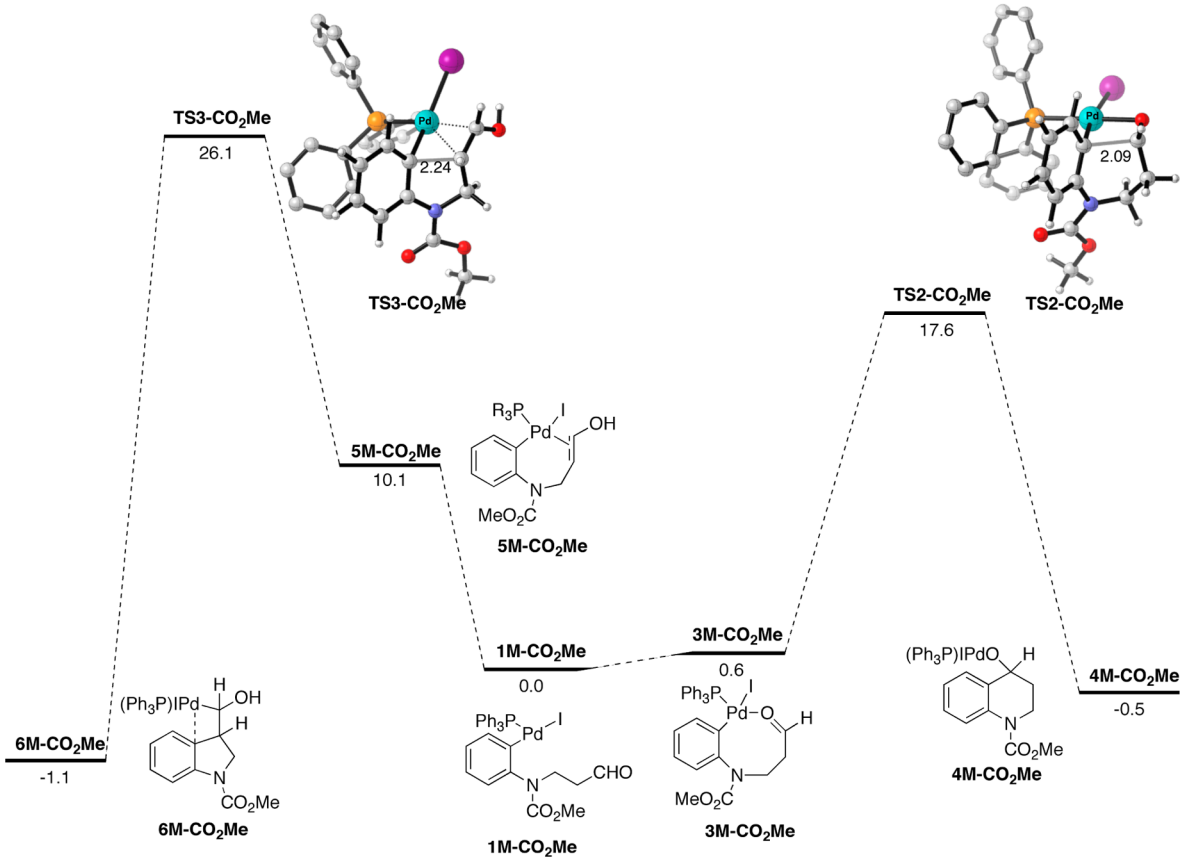
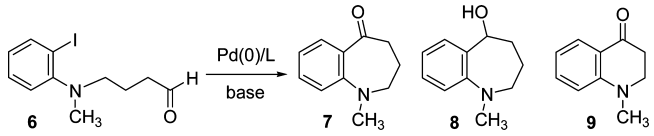


Figure 4. Computed reaction profiles for model aldehyde **1M-CO$_2$Me**. Free energies (ΔG_{298}) are given in kcal/mol and bond distances in angstroms. Hydrogen atoms at the PPh_3 ligand were omitted for clarity. All data have been computed at the PCM(toluene)-B3LYP/def2-SVP level.

Table 2. Pd(0)-Catalyzed Reactions of 6



entry	catalyst[a]	base/additives[a]	solvent/temp (°C)	time (h)	yield (%)[b]
1	$Pd_2(dba)_3$ (0.05) (^{t}Bu)$_3$PH·BF_4 (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	18[c]	**7** (35)[d]
2	$Pd_2(dba)_3$ (0.05) dtpf (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	24[c]	**7** (38)[d]
3	$Pd_2(dba)_3$ (0.05) (*o*-tolyl)$_3$P (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	8[c]	**7** (18), **8** (5), **9** (25)
4	Pd $(PPh_3)_4$ (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	18[c]	**7** (30), **8** (11), **9** (12)
5	$Pd_2(dba)_3$ (0.05) xantphos (0.1)	^{t}BuOK (1,5), phenol (3), Et_3N (10)	THF/75	24	**9** (46)

[a]Equivalents in parentheses. [b]Yields refer to pure products isolated by flash chromatography. [c]The reaction was carried out in a sealed tube. [d]Traces of **8** and **9** were also observed in the crude reaction mixture.

reaction may occur directly from **1M-enol** via **TS3**, which proceeds with a lower barrier energy.

According to the computed data, one should expect a favored (or exclusive) formation of nucleophilic addition products (**3** and **4**) over the *α*-arylation product **2** due to two reasons: (a) the former process is kinetically favored ($\Delta\Delta G^{\ddagger}_{298}$ = 11.2 kcal/mol) and (b) the energetic cost associated with the endergonic enolization process. This is in agreement with the experimental results (Table 1), which show a clear bias toward the formation of products **3** and **4** over indole **2** when PPh_3 is used as ligand. At this point, it cannot be safely discarded that the production of indole **2** finds its origin on the high temperature (110 °C) used experimentally, which makes the **TS3**, or even **TS4** and **TS5**, pathways feasible and therefore competitive to the **TS2** pathway. Interestingly, the same conclusions can be qualitatively drawn from the data computed using PH_3 as ligand since there are no significant differences between these data and those obtained using PPh_3.

Moreover, it should be noted that a similar competition between the nucleophilic addition and the enolate arylation had been also observed in the palladium-catalyzed reactions of *β*-(2-iodoanilino) ketones bearing a CO_2Me group at the nitrogen.[5d] Previous calculations showed that the introduction of a CO_2Me group hampers the delocalization of the nitrogen lone-pair into the aryl *π*-system, thus decreasing the nucleophilicity of the reactive arylic carbon atom.[19] As a consequence, a notable increase of the activation barrier of the nucleophilic addition is observed. Furthermore, the presence of an electron-with-

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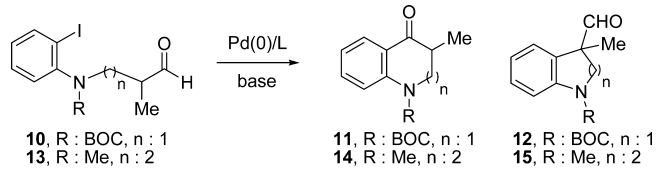
Table 3. Pd(0)-Catalyzed Reactions of 10 and 13



entry	aldehyde	catalyst[a]	base/additives[a]	solvent/temp (°C)	time (h)	yield (%)[b]
1	**10**	$Pd_2(dba)_3$ (0.05) ($^tBu)_3PH{\cdot}BF_4$ (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	24[c]	**5** (not quantified)
2	**10**	$Pd_2(dba)_3$ (0.05) dtpf (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	19[c]	**11** (31)
3	**10**	$Pd_2(dba)_3$ (0.05) (*o*-tolyl)$_3$P (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	24[c]	**11** (30)
4	**10**	Pd $(PPh_3)_4$ (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	24[c]	**11** + 12 (70, 3.5:1)
5	**13**	$Pd_2(dba)_3$ (0.05) ($^tBu)_3PH{\cdot}BF_4$ (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	24[c]	**14** (42)
6	**13**	$Pd_2(dba)_3$ (0.05) dtpf (0.1)	Cs_2CO_3 (3), Et_3N (6)	toluene/110	24[c]	**14** (45)
7	**13**	$Pd_2(dba)_3$ (0.05) xantphos (0.1)	^tBuOK (1,5), phenol (3), Et_3N (6)	THF/75	24	**15** (93)

[a]Equivalents in parentheses. [b]Yields refer to products isolated by flash chromatography. [c]The reaction was carried out in a sealed tube.

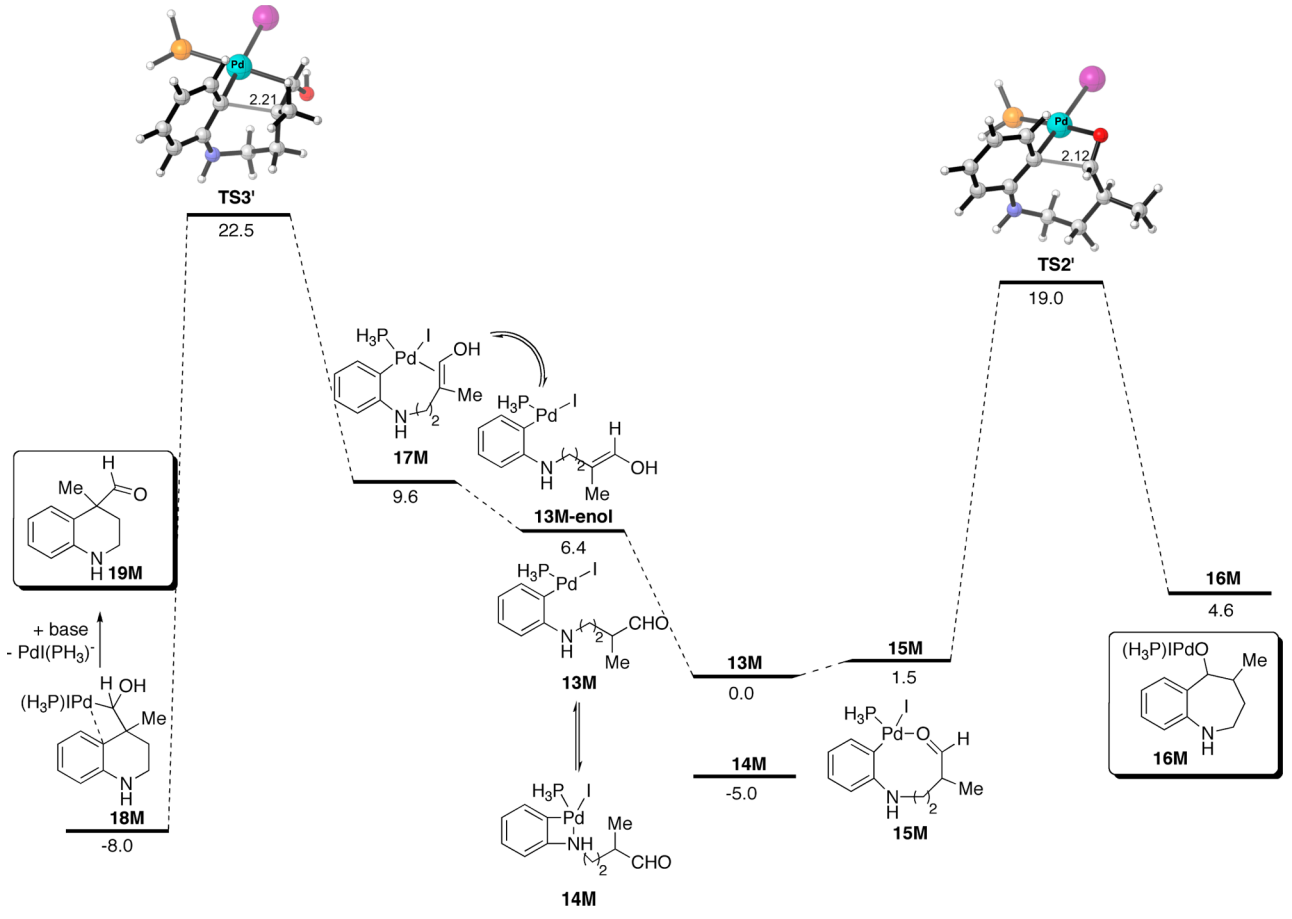


Figure 5. Computed reaction profiles for model aldehyde **13M**. Free energies (ΔG_{298}) are given in kcal/mol and bond distances in angstroms. All data have been computed at the PCM(toluene)-B3LYP/def2-SVP level.

drawing group at the nitrogen atom makes the α-arylation process kinetically easier.[19] As the aldehyde **1** bears a BOC group attached to nitrogen atom, we also computed the competence between the α-arylation and nucleophilic addition reactions on the corresponding more realistic model aldehyde **1M-CO$_2$Me**, where the hydrogen atom attached to the nitrogen atom was replaced by a CO_2Me group. We focused only on the processes involving the corresponding saddle points **TS2-CO$_2$Me** and **TS3-CO$_2$Me**, which lead to the nucleophilic addition and α-arylation reaction products, respectively (Figure 4), and constitute the rate determining steps of both transformations. As expected, the introduction of the electron-withdrawing group increases the activation barrier of the nucleophilic attack ($\Delta\Delta G^{\ddagger}_{298}$ = 2.2 kcal/mol, comparing the processes involving **TS2** and **TS2-CO$_2$Me**) and leads also to a slight increase of the α-arylation barrier energy ($\Delta\Delta G^{\ddagger}_{298}$ = 1.0 kcal/mol, comparing the processes involving **TS3** and **TS3-CO$_2$Me**). Despite that, similar conclusions to those commented above with the less-realistic model **1M** can be drawn,

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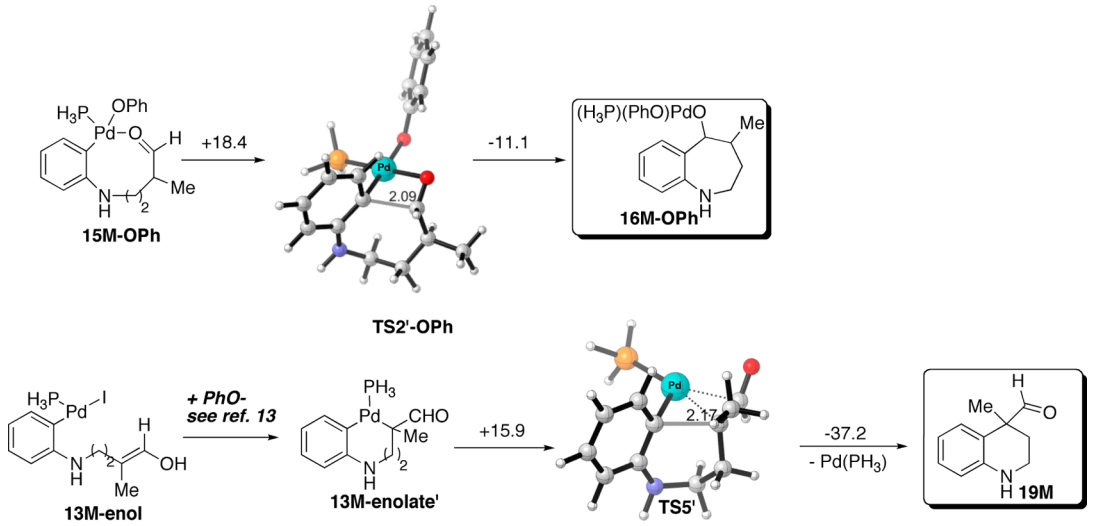
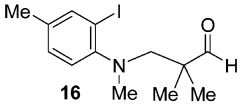
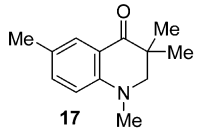
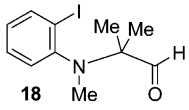
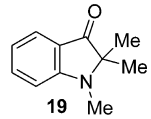


Figure 6. Computed reaction profiles for model aldehyde **13M** in the presence of PhO^-. Free energies (ΔG_{298}) are given in kcal/mol and bond distances in angstroms. All data have been computed at the PCM(toluene)-B3LYP/def2-SVP level.

Table 4. Pd(0)-Catalyzed Reactions of 16 and 18[a]

entry	aldehyde	ligand	time	yield (%)[b]
	 **16**			 **17**
1	**16**	dtpf (0.1)	36 h	**17** (70%)[c]
2	**16**	$(^t\text{Bu})_3\text{PH}\cdot\text{BF}_4$ (0.1)	36 h	**17** (98%)
3	**16**	$(o\text{-tolyl})_3\text{P}$ (0.1)	36 h	**17** (85%)
	 **18**			 **19**
4	**18**	dtpf (0.1)	36 h	**19** (80%)
5	**18**	$(^t\text{Bu})_3\text{PH}\cdot\text{BF}_4$ (0.1)	28 h	**19** (82%)
6	**18**	$(o\text{-tolyl})_3\text{P}$ (0.1)	36 h	**19** (75%)

[a]The reactions were carried out using $Pd_2(dba)_3$ (0.05 equiv), ligand (0.1 equiv), Cs_2CO_3 (3 equiv) and Et_3N (6 equiv) in toluene at 110 °C in a sealed tube. [b]Yields refer to pure products isolated by flash chromatography. [c]Traces of **16** were also observed in the crude reaction mixture.

i.e., a favored (or exclusive) formation of nucleophilic addition products (**3** and **4**) over the α-arylation product **2**.

The palladium-catalyzed cyclization reaction of ketones has been found to be quite sensitive to the length of the tether connecting the nitrogen atom and the carbonyl group.[5d,19] Therefore, we decided to explore the palladium-catalyzed reaction of the higher homologue aldehyde **6** as well (Table 2).

The acylation process was the only reaction pathway observed when **6** was treated with $Pd_2(dba)_3$ and Cs_2CO_3 in the presence of either $P(^t\text{Bu})_3$ or dtpf (entries 1 and 2), allowing the isolation of benzo[*b*]azepin-5-one **7** in 35 and 38% yields, respectively. On the contrary, treatment of **6** under the same reaction conditions but using $P(o\text{-tolyl})_3$ as the ligand afforded a mixture of **7**, alcohol **8** and unexpectedly tetrahydroquinolone **9** (entry 3). The same products were obtained when using $Pd(PPh_3)_4$ as the catalyst (entry 4). Interestingly, the Pd-catalyzed reaction of **6** using $KO^t\text{Bu}$ as the base in the presence of an excess of phenol and the ligand xantphos in THF, a combination that should favor the α-arylation reaction,[13] resulted in the exclusive formation (46% isolated yield) of tetrahydroquinolone **9** (Entry 5).[21]

The reactions of β-amino aldehyde **10** and γ-amino aldehyde **13**, both bearing a methyl group placed at the α-position of the carbonyl group, were next explored (Table 3).

Dtpf and $P(o\text{-tolyl})_3$ were the most effective ligands for the Pd-catalyzed acylation reaction of β-amino aldehyde **10** (entries 2 and 3, Table 3). However, tetrahydroquinolone **11** was isolated in only 30% yield. The use of $P(^t\text{Bu})_3$, which was effective in the acylation of **1**, now resulted in the total decomposition of aldehyde **10** (entry 1). Finally, when PPh_3 was used as the ligand, a 3.5:1 mixture of ketone **11** and the α-arylation aldehyde **12** was obtained in a combined 70% reaction yield (entry 4).

The acylation process was also the only reaction pathway observed in the palladium-catalyzed cyclization of aldehyde **13** when using either $P(^t\text{Bu})_3$ or dtpf as the ligand (entries 5 and 6). As expected, the cyclization of **13** using $KO^t\text{Bu}$ as the base in the presence of an excess of phenol and the ligand xantphos

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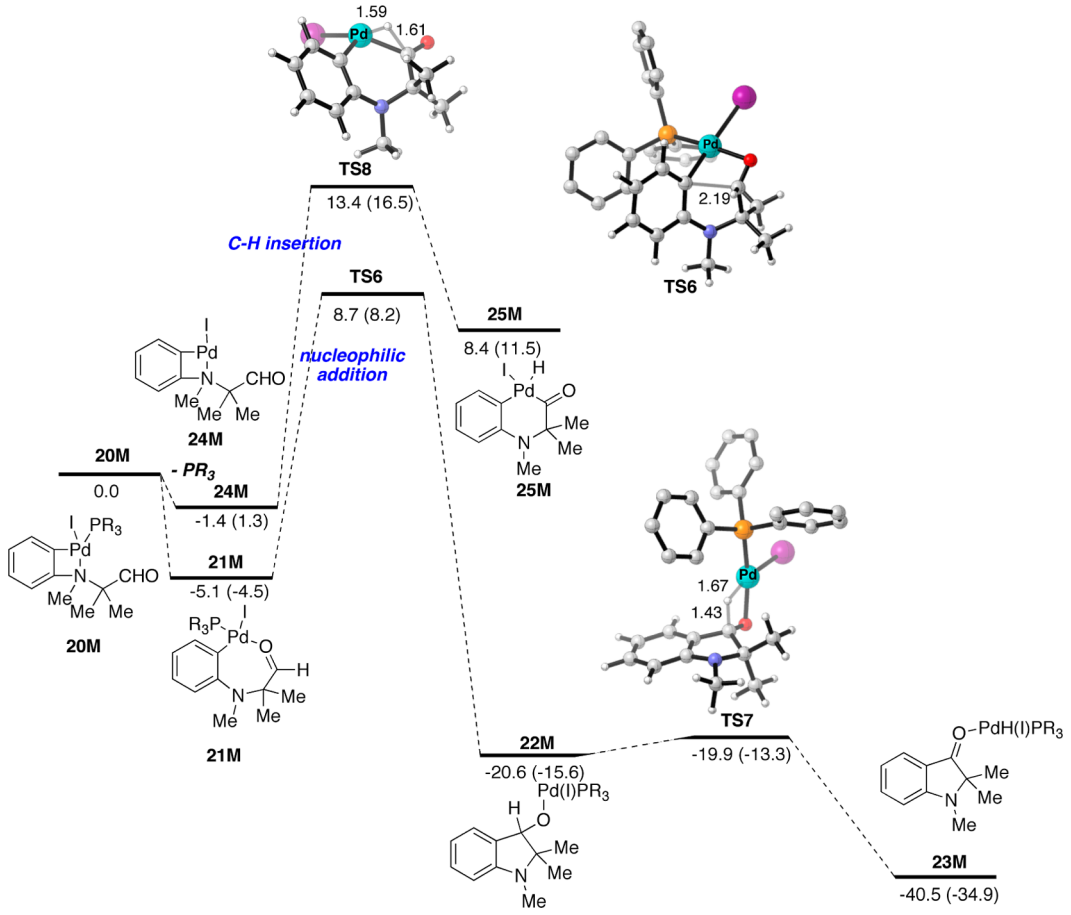

Figure 7. Computed reaction profile for complex **20M**. Free energies (ΔG_{298}) are given in kcal/mol (plain values refer to PPh_3, whereas values in parentheses refer to PH_3) and bond distances in angstroms. Hydrogen atoms at the PPh_3 ligand were omitted for clarity. All data have been computed at the PCM(toluene)-B3LYP/def2-SVP level.

resulted in the chemoselective formation of the α-arylation aldehyde **15**, which was isolated in 93% yield (entry 7).

Similar to the above computational results on model aldehyde **1M**, the calculations on the homologous aldehyde **13M** using the model PH_3 ligand (Figure 5) indicate that the nucleophilic addition reaction is again preferred over the α-arylation process (the relative free energy of **TS2′** over **13M** is +19.0 kcal/mol, whereas a higher value of +22.5 kcal/mol is computed for **TS3′**). This is in nice agreement with the exclusive formation of ketone **14** observed experimentally (entries 5 and 6, Table 3). This species is produced from complex **16M** through a β-hydride elimination reaction (vide infra).

Interestingly, the combination of xantphos, phenol and KO^{t}Bu in the reaction leads to the complete switch of the reaction pathway toward the α-arylation process (entry 7, Table 3). As above-mentioned, the use of strong bases (e.g., KO^{t}Bu) favors the α-arylation reaction in the cyclization reactions of related esters and amides.[12] In addition, we reported that the presence of PhO^- in the reaction switches on the reaction pathway involving **TS5′** making the nucleophilic addition (via **TS2′**) more difficult.[13] Similarly, for the case considered herein, the replacement of the iodide ligand by a phenoxy ligand on **15M** provokes an increase of the corresponding activation barrier ($\Delta\Delta G^{\ddagger}_{298}$ = 0.9 kcal/mol respect to the analogous reaction involving **TS2′**) for the nucleophilic attack through the saddle point **TS2′-OPh** (Figure 6). This makes the α-arylation process (through **TS5′**, computed activation barrier of 15.9 kcal/mol) the most kinetically favorable process, therefore leading to the exclusive formation of ketone **19M** (ketone **15** in the experiment).

The acylation reaction was finally extended to the non-enolizable amino aldehydes **16** and **18**, lacking hydrogen atoms placed at the α-position to the carbonyl group and therefore unable to undergo the α-arylation reaction (Table 4). For the Pd-catalyzed reactions of these aldehydes, only the three phosphines that afforded the best chemoselectivity in the above studies were used. As expected, the acylation products **17** and **19** were obtained exclusively in good to excellent yields.

We further explore the latter process by means of computational tools. As readily seen in Figure 7, complex **21M** (the analogous complex to **3M** in Figure 2, where the oxygen atom of the carbonyl group is coordinated to the palladium) easily evolves to complex **22M** through the transition state **TS6** with an activation barrier ($\Delta G^{\ddagger}_{298}$ = 13.8 kcal/mol) comparable to that involving the analogous saddle point **TS2** (Figure 2). Complex **22M** will be transformed into the corresponding alcohol by protonolysis of the O−Pd bond or alternatively can undergo a β-hydride elimination process to produce complex **23M** via **TS7**. This reaction occurs with a very low barrier energy ($\Delta G^{\ddagger}_{298}$ = 0.7 kcal/mol) in a highly exergonic transformation (ΔG_{298} = −19.8 kcal/mol), which clearly shows the easiness of this process. Complex **23M** will be finally converted into the experimentally observed ketone **19** by

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the simple base-mediated decoordination of the carbonyl group regenerating the active Pd(0) catalyst.

An alternative mechanism involving the insertion of the σ-aryl palladium(II) species into the formyl C−H bond has been suggested to explain some related acylation processes.[4g,15,22] Our calculations indicate that the C−H insertion process, which transforms the initial four-membered palladacycle **24M** (formed from **20M** after the release of the phosphine ligand) into **25M** via **TS8**,[23] is not competitive in this transformation in view of the higher activation barrier and endergonicity compared to the nucleophilic addition reaction (via **TS6**). The preference for the latter process over the C−H insertion reaction may be ascribed to the high nucleophilicity of the carbon atom directly attached to the transition metal because of the π-donor effect of the *ortho*-nitrogen atom.[19]

CONCLUSION

In summary, we have demonstrated that the chemoselectivity (i.e., the competition between nucleophilic addition and α-arylation) of the palladium-catalyzed cyclization reactions of (2-iodoanilino)-aldehydes can be indeed modified (in principle, at will) with the adequate selection of the initial substrate, reaction conditions, and additives. In general, (2-iodoanilino)-aldehydes lead mainly to the formation of nucleophilic addition derived products when Cs_2CO_3/Et_3N is used as base. Regarding the phosphine ligand, the best results for the acylation reaction are obtained with sterically hindered phosphines, finding a direct correlation between the steric demand of the ligand and the observed chemoselectitity. Interestingly, dtpf is the most effective ligand for the present acylation reaction. Although it contains two phosphorus donors, dtpf is probably ligated to the metal in a κ^1-fashion.[24] On the contrary, the use of stronger bases like K^{t}OBu (in the presence of PhOH) results mainly in the formation of α-arylation reaction products. As we have previously observed in the reaction of β-(2-iodoanilino)-ketones,[13] xantphos is the phosphine of choice for the α-arylation process. DFT calculations carried out on model compounds suggest that the preference of the nucleophilic addition over the α-arylation reaction does not only depend on the corresponding barrier energy differences but also on the energetic cost associated to the enolization reaction of the aldehyde formed after the initial oxidative addition process. The alternative mechanism involving the insertion of the σ-aryl palladium(II) species into the formyl C−H bond, which has been suggested to explain some related acylation processes,[4g,15,22] is not competitive in this transformation because of a higher activation barrier and endergonicity. The preference of the carbopalladation of the C═O group over the C−H insertion reaction may be ascribed to the high nucleophilicity of the carbon atom directly attached to the transition metal because of the π-donor effect of the *ortho*-nitrogen atom.

COMPUTATIONAL DETAILS

All the calculations reported in this paper were obtained with the Gaussian 09 suite of programs.[25] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[26] using the double-ζ quality plus polarization def2-SVP basis set[27] for all atoms (this basis sets includes effective core potentials, ECPs, for palladium and iodine atoms). Reactants and products were characterized by frequency calculations[28] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the intrinsic reaction coordinate (IRC) method.[29] Solvents effects were taken into account using the polarizable continuum model (PCM).[30] Single point calculations (PCM-B3LYP/def2-SVP) on the gas-phase optimized geometries were performed to estimate the change in the Gibbs energies in the presence of toluene as solvent.

EXPERIMENTAL SECTION

General Methods. All commercially available reagents were used without further purification. Aldehyde **2**,[31] iodoaniline **5**,[32] and dihydroquinolones **3**,[33] **9**[7] and **17**[6] are known compounds. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution, using Me_4Si as the internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. TLC was carried out on SiO_2, and the spots were located with UV light.

3-[*N*-*tert*-Butoxycarbonyl)-*N*-(2-iodophenyl)amino]propanal (1).[34] ^{1}H NMR (400 MHz) δ 1.34 (s, 9H), 2.77 (m, 2H), 3.68 (dt, *J* = 14.4 and 6.8 Hz, 1H), 4.13 (m, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 9.79 (s, 1H); ^{13}C NMR (100.5 MHz) δ 28.1 (CH_3), 43.0 (CH_2), 43.4 (CH_2), 80.7 (C), 100.3 (C), 128.9 (CH), 129.1 (CH), 129.6 (CH), 139.6 (CH), 144.2 (C), 153.9 (C), 200.8 (CH); HRMS (ESI-TOF) calcd for $C_{14}H_{19}INO_3$ 376.0410 $[M + H]^+$, found 376.0409.

***N*-(3-Butenyl)-2-iodoaniline.** To a solution of 2-iodoaniline (1 g, 5.57 mmol) in dry THF (20 mL), cooled to −78 °C under Argon atmosphere, methyllithium (3.56 mL of 1.6 M solution in diethyl ether, 5.7 mmol) was added dropwise, and the resulting solution was stirred at −78 °C for 30 min. 4-Bromo-1-butene (0.7 mL, 6.86 mmol) was added, and stirring was continued for 10 min at −78 °C. The mixture was allowed to warm to room temperature and then poured into saturated NH_4Cl aqueous solution. The reaction mixture was extracted with diethyl ether. The organic extracts were washed with saturated $NaHCO_3$ aqueous solution, dried, and concentrated. The residue was purified by flash chromatography (SiO_2, hexanes) to give *N*-(3-butenyl)-2-iodoaniline (0.4 g, 32%) as a colorless oil: ^{1}H NMR (300 MHz) δ 2.44 (m, 2H), 3.22 (t, *J* = 6.6 Hz, 2H), 4.21 (bb, 1H), 5.13−5.25 (m, 2H), 5.85 (m, 1H), 6.43 (ddd, *J* = 8.1, 7.2, and 1.5 Hz, 1H), 6.56 (dd, *J* = 8.4 and 1.5 Hz, 1H), 7.21 (ddd, *J* = 8.4, 7.2, and 1.5 Hz, 1H), 7.65 (dd, *J* = 8.1 and 1.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 33.4 (CH_2), 43.1 (CH_2), 85.4 (C), 110.6 (CH), 117.5 (CH_2), 118.4 (CH), 129.3 (CH), 135.3 (CH), 138.9 (CH), 147.1 (C).

***N*-(3-Butenyl)-2-iodo-*N*-methylaniline.** A mixture of *N*-(3-butenyl)-2-iodoaniline (0.59 g, 2.16 mmol), K_2CO_3 (0.59 g, 4.3 mmol), and iodomethane (1.1 mL, 17.2 mmol) in acetonitrile (5 mL) was stirred at 50 °C in a sealed tube for 65 h. The solvent was removed in vacuo, and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried and concentrated to give *N*-(3-butenyl)-2-iodo-*N*-methylaniline (0.62 g, quantitative) as pale yellow oil, which was used in the next step without purification: ^{1}H NMR (300 MHz) δ 2.30 (m, 2H), 2.72 (s, 3H), 3.01 (m, 2H), 4.97−5.09 (m, 2H), 5.85 (m, 1H), 6.78 (ddd, *J* = 8.1, 7.2, and 1.5 Hz, 1H), 7.09 (dd, *J* = 8.1 and 1.5 Hz, 1H), 7.31 (ddd, *J* = 8.1, 7.2, and 1.5 Hz, 1H), 7.85 (dd, *J* = 8.1 and 1.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 32.0 (CH_2), 42.4 (CH_3), 56.2 (CH_2), 99.1 (C), 115.7 (CH_2), 122.0 (CH), 125.3 (CH), 128.9 (CH), 136.2 (CH), 140.0 (CH), 154.0 (C).

4-[*N*-(2-Iodophenyl)-*N*-methylamino]butanol. To a solution of *N*-(3-butenyl)-2-iodo-*N*-methylaniline (0.62 g, 2.16 mmol) in dry THF (4 mL), 9-BBN (7.5 mL of 0.5 M solution in THF, 3.75 mmol) was added at room temperature under Argon. The solution was stirred for 18 h, cooled at 0 °C, and THF (25 mL) and water (3 mL) were added. The mixture was allowed to warm to room temperature and then was cooled again at 0 °C, and 3 M solution of NaOH (2 mL) and 30% H_2O_2 (3 mL) was added. The mixture was stirred at room temperature for 1.5 h and at 50 °C for 1.5 h. The reaction mixture was extracted with EtOAc. The organic extracts were dried and concentrated. The residue was purified by flash chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2-MeOH 1%) to give 4-[*N*-(2-iodophenyl)-*N*-methylamino]butanol (0.65 g, 99%) as a brown

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amorphous solid: ^{1}H NMR (300 MHz) δ 1.62 (m, 4H), 2.69 (s, 3H), 2.99 (m, 2H), 3.66 (m, 2H), 6.79 (ddd, J = 8.1, 7.2, and 1.5 Hz, 1H), 7.09 (dd, J = 7.8 and 1.5 Hz, 1H), 7.30 (ddd, J = 7.8, 7.2, and 1.5 Hz, 1H), 7.85 (dd, J = 8.1 and 1.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 24.0 (CH_2), 30.3 (CH_2), 43.0 (CH_3), 56.0 (CH_2), 62.8 (CH_2), 99.2 (C), 122.0 (CH), 125.4 (CH), 128.9 (CH), 140.0 (CH), 154.0 (C).

4-[*N*-(2-Iodophenyl)-*N*-methylamino]butanal (6). A solution of DMSO (0.53 mL, 7.46 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of oxalyl chloride (0.32 mL, 3.83 mmol) in CH_2Cl_2 (10 mL) at −60 °C. The reaction mixture was stirred for 5 min, and 4-[*N*-(2-iodophenyl)-*N*-methylamino]butanol (0.65 g, 2.13 mmol) in CH_2Cl_2 (30 mL) was added dropwise. The mixture was stirred at −60 °C for 15 min, and Et_3N (2.5 mL, 17.9 mmol) was added. After 5 min, the reaction mixture was allowed to warm to room temperature. Water was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried, and the solvent was removed under a vacuum. The residue was purified by flash chromatography (SiO_2, from hexanes to hexanes−EtOAc 20%) to give 4-[*N*-(2-iodophenyl)-*N*-methylamino]butanal (**6**, 0.57 g, 88%) as a colorless oil: ^{1}H NMR (300 MHz) δ 1.86 (m, 2H), 2.59 (td, J = 7.2 and 1.5 Hz, 2H), 2.67 (s, 3H), 2.98 (t, J = 6.9 Hz, 2H), 6.80 (ddd, J = 8.1, 7.2, and 1.5 Hz, 1H), 7.10 (dd, J = 8.1 and 1.5 Hz, 1H), 7.31 (ddd, J = 8.1, 7.2, and 1.5 Hz, 1H), 7.85 (dd, J = 8.1 and 1.5 Hz, 1H), 9.82 (t, J = 1.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 20.0 (CH_2), 41.4 (CH_2), 42.9 (CH_3), 55.1 (CH_2), 99.4 (C), 122.2 (CH), 125.7 (CH), 129.0 (CH), 139.9 (CH), 153.9 (C), 202.3 (CH); HRMS (ESI-TOF) calcd for $C_{11}H_{15}INO$ 304.0193 $[M + H]^+$, found 304.0186.

***N*-(*tert*-Butoxycarbonyl)-*N*-(2-methyl-2-propenyl)-2-iodoaniline.** A solution of *N*-(*tert*-butoxycarbonyl)-2-iodoaniline (0.6 g, 1.88 mmol) in dry THF (2 mL) was added at 0 °C under Argon to a suspension of NaH (60% in oil, 90 mg, 2.26 mmol) in dry THF (8 mL). The resulting mixture was stirred for 15 min at 25 °C and cooled again to 0 °C. DMF (2 mL) and 3-bromo-2-methylpropene (0.23 mL, 2.26 mmol) were added, and the mixture was stirred for 10 min at 0 °C and at 25 °C overnight. Saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The organic extracts were dried, and the solvent evaporated under a vacuum. The residue was purified by flash chromatography (SiO_2, from hexanes to hexanes−EtOAc 5%) to give *N*-(*tert*-butoxycarbonyl)-*N*-(2-methyl-2-propenyl)-2-iodoaniline (0.48 g, 69%) as a colorless oil: ^{1}H NMR (300 MHz, mixture of rotamers) δ 1.36 and 1.53 (two broad s, 9H), 1.82 (s, 3H), 3.49 (d, J = 15.6 Hz, 1H), 4.42−4.63 (m, 1H), 4.70−5.01 (m, 2H), 6.97 (m, 1H), 7.14 (m, 1H), 7.30 (m, 1H), 7.87 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75.4 MHz, major rotamer) δ 20.5 (CH_3), 28.2 (CH_3), 55.1 (CH_2), 80.2 (C), 100.0 (C), 113.2 (CH_2), 128.5 (2 CH), 129.7 (CH), 139.4 (CH), 141.2 (C), 144.5 (C), 154.2 (C); HRMS (ESI-TOF) calcd for $C_{11}H_{13}INO_2$ 317.9985 $[M - C_4H_7]^+$, found 317.9986.

3-[*N*-*tert*-Butoxycarbonyl)-*N*-(2-iodophenyl)amino]-2-methylpropanol. To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(2-methyl-2-propenyl)-2-iodoaniline (0.48 g, 1.29 mmol) in dry THF (2 mL), 9-BBN (4.5 mL of 0.5 M solution in THF, 2.25 mmol) was added at room temperature under Argon. The solution was stirred for 18 h, cooled at 0 °C, and THF (15 mL) and water (2 mL) were added. The mixture was allowed to warm to room temperature and then was cooled again at 0 °C, and 3 M solution of NaOH (1.1 mL) and 30% H_2O_2 (1.9 mL) was added. The mixture was stirred at room temperature for 1.5 h and at 50 °C for 1.5 h. The reaction mixture was extracted with EtOAc. The organic extracts were dried and concentrated. The residue was purified by flash chromatography (SiO_2, from hexanes to hexanes−EtOAc 30%) to give 3-[*N*-*tert*-butoxycarbonyl)-*N*-(2-iodophenyl)amino]-2-methylpropanol (0.5 g, 99%) as a colorless oil: ^{1}H NMR (300 MHz, mixture of rotamers) δ 0.92 and 0.94 (two d, J = 6.9 Hz, 3H), 1.34 and 1.36 (two s, 9H), 2.85 (dd, J = 14.7 and 4.2 Hz, 1H), 3.41 (td, J = 14.4 and 4.8 Hz, 1H), 3.53 (broad t, J = 9.3 Hz, 1H), 3.70 (m, 1H), 3.82 (m, 1H), 3.97 (dd, J = 14.7 and 11.1 Hz, 1H), 6.94−7.04 (m, 1H), 7.08 and 7.20 (two dd, J = 8 and 1.5 Hz, 1H), 7.30−7.39 (m 1H), 7.84−7.92 (m, 1H); ^{13}C NMR (75.4 MHz, mixture of rotamers) δ 14.9 (CH_3, major), 15.2 (CH_3, minor), 27.4 (CH_3, minor), 28.1 (CH_3, major), 34.3 (CH, major), 35.2 (CH, minor), 51.0 (CH_2, major), 53.2 (CH_2, minor), 63.3 (CH_2, major), 64.4 (CH_2, minor), 80.9 (C), 99.8 (C, major), 100.1 (C, minor), 128.4 (CH, minor), 128.8 (CH, major), 128.9 (CH, major), 129.0 (CH, minor), 129.1 (CH, minor), 129.5 (CH, major), 139.6 (CH, minor), 139.7 (CH, major), 144.3 (C, major), 145.7 (C, minor), 155.4 (C, minor), 155.7 (C, major); HRMS (ESI-TOF) calcd for $C_{15}H_{23}INO_3$ 392.0717 $[M + H]^+$, found 392.0731.

3-[*N*-*tert*-Butoxycarbonyl)-*N*-(2-iodophenyl)amino]-2-methylpropanal (10). A solution of DMSO (0.36 mL, 5 mmol) in CH_2Cl_2 (3 mL) was added dropwise to a solution of oxalyl chloride (0.22 mL, 2.57 mmol) in CH_2Cl_2 (7 mL) at −60 °C. The reaction mixture was stirred for 5 min and 3-[*N*-*tert*-butoxycarbonyl)-*N*-(2-iodophenyl)-amino]-2-methylpropanol (0.5 g, 1.28 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The mixture was stirred at −60 °C for 15 min, and Et_3N (1.7 mL, 12 mmol) was added. After 5 min, the reaction mixture was allowed to warm to room temperature. Water was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried, and the solvent was removed under a vacuum. The residue was purified by flash chromatography (SiO_2, from hexanes to hexanes−EtOAc 30%) to give 3-[*N*-*tert*-butoxycarbonyl)-*N*-(2-iodophenyl)amino]-2-methylpropanal (**10**, 0.46 g, 93%) as a colorless oil: ^{1}H NMR (300 MHz, mixture of rotamers) δ 1.23 and 1.26 (two d, J = 7.2 Hz, 3H), 1.43 and 1.45 (two s, 9H), 2.75 and 2.89 (two m, 1H), 3.31 (dd, J = 14.4 and 4.8 Hz, 0.5 H), 3.74 (dd, J = 14.4 and 7.5 Hz, 0.5 H), 4.01 (dd, J = 14.4 and 6 Hz, 0.5 H), 4.37 (dd, J = 14.4 and 10.2 Hz, 1H), 7.11 (m, 1H), 7.23−7.51 (m, 2H), 7.98 (d, J = 7.8 Hz, 1H), 9.76 (d, J = 3.3 Hz, 0.5 H), 9.82 (d, J = 1.5 Hz, 0.5 H); ^{13}C NMR (75.4 MHz, mixture of rotamers) δ 11.9 (CH_3), 12.0 (CH_3), 28.0 (CH_3), 46.0 (CH), 46.1 (CH), 50.0 (CH_2), 50.4 (CH_2), 76.6 (C), 80.5 (C), 99.8 (C), 128.8 (CH), 128.9 (CH), 129.7 (CH), 103.2 (CH), 139.4 (CH), 139.5 (CH), 143.8 (C), 144.5 (C), 154.0 (C), 154.1 (C), 203.3 (CH), 203.4 (CH); HRMS (ESI-TOF) calcd for $C_{15}H_{20}INNaO_3$ 412.0380 $[M + Na]^+$, found 412.0375.

***N*-(3-Methyl-3-butenyl)-2-iodoaniline.** Operating as in the preparation of *N*-(3-butenyl)-2-iodoaniline and starting from 2-iodoaniline (1 g, 4.56 mmol) and 4-bromo-2-methyl-1-butene (1.36 g, 9.13 mmol), *N*-(3-methyl-3-butenyl)-2-iodoaniline (0.45 g, 34%) was obtained as a pale yellow oil after flash chromatography (SiO_2, hexanes): ^{1}H NMR (300 MHz) δ 1.77 (s, 3H), 2.40 (t, J = 6.6 Hz, 2H), 3.23 (m, 2H), 4.20 (bb, 1H), 4.87 (m, 1H), 4.91 (m. 1H), 6.42 (ddd, J = 8.1, 7.5, and 1.5 Hz, 1H), 6.55 (dd, J = 8.1 and 1.5 Hz, 1H), 7.19 (ddd, J = 8.1, 7.5, and 1.5 Hz, 1H), 7.64 (dd, J = 8.1 and 1.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 21.9 (CH_3), 37.1 (CH_2), 41.7 (CH_2), 85.3 (C), 110.5 (CH), 112.9 (CH_2), 118.4 (CH), 129.3 (CH), 138.9 (CH), 142.5 (C), 147.2 (C).

***N*-Methyl-*N*-(3-methyl-3-butenyl)-2-iodoaniline.** Operating as in the preparation of *N*-(3-butenyl)-2-iodo-*N*-methylaniline and starting from *N*-(3-methyl-3-butenyl)-2-iodoaniline (0.58 g, 2 mmol), crude *N*-methyl-*N*-(3-methyl-3-butenyl)-2-iodoaniline (0.58 g, 97%) was obtained as a pale yellow oil, which was used in the next step without purification: ^{1}H NMR (300 MHz) δ 1.74 (s, 3H), 2.27 (m, 2H), 2.73 (s, 3H), 3.06 (m, 2H), 4.68 (m, 1H), 4.73 (m, 1H), 6.77 (ddd, J = 8.1, 7.2, and 1.5 Hz, 1H), 7.09 (dd, J = 7.8 and 1.5 Hz, 1H), 7.30 (ddd, J = 7.8, 7.2, and 1.5 Hz, 1H), 7.85 (dd, J = 8.1 and 1.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 22.8 (CH_3), 35.7 (CH_2), 42.3 (CH_3), 55.6 (CH_2), 99.0 (C), 110.9 (CH_2), 122.0 (CH), 125.2 (CH), 128.9 (CH), 140.0 (CH), 143.8 (C), 154.2 (C).

4-[*N*-(2-Iodophenyl)-*N*-methylamino]-2-methylbutanal (13). Operating as in the preparation of **10**, the sequence hydroboration/oxidation−hydrolysis/Swern oxidation starting from *N*-methyl-*N*-(3-methyl-3-butenyl)-2-iodoaniline (0.58 g, 1.93 mmol), afforded 4-[*N*-(2-iodophenyl)-*N*-methylamino]-2-methylbutanal (**13**, 200 mg, 33%) as a pale yellow oil after flash chromatography (SiO_2, CH_2Cl_2): ^{1}H NMR (300 MHz) δ 1.11 (d, J = 6.9 Hz, 3H), 1.53 (m, 1H), 2.01 (m, 1H), 2.58 (m, 1H), 2.68 (s, 3H), 3.01 (m, 2H), 6.80 (ddd, J = 8.1, 7.2, and 1.5 Hz, 1H), 7.10 (dd, J = 8.1 and 1.5 Hz, 1H), 7.31 (ddd, J = 8.1, 7.2, and 1.5 Hz, 1H), 7.85 (dd, J = 8.1 and 1.5 Hz, 1H), 9.67 (t, J = 1.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 13.4 (CH_3), 28.3 (CH_2), 43.0 (CH_3), 44.0 (CH), 53.6 (CH_2), 99.4 (C), 122.2 (CH), 125.7 (CH), 129.0 (CH), 140.0 (CH), 153.9 (C), 204.7 (CH); HRMS (ESI-TOF) calcd for $C_{12}H_{17}INO$ 318.0349 $[M + H]^+$, found 318.0346.

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3-[*N*-(2-Iodo-4-methylphenyl)-*N*-methylamino]-2,2-dimethylpropanol. To a cooled (−30 °C) solution of methyl 3-[*N*-(2-iodo-4-methylphenyl)-*N*-methylamino]-2,2-dimethylpropionate[6] (0.85 g, 2.35 mmol) in CH_2Cl_2 (45 mL), DIBAL-H (3.5 mL of 1 M solution in hexanes, 3.5 mmol) was added dropwise. After 3 h at room temperature, the reaction mixture was poured into a saturated NH_4Cl aqueous solution, and stirring was continued for 1.5 h. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with saturated $NaHCO_3$ aqueous solution. The organic extracts were dried, and the solvent was removed under a vacuum. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2) to give 3-[*N*-(2-iodo-4-methylphenyl)-*N*-methylamino]-2,2-dimethylpropanol (0.63 g, 81%) as a gum: ^{1}H NMR (300 MHz) δ 0.87 (s, 6H), 2.26 (s, 3H), 2.70 (s, 3H), 3.03 (s, 2H), 3.10 (bb, 1H), 3.47 (s, 2H), 7.13 (m, 2H), 7.68 (m, 1H); ^{13}C NMR (75.4 MHz) δ 20.2 (CH_3), 23.9 (2 CH_3), 37.3 (C), 48.4 (CH_3), 66.0 (CH_2), 71.8 (CH_2), 99.9 (C), 123.2 (CH), 130.1 (CH), 136.0 (C), 140.2 (CH), 153.4 (C).

3-[*N*-(2-Iodo-4-methylphenyl)-*N*-methylamino]-2,2-dimethylpropanal (16). Operating as in the preparation of **10** and starting from 3-[*N*-(2-iodo-4-methylphenyl)-*N*-methylamino]-2,2-dimethylpropanol (0.63 g, 1.89 mmol), 3-[*N*-(2-iodo-4-methylphenyl)-*N*-methylamino]-2,2-dimethylpropanal (**16,** 0.58 g, 93%) was obtained as a colorless oil after flash chromatography (SiO_2, CH_2Cl_2): ^{1}H NMR (300 MHz) δ 1.09 (s, 6H), 2.26 (s, 3H), 2.61 (s, 3H), 3.19 (s, 2H), 7.09 (m, 2H), 7.66 (m, 1H), 9.58 (s, 1H); ^{13}C NMR (75.4 MHz) δ 20.2 (CH_3), 20.8 (2 CH_3), 46.8 (CH_3), 48.3 (C), 63.6 (CH_2), 100.2 (C), 123.4 (CH), 130.0 (CH), 136.1 (C), 140.2 (CH), 152.6 (C), 206.4 (CH); HRMS (ESI-TOF) calcd for $C_{13}H_{19}INO$ 332.0506 $[M + H]^+$, found 332.0510.

Methyl 2-[*N*-(2-iodophenyl)-*N*-methylamino]-2-methylpropanoate. LiHMDS (1 M solution in THF, 24 mL, 24 mmol) was added dropwise at 0 °C to a solution of methyl 2-[*N*-(2-iodophenyl)-*N*-methyl]acetate[35] (925 mg, 3.03 mmol) in dry THF (10 mL). The reaction mixture was stirred at 0 °C for 30 min, and then MeI (2.9 mL, 45.5 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight. After hydrolysis with saturated NH_4Cl aqueous solution, the aqueous layer was extracted twice with diethyl ether, and the combined organic extracts were washed with brine and dried. Evaporation of the solvent afforded crude methyl 2-[*N*-(2-iodophenyl)-*N*-methylamino]-2-methylpropanoate (915 mg, 90%) as a gum, which was used in the next step without purification: ^{1}H NMR (300 MHz) δ 1.40 (bb, 6H), 2.74 (s, 3H), 3.77 (s, 3H), 6.88 (ddd, J = 8.1, 7.5, and 1.5 Hz, 1H), 7.28 (ddd, J = 7.8, 7.5, and 1.5 Hz, 1H), 7.48 (dd, J = 8.1 and 1.5 Hz, 1H), 7.87 (dd, J = 7.8 and 1.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 25.5 (broad, 2 CH_3), 38.6 (CH_3), 51.5 (CH_3), 62.9 (C), 106.8 (C), 127.5 (CH), 128.6 (CH), 128.9 (CH), 139.1 (CH), 151.8 (C), 176.5 (C).

2-[*N*-(2-Iodophenyl)-*N*-methylamino]-2-methylpropanol. Operating as in the preparation of 3-[*N*-(2-iodo-4-methylphenyl)-*N*-methylamino]-2,2-dimethylpropanol and starting from methyl 2-[*N*-(2-iodophenyl)-*N*-methylamino]-2-methylpropanoate (915 mg, 2.75 mmol), 2-[*N*-(2-iodophenyl)-*N*-methylamino]-2-methylpropanol (410 mg, 49%) was obtained as an amorphous solid after flash chromatography (SiO_2, CH_2Cl_2): ^{1}H NMR (300 MHz) δ 0.93 (s, 3H), 1.24 (s, 3H), 2.56 (s, 3H), 3.16 (dd, J = 10.5 and 9.9 Hz, 1H), 3.54 (d, J = 9.9 Hz, 1H), 3.78 (d, J = 10.5 Hz, 1H), 6.93 (ddd, J = 8.1, 7.5, and 1.5 Hz, 1H), 7.33 (ddd, J = 8.1, 7.5, and 1.5 Hz, 1H), 7.43 (dd, J = 8.1 and 1.5 Hz, 1H), 7.89 (dd, J = 8.1 and 1.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 19.1 (CH_3), 24.6 (CH_3), 36.8 (CH_3), 59.5 (C), 68.4 (CH_2), 106.2 (C), 127.8 (CH), 128.1 (CH), 129.1 (CH), 139.2 (CH), 151.0 (C).

2-[*N*-(2-Iodophenyl)-*N*-methylamino]-2-methylpropanal (18). Operating as in the preparation of **10** and starting from 2-[*N*-(2-iodophenyl)-*N*-methylamino]-2-methylpropanol (485 mg, 1.59 mmol), 2-[*N*-(2-iodophenyl)-*N*-methylamino]-2-methylpropanal (**18**, 350 mg, 73%) was obtained as a pale yellow oil after flash chromatography (SiO_2, CH_2Cl_2): ^{1}H NMR (300 MHz) δ 1.17 (bb, 6H), 2.59 (s, 3H), 6.94 (m, 1H), 7.34 (m, 2H), 7.92 (dm, J = 8.4 Hz, 1H), 9.71 (s, 1H); ^{13}C NMR (75.4 MHz) δ 18.0 (broad, CH_3), 21.0 (broad, CH_3), 38.9 (CH_3), 66.1 (C), 106.8 (C), 128.0 (CH), 128.6 (CH), 129.1 (CH), 139.5 (CH), 149.9 (C), 204.2 (CH); HRMS (ESI-TOF) calcd for $C_{11}H_{15}INO$ 304.0193 $[M + H]^+$, found 304.0191.

Representative Procedure for the Pd(0)-Catalyzed Acylation (Table 1, Entry 18). A mixture of aldehyde **1** (75 mg, 0.2 mmol), Cs_2CO_3 (195 mg, 0.6 mmol), Et_3N (0.17 mL, 1.2 mmol), $Pd_2(dba)_3$ (9 mg, 0.01 mmol), and dtpf (9.5 mg, 0.02 mmol) in toluene (8 mL) was stirred at 110 °C in a sealed tube for 19 h. The reaction mixture was poured into water and extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO_2, from hexanes to hexanes−EtOAc 10%) to give dihydroquinolin-4-one **3** (32 mg, 65%) as a pale yellow oil.

Representative Procedure for the Pd(0)-Catalyzed α-Arylation Using KO-*t*-Bu as the Base (Table 3, Entry 7). To a solution of aldehyde **13** (75 mg, 0.24 mmol) in THF (10 mL) were added under argon phenol (68 mg, 0.72 mmol), KO-*t*-Bu (0.36 mmol, 0.36 mL of 1 M solution in *tert*-butyl alcohol), Et_3N (0.2 mg, 1.44 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), and xantphos (14 mg, 0.024 mmol). The solution was heated at 75 °C for 24 h. After being cooled at room temperature, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and 1 N aqueous NaOH. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2) to give aldehyde **15** (42 mg, 93%) as a colorless oil.

1-(*tert*-Butoxycarbonyl)-2,3-dihydro-1*H*-quinolin-4-one (3). Pale yellow oil, (32 mg, 65%; Table 1, Entry 18): ^{1}H NMR (300 MHz) δ 1.56 (s, 9H), 2.77 (t, J = 6.3 Hz, 2H), 4.16 (t, J = 6.3 Hz, 2H), 7.15 (ddd, J = 7.5, 7.2, and 1.5 Hz, 1H), 7.50 (ddd, J = 8.5, 7.2, and 1.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.99 (dd, J = 7.5 and 1.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 28.3 (CH_3), 39.0 (CH_2), 44.3 (CH_2), 82.1 (C), 123.6 (CH), 123.8 (CH), 124.9 (C), 127.3 (CH), 133.9 (CH), 144.1 (C), 152.7 (C), 194.1 (C); HRMS (ESI-TOF) calcd for $C_{14}H_{18}NO_3$ 248.1287 $[M + H]^+$, found 248.1283.

1-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydroquinolin-4-ol (4). White amorphous solid, (13 mg, 26%; Table 1, Entry 7): ^{1}H NMR (400 MHz) δ 1.53 (s, 9H), 1.87 (bb, 1H), 1.96−2.12 (m, 2H), 3.59 (ddd, J = 13, 10, and 4 Hz, 1H), 4.04 (ddd, J = 13, 5.6, and 4.8 Hz, 1H), 4.76 (t, J = 4.4 Hz, 1H), 7.07 (td, J = 7.6 and 1.2 Hz, 1H), 7.24 (ddd, J = 8, 7.6, and 1.5 Hz, 1H), 7.38 (dd, J = 7.6 and 1.5 Hz, 1H), 7.78 (d, J = 8 Hz, 1H); ^{13}C NMR (100.5 MHz) δ 28.3 (CH_3), 31.9 (CH_2), 40.4 (CH_2), 65.9 (CH), 81.2 (C), 123.4 (CH), 123.6 (CH), 127.9 (CH), 128.1 (CH), 130.5 (C), 137.8 (C), 153.5 (C); HRMS (ESI-TOF) calcd for $C_{14}H_{20}NO_3$ 250.1443 $[M + H]^+$, found 250.1440.

1-Methyl-1,2,3,4-tetrahydrobenzo[*b*]azepin-5-one (7). Brown oil, (17 mg, 38%; Table 2, Entry 2): ^{1}H NMR (300 MHz) δ 2.23 (quint, J = 6.9 Hz, 2H), 2.78 (t, J = 6.9 Hz, 2H), 3.11 (s, 3H), 3.23 (t, J = 6.9 Hz, 2H), 6.81 (ddd, J = 8.1, 7.2, and 0.9 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 7.33 (ddd, J = 8.4, 7.2, and 1.8 Hz, 1H), 7.76 (dd, J = 8.1 and 1.8 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 31.0 (CH_2), 40.0 (CH_3), 40.9 (CH_2), 57.2 (CH_2), 113.8 (CH), 117.9 (CH), 127.0 (C), 129.7 (CH), 132.4 (CH), 154.1 (C), 203.0 (C); HRMS (ESI-TOF) calcd for $C_{11}H_{14}NO$ 176.1070 $[M + H]^+$, found 176.1070.

1-Methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ol (8). Pale yellow oil, (5 mg, 11%; Table 2, Entry 4): ^{1}H NMR (400 MHz) δ 1.63 (m, 1H), 1.84 (m, 1H), 1.90−2.06 (m, 2H), 2.82 (m, 1H), 2.84 (s, 3H), 3.00 (m, 1H), 4.15 (bb, 1H), 4.81 (dd, J = 6.4 and 3.2 Hz, 1H), 6.95−7.02 (m, 2H), 7.18−7.24 (m, 2H); ^{13}C NMR (100.5 MHz) δ 24.4 (CH_2), 32.4 (CH_2), 42.1 (CH_3), 56.9 (CH_2), 74.2 (CH), 116.9 (CH), 122.2 (CH), 127.0 (CH), 127.9 (CH), 137.1 (C), 150.0 (C); HRMS (ESI-TOF) calcd for $C_{11}H_{16}NO$ 178.1226 $[M + H]^+$, found 178.1227.

1-(*tert*-Butoxycarbonyl)-2-methyl-2,3-dihydro-1*H*-quinolin-4-one (11). Pale yellow oil, (16 mg, 31%; Table 3, Entry 2): ^{1}H NMR (300 MHz) δ 1.24 (d, J = 6.9 Hz, 3H), 1.56 (s, 9H), 2.77 (m, 1H), 3.69 (dd, J = 13.5 and 9.6 Hz, 1H), 4.33 (dd, J = 13.5 and 4.5 Hz, 1H), 7.14 (ddd, J = 7.8, 7.2, and 1.2 Hz, 1H), 7.48 (ddd, J = 8.4, 7.2, and 1.8 Hz, 1H), 7.78 (dd, J = 8.4 and 0.6 Hz, 1H), 8.00 (ddd, J = 7.8, 1.8, and 0.6 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 12.7 (CH_3), 28.3 (CH_3), 42.5 (CH), 50.3 (CH_2), 82.1 (C), 123.4 (CH), 123.7 (CH), 124.1 (C),

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127.6 (CH), 133.7 (CH), 144.0 (C), 153.0 (C), 196.9 (C); HRMS (ESI-TOF) calcd for $C_{15}H_{20}NO_3$ 262.1438 $[M + H]^+$, found 262.1442.

1-(*tert*-Butoxycarbonyl)-3-methyl-2,3-dihydro-1*H*-indole-3-carboxaldehyde (12). (Table 3, Entry 4): ^{1}H NMR (300 MHz, significant signals from a 3.5:1 mixture of **11** and **12**) δ 1.58 (s, 3H), 3.68 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 7.00 (td, J = 7.5 and 0.9 Hz, 1H), 7.27 (td, J = 7.5 and 1.2 Hz, 1H), 9.56 (s, 1H).

1,4-Dimethyl-1,2,3,4-tetrahydrobenzo[*b*]azepin-5-one (14). Pale yellow oil, (20 mg, 45%; Table 3, Entry 6): ^{1}H NMR (400 MHz) δ 1.16 (d, J = 6 Hz, 3H), 1.69 (td, J = 12 and 4.8 Hz, 1H), 2.52 (m, 1H), 3.03−3.15 (m, 2H), 3.12 (s, 3H), 3.32 (dd, J = 14.4 and 6.8 Hz, 1H), 6.80 (dd, J = 7.6 and 7.2 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 7.31 (ddd, J = 8.4, 7.2, and 1.6 Hz, 1H), 7.74 (dd, J = 7.6 and 1.6 Hz, 1H); ^{13}C NMR (100.5 MHz) δ 15.0 (CH_3), 39.9 (CH_3), 40.9 (CH_2), 43.7 (CH), 56.8 (CH_2), 113.3 (CH), 117.5 (CH), 126.8 (C), 129.9 (CH), 132.0 (CH), 153.5 (C), 205.2 (C); HRMS (ESI-TOF) calcd for $C_{12}H_{16}NO$ 190.1226 $[M + H]^+$, found 190.1223.

1,4-Dimethyl-1,2,3,4-tetrahydroquinoline-4-carboxaldehyde (15). Colorless oil, (42 mg, 93%; Table 3, Entry 7): ^{1}H NMR (300 MHz) δ 1.41 (s, 3H), 1.73 (ddd, J = 13.5, 6.6, and 4.2 Hz, 1H), 2.29 (ddd, J = 13.5, 7.8, and 4.5 Hz, 1H), 2.91 (s, 3H), 3.23 (m, 2H), 6.69 (dd, J = 8.4 and 1.2 Hz, 1H), 6.71 (td, J = 7.5 and 1.2 Hz, 1H), 6.95 (dd, J = 7.5 and 1.2 Hz, 1H), 7.17 (ddd, J = 8.4, 7.5, and 1.2 Hz, 1H), 9.46 (s, 1H); ^{13}C NMR (75.4 MHz) δ 23.6 (CH_3), 29.8 (CH_2), 39.3 (CH_3), 46.9 (CH_2), 48.3 (C), 111.8 (CH), 116.9 (CH), 121.6 (C), 128.3 (CH), 128.5 (CH), 146.8 (C), 202.1 (CH); HRMS (ESI-TOF) calcd for $C_{12}H_{16}NO$ 190.1226 $[M + H]^+$, found 190.1224.

1,2,2-Trimethylindolin-3-one (19). Yellow oil, (36 mg, 82%; Table 4, Entry 5): ^{1}H NMR (300 MHz) δ 1.24 (s, 6H), 2.94 (s, 3H), 6.68 (t, J = 7.8 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 7.45 (dd, J = 8.1 and 7.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 21.2 (2 CH_3), 27.1 (CH_3), 66.9 (C), 108.3 (CH), 116.6 (CH), 118.4 (C), 125.0 (CH), 137.4 (CH), 159.5 (C), 204.2 (CH); HRMS (ESI-TOF) calcd for $C_{11}H_{14}NO$ 176.1070 $[M + H]^+$, found 176.1068.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of new compounds and Cartesian coordinates and free energies of all species discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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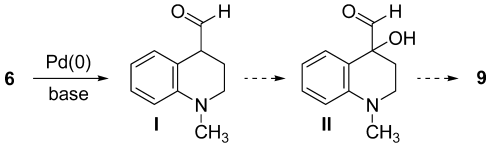

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