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NH_2 As a Directing Group: From the Cyclopalladation of Amino Esters to the Preparation of Benzolactams by Palladium(II)-Catalyzed Carbonylation of N-Unprotected Arylethylamines

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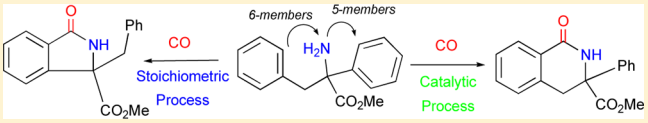
Supporting Information

ABSTRACT: An unusual NH_2-directed Pd(II)-catalyzed carbonylation of quaternary aromatic α-amino esters to yield benzolactams has been developed. The steric hindrance around the amino group is pivotal for the success of the process. The stoichiometric cyclometalation of a variety amino esters has been studied in order to evaluate the influence of the different variables (size of the metallacycle, aromatic ring substituents, and steric bulk) in the process, and a complete kinetico-mechanistic study of the cyclopalladation process has been carried out. The experimental results indicate that the full substitution of the carbon in the α position of the amino esters plays an important role in their cyclopalladation reaction. The reaction shows a strong bias toward six-membered lactams over the five-membered analogues, which can be explained by a greater reactivity of the six-membered palladacycles.



INTRODUCTION

The development of selective methods for the direct conversion of carbon−hydrogen bonds into carbon−heteroatom and carbon−carbon bonds remains a critical challenge in organic chemistry. An interesting approach to address this issue involves the use of substrates that contain coordinating atoms (or directing groups)[1] that bind to the metal center in a first step; a further rearrangement of some atoms allows the C−H bond activation. The latter process, at stoichiometric scale, is the well-known cyclometalation reaction.[2] The first cyclometalated compounds were reported in the mid 1960s.[3] Since then, this reaction has been extensively studied and has acquired a great interest given the application of metallacycles in many areas, which include organic synthesis, catalysis, design of metalomesogens and antitumoral drugs, asymmetric synthesis, resolution of racemic ligands, intermolecular aromatic C−H bond activation, and the synthesis and reactivity of organometallic complexes with biologically relevant ligands.[4] In this respect, the development of ligand-directed reactions has led to a renewed interest in the cyclometalation reactions. Palladium complexes are particularly attractive catalysts for such transformations because ligand-directed C−H functionalization at palladium centers can be used to obtain different types of C−Y bonds (Y being carbon, oxygen, nitrogen, sulfur, or halogen). Furthermore, palladium can activate C−H bonds both at sp^2 and sp^3 sites, and a wide range of catalytic processes have been described with different nitrogen-based directing groups. These include imines, oxime ethers, azobenzenes, amides, *N*-alkylanilines, benzodiazepines, pyridines, pyrazoles, and isoxazolines. Oxygen-based ligands, such as carboxylic acids and aldehydes, have also been used as directing groups in some cases.[1,5] In contrast, to the best of our knowledge, the use of primary amines as directing groups has not been described so far.

The transition-metal-catalyzed carbonylation of arenes with gaseous CO is a significant chemical transformation, since it extends the carbon chain length and also introduces a synthetically versatile carbonyl group. Arenes were first carbonylated to obtain carboxylic acids by Fujiwara et al. in 1980 using $Pd(AcO)_2$ under 15 atm of CO and the arene substrates as solvent.[6] However, no control over regioselectivity was observed for substituted arenes. This problem has been overcome by different research groups using the directing group approach.[1,7] Thus, Yu et al. has very recently described the palladium acetate-catalyzed carbonylation of anilides to obtain *N*-acyl anthranilic acids.[7d] Similarly, Orito et al. have reported the

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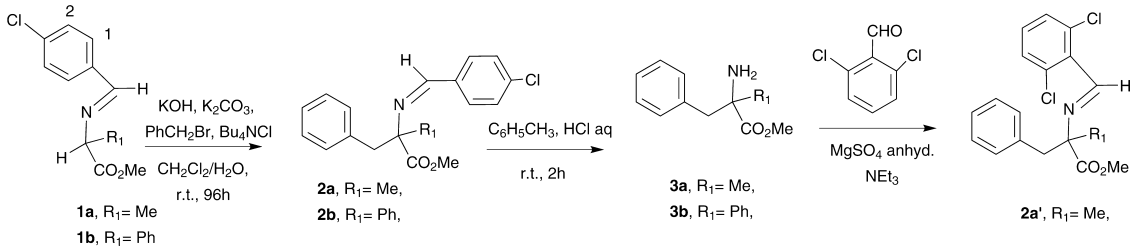
Scheme 1. Synthesis of Imines 2 and Aminoesters 3



direct carbonylation of aromatic C−H bonds with CO in *N*-alkyl-*ω*- arylalkylamines to obtain benzolactams using a $Pd(AcO)_2$/$Cu(AcO)_2$/air system in toluene solution at 120 °C.[7b,8] However, the authors stated, "carbonylation of primary amines, including benzylic amines or phenylethylamines, under the same conditions, produced no benzolactams but produced ureas in good yields." It should be noted that Pd(II) catalysts are readily reduced by CO, in a reaction that also produces Ac_2O, which could cause secondary reactions with primary amines.[9] Thus, a method for catalyzed C−H activation/carbonylation of primary amines under a CO environment has not been established.

Here we describe the preparation of benzolactams *via* palladium acetate-catalyzed aromatic carbonylation of quaternary *α*-amino *α*-alkyl esters, by an unusual process that uses NH_2 as a directing group.[10]

RESULTS AND DISCUSSION

As part of an ongoing research project on bioorganometallic chemistry,[11] we attempted the cyclometalation of imines RCH═NC(Me)(CH_2Ph)(COOMe) (**2a**: R = 4-ClC_6H_4; **2a′**: R = 2,6-$Cl_2C_6H_3$), derived from a quaternary *α*-amino ester, with $Pd(AcO)_2$ in toluene or acetic acid solution. Ligand **2a** was obtained by alkylation of imine **1a** with a mixture of KOH, K_2CO_3, and benzyl bromide. Ligand **2a′** was prepared from amino ester **3a** (obtained by hydrolysis of the imine **2a**) via a condensation reaction with 2,6-dichlorobenzaldehyde. The direct alkylation of the imine **1a′**, 2,6-$Cl_2C_6H_3$CH═NCH(Me)-(COOMe), gave a low yield of **2a′**; probably the steric hindrance of the di-*ortho*-chloro-substituted fragment (Scheme 1) hampers the process.

Treatment of imines **2a** and **2a′** with $Pd(AcO)_2$ in toluene or acetic acid solution at 80 °C did not produce the expected imine palladacycles. Only compound **5a**, [PdCl(CN)(PPh_3)] (CN being the metalated amino ester), was isolated, in low yield, after subsequent reaction with LiCl and PPh_3. Reaction of the free amino ester **3a** under the same conditions produced palladacycle **5a** in a much better yield, 50% (Scheme 2). Nevertheless, proton NMR batch monitoring of the reaction between **2a** and palladium acetate, under milder conditions, allowed the detection of the metalated imine (see below).

The preferential metalation of the aminoesters with respect to the corresponding imine derivatives is an unexpected result because closely related imines, derived from methyl glycinate, alaninate, valinate, and tyrosinate, have been reported to metalate in good yields;[11c] furthermore, the cyclometalation of primary amines has always been considered problematic.[12]

Bearing these facts in mind, we tried to extend the above cyclopalladation process to amino esters **3b−f** (Scheme 2), readily obtained by alkylation of the imines arising from commercial *α*-amino acid or *α*-amino ester hydrochlorides by standard procedures.[13] These were selected in order to study the influence of the different variables (size of the metallacycle formed, substituents in the aromatic ring, and steric bulk) in the process. Thus, ligand **3f** seems especially interesting due to the fact that it can afford two different metallacycles: one by activation of an unsubstituted benzene ring and the other by metalation of a MeO-substituted aromatic ring. Ligand **3b** is also remarkable, as it can afford either a five- or a six-membered metallacycle, depending on which aromatic ring undergoes the metalation reaction.

The reaction between amino esters **3a−f** and palladium acetate in toluene at 80 °C afforded, as expected, the dinuclear acetato-bridged compounds **4a−f** (X = AcO). Dinuclear halide-bridged compounds **4a−f** (X = Cl or Br) can also be obtained by reaction of the dinuclear acetato-bridged compounds with lithium halide in acetone at room temperature (30 min). Unfortunately, all attempts to purify the dinuclear six-membered metallacycles, either by column chromatography or by recrystallization, were unsuccessful, the complexes partially decomposing during the purification processes. In contrast **4b** (X = Br) can be purified by flash chromatography (hexane/EtAcO, 8:2) to afford the five-membered palladacycle **4b(5)** in 72% yield (see Experimental Section). Consequently, the preparation of the more stable mononuclear compounds **5** was attempted (see Scheme 2). The reaction was carried out from the acetato derivatives **4** (X = AcO) by reaction with PPh_3 and the corresponding lithium halide. Compounds **5** could be purified by column chromatography and isolated in good yields, as expected.

The yields of the metalation reactions of amino esters **3a**, **3d**, and **3e** to afford the corresponding six-membered metallacycles do not vary significantly, showing that the substituents on the aromatic ring that experience metalation do not play a significant role in the process. This fact has already been observed in the kinetico-mechanistic studies carried out on a family of carefully tuned imine derivatives.[14] Furthermore, metalation of both aromatic rings, in a equimolar ratio, is observed with ligand **3f**, which agrees with the nonelectrophilic substitution behavior of the observed process. The sequence is better explained through a mechanism involving a concerted proton abstraction from the metalating C−H unit by an ancillary ligand. The trends observed in the thermal and pressure activation parameters obtained in the above-mentioned studies suggest that once the C−H bond being activated reaches its correct positioning, the process is fairly independent of its electronic nature.[14] Recent computational studies of C−H bond activation at late transition metal systems indicate that assistance via coligands (especially carboxylates) is a good way of cleaving these bonds; the term "ambiphilic metal ligand activation" has been proposed to describe such reactions.[15] In contrast, the size of the metallacycle seems to play an important role in the cyclometalation reaction; metalation of ligand **3b** affords the five-membered metallacycle as the major isomer with respect to the six-membered analogue (6:1 ratio, by proton NMR).

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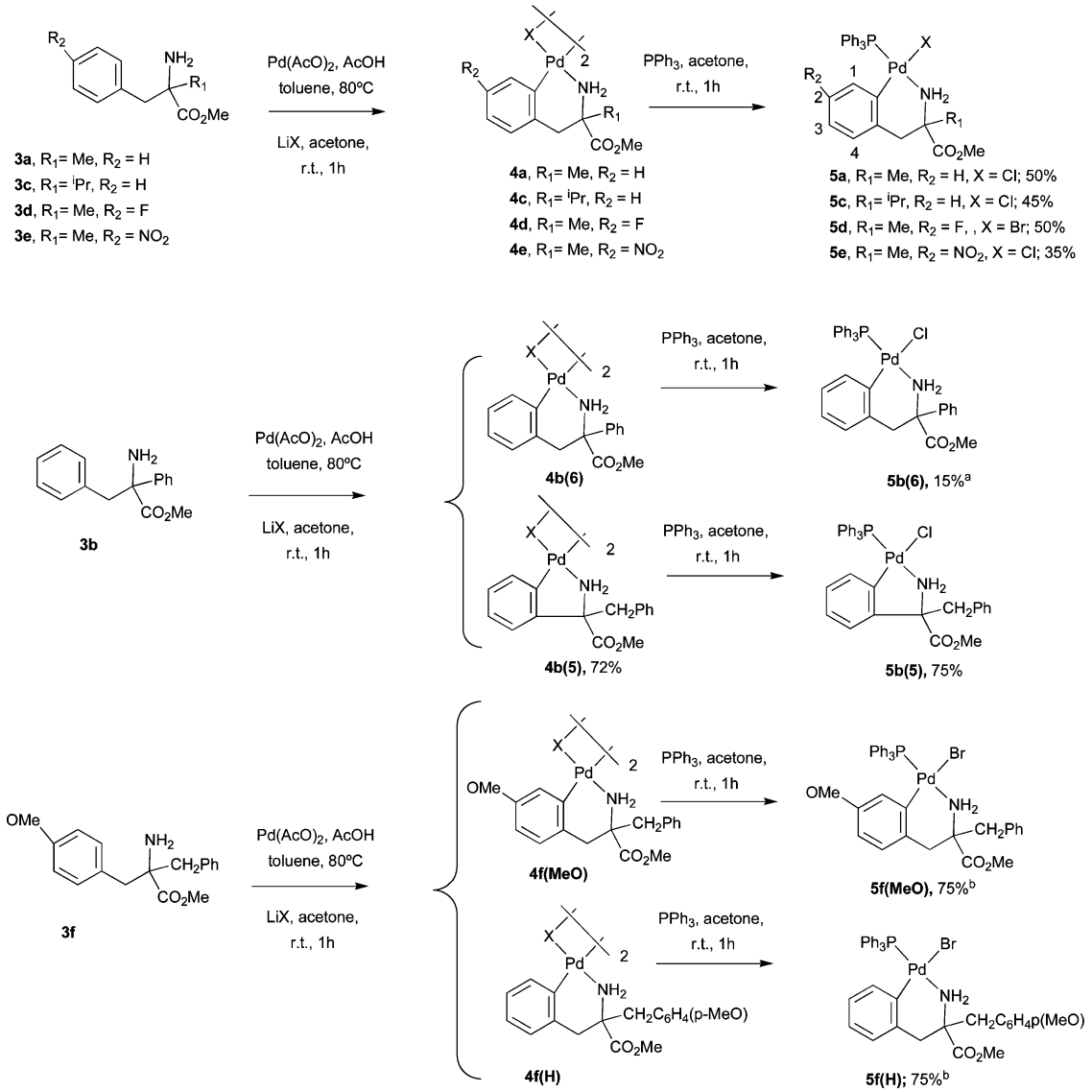
Scheme 2. Synthesis of Cyclometalated Compounds and 5[c]



[a]Detected by proton NMR. [b]1:1 mixture of regioisomers. [c]Compounds **4a**, **4b(6)**, **4c**, **4d**, **4e**, and **4f** could not be purified.

Good XRD-quality crystals of compounds **5a** and **5c** and the six-membered-ring isomer of **5b**, **5b(6)**, were obtained by vapor diffusion at 298 K of mixtures CH_2Cl_2/MeOH, CH_2Cl_2/C_6H_{14}, and MeC_6H_5/C_6H_{14}, respectively (Figures 1−3). It should be noted that the six-membered metallacycle **5b(6)** crystallizes from the mixture of five- and six-membered **5b** compounds, despite **5b(6)** being the minor component of the mixture. The strong intermolecular interactions present in the structure of this compound (see below) easily explain this fact.

For all compounds the distances between palladium and the coordinated atoms are similar to those reported, and the smallest angle in the coordination sphere of palladium corresponds to the C−Pd−N bite angle (Table 1).[16] The phosphorus and nitrogen atoms adopt a *trans* arrangement, the six-membered metallacycle has a boat conformation in all cases, and the coordination plane shows a slight tetrahedral distortion in both **5a** and **5c**.

The structures of compounds **5c** and **5b(6)** reveal diverse intermolecular interactions: conventional NH···O hydrogen bonds and nonconventional CH···O and CH···X hydrogen bonds. In contrast the crystal structure of **5a** reveals only nonconventional C−H···O hydrogen bonds.

The unexpected results found in the cyclopalladation of some of these ligands prompted us to carry out a complete kinetico-mechanistic study on the reaction between palladium acetate, amino esters **3a**, **3b**, and **3f**, and imine **2a** in toluene solution. The experiments were performed at [Pd]:[N-donor ligand] ratios within the 0.9−1.1 margin to avoid the formation of the dead-end *trans*-$[Pd(AcO)_2(\text{N-donor})_2]$ species, while having practically all the reactants as {Pd(AcO)(N-donor)} metalating units.[17] The reactions were monitored by UV−vis spectroscopy in the full 300−800 nm range, with *absorbance versus time* traces derived where larger differences were detected. The kinetic and thermal and pressure activation parameters thus obtained are collected in Table 2 (Figure 4). The parameters corresponding to the cyclopalladation of the *N*-benzylideneamine and benzylamine, previously reported,[12b,17b] have also been included in the same table for comparative purposes. The values obtained fall within the range of the values determined for similar systems, involving a large organization on going to the

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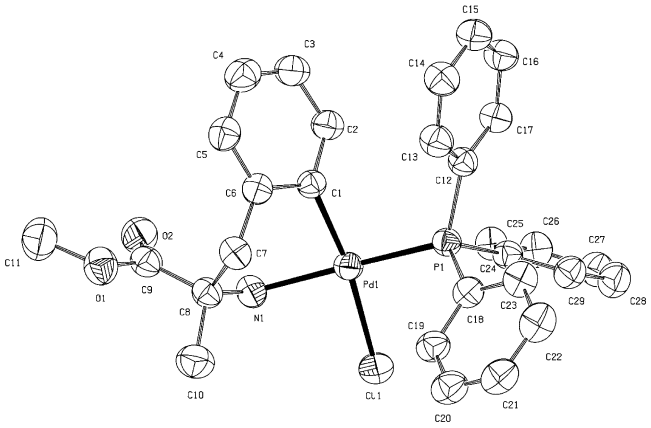

Figure 1. ORTEP plot of **5a**. Hydrogen atoms have been omitted for clarity.

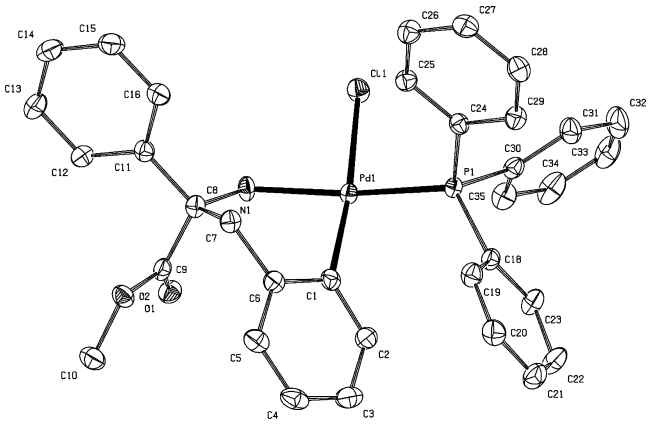

Figure 2. ORTEP plot of **5b(6)**. Hydrogen atoms have been omitted for clarity.

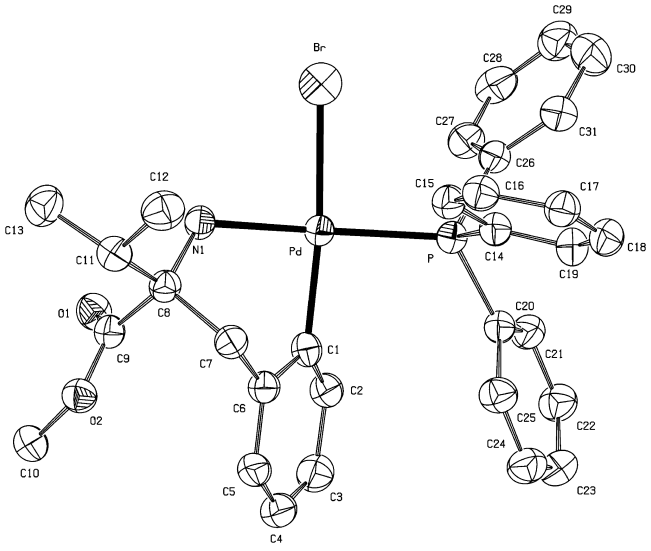

Figure 3. ORTEP plot of **5c**. Hydrogen atoms have been omitted for clarity.

transition state, which is accompanied by an important contraction in volume.

At a first glance it is evident that the cyclometalation of amino esters **3a**, **3b**, and **3f** in toluene is definitively faster than for other N-donor ligands previously studied.[14,17] For amino esters **3a** and **3b** it is also clear that this effect is related with a noticeable decrease in $\Delta S^{\ddagger}$ requirements, while for amino ester **3f** the difference in $\Delta H^{\ddagger}$ is responsible for this fact. In this respect, the feasibility of the separation of the five- and six-membered contributions to the metalation of amino ester **3b**, by NMR measurements on the final reaction mixture, allows a deeper view of the differences. While the differences in $\Delta H^{\ddagger}$ favor the formation of the five-membered metallacycles, the entropic terms indicate a less demanding process for the formation of the six-membered derivative, probably due to the greater flexibility of the starting material arrangement.

Table 1. Selected Bond Lengths (in Å) and Bond Angles (in deg) of 5a, 5c, and 5b(6)

	5a	5c	5b(6)
Bond Lengths			
Pd(1)−C(1)	1.986(3)	2.037(5)	2.003(2)
Pd(1)−N(1)	2.136(3)	2.134(4)	2.131(2)
Pd(1)−P(1)	2.2488(15)	2.255(2)	2.2507(11)
Pd(1)−X(1)[a]	2.4198(13)	2.4874(14)	2.4056(9)
N(1)−C(8)	1.480(4)	1.480(6)	1.502(3)
O(2)−C(9)	1.320(4)	1.349(6)	1.333(3)
O(2)−C(10)	1.459(5)	1.445(6)	1.453(3)
O(1)−C(9)	1.203(4)	1.180(6)	1.210(3)
Bond Angles			
C(1)−Pd(1)−N(1)	84.61(11)	89.14(17)	88.29(9)
C(1)−Pd(1)−P(1)	93.52(9)	92.76(14)	93.75(7)
N(1)−Pd(1)−X(1)[a]	86.08(9)	85.96(12)	85.41(6)
P(1)−Pd(1)−X(1)[a]	96.12(5)	92.78(6)	92.58(3
C(7)−C(8)−N(1)	109.6(3)	109.1(4)	109.28(18)
C(8)−C(9)−O(1)	124.6(3)	123.9(4)	123.8(2
C(8)−C(9)−O(2)	111.4(3)	111.0(4)	112.0(2)

[a]X = Cl for **5a** and **5c(6)**, and X = Br for **5c**.

A further comparison is also possible between the cyclometalation of amino ester **3a** and its corresponding imino derivative, **2a**; for this system the cyclometalation of the imine derivative is ca. 30-fold slower than that of the amino ester. The effect is, nevertheless, not originated in the separate values of $\Delta H^{\ddagger}$ or $\Delta S^{\ddagger}$, and the acceleration decreases to 10-fold at 300 K due to the much larger temperature dependence of the reaction rate of the amino ester.[18] Probably the higher rigidity of the starting imine material induces the need for a more demanding organization on going to the transition state providing lesser enthalpic requirements. This is especially relevant as far as the initial preparative observation (see before) of compound **4a** as the sole metalated compound on reaction of **2a** with $Pd(AcO)_2$ at 80 °C. It is evident that the metalated Pd(II) center promotes the hydrolysis of the cyclometalated imine derivative under the preparative conditions, and the consequent faster metalation of the amino ester occurs within the reaction mixture. Some preliminary kinetic runs indicate that the cyclometalated **2a** derivative undergoes the C═N bond hydrolysis process at a rate of 3.5×10^{-5} s^{-1} at 350 K in toluene solution, producing compound **4a**.

Given the fact that an acceleration of the cyclopalladation reactions is observed in protic media, due to the formation of a highly ordered ambiphilic transition state very sensitive to the presence of any protons, the use of acetic acid as solvent was also tried in the present study.[14,19] Surprisingly, the monitoring of the cyclopalladation reaction in acetic acid of amino ester **3a** does not produce the expected rate enhancement. In fact, the values measured for $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta V^{\ddagger}$ follow the opposite trend from what has been observed previously, i.e., increase in the enthalpic

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Table 2. Kinetic and Activation Parameters for the Cyclometalation Reactions Studied

metalating ligand	solvent	$10^4 \times {}^{350}k$ /s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K−1 mol^{-1}	$\Delta V^{\ddagger}$/cm^3 mol^{-1}
N-benzylamine[12b]	toluene	22	73	−91	−16
	acetic acid	100	100	3	−11
3a	toluene	170	81 ± 2	−50 ± 6	−13 ± 1
	acetic acid	53	49 ± 2	−152 ± 7	−16 ± 2
3b	toluene	460	71 ± 4	−71 ± 14	not measured[a]
five-membered metalation contribution[b]		580	70 ± 1	−72 ± 1	
six-membered metalation contribution[b]		350	76 ± 2	−59 ± 7	
3f	toluene	520	50 ± 2	−130 ± 5	not measured[a]
N-benzylidenbenzylamine[17b]	toluene	24	52 ± 3	−150 ± 10	−15 ± 2
2a	toluene	4.8	62 ± 3	−135 ± 10	−14 ± 2

[a]Not measured given the impossibility of separation of the five- and six-membered cyclometalation contribution under the conditions needed. [b]Proton NMR monitoring at different temperatures of the final five- to six-membered cyclometalated compound ratio allows the estimation of the $k_{5\text{-membered}}/k_{6\text{-membered}}$ value and thus the contribution of each reaction to the overall process.

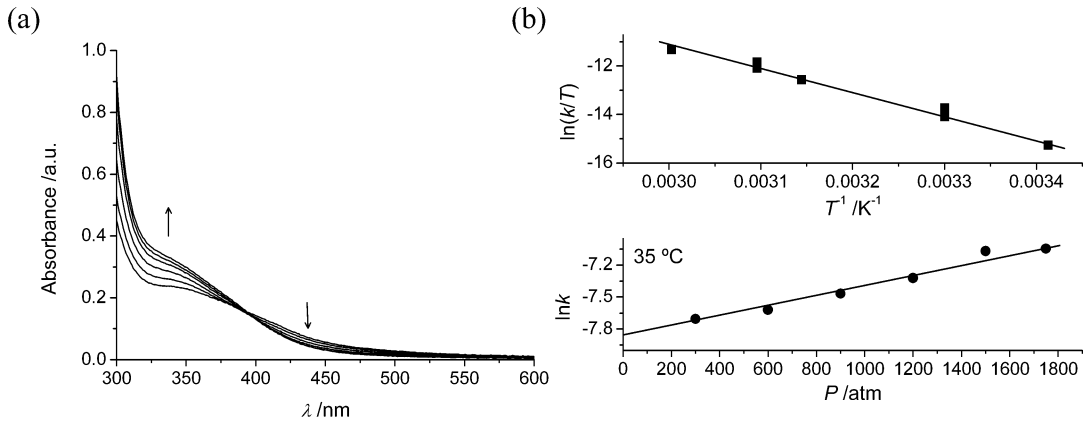
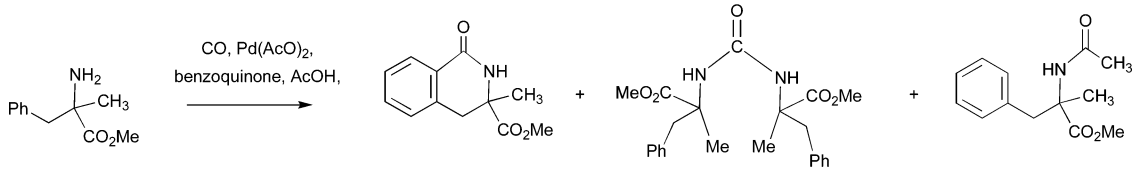


Figure 4. (a) UV−vis spectral changes observed for the reaction of an equimolar mixture of palladium acetate and amino ester **3b** in toluene at 30 °C, total time 150 min. (b) Eyring (top) and ln *k* versus *P* (bottom) plots for the reaction of amino ester **3a**.

Table 3. Optimization of Carbonylation of 3a



3a **6a** **7a** **8a**

entry	*t*/h	T/°C	benzoquinone (% molar)	overall yield (%)	**6a**/**7a**/**8a** ratio
1[a]	6	reflux	100	98	80:—:20
2	6	65	100	95	58:—:42
3	6	reflux	200	91	90:—:10
4[b]	6	reflux	100	92	70:—:30
5	6	reflux	135	98	86:—:14
6	3	reflux	200	94	84:—:16

[a]2% molar of $Pd(OAc)_2$. [b]Two-fold **3a** and benzoquinone concentration.

demands and less negative entropy, accompanied by practically the same compression. Obviously, the existence of some interactions between the polar groups of the amino ester and the acetic acid used as a solvent has to be considered responsible for this observed difference. In this respect, the X-ray determined structure of **5a**, **5c**, and **5b(6)** (see above) clearly shows the tendency of these amino esters to form hydrogen bond interactions. This lack of enhancement of the metalation process in acetic acid solution is rather relevant for the catalytic results indicated below. It is clear from the results obtained from the kinetic experiments that the effect of the acetic acid solvent in the catalysis cannot be related to the formation of the cyclometalated derivative.

Summarizing, the results indicate that the full substitution of the carbon in the α position of the amino esters plays a pivotal role in their cyclopalladation reaction behavior. The difference between the $\Delta S^{\ddagger}$ values of metalation of amino ester **3a** (-50 J K^{-1} mol^{-1}) and benzylamine (-91 J K^{-1} mol^{-1}) suggests that this effect is related with a noticeable decrease in $\Delta S^{\ddagger}$ requirements. This specificity can also be related with the

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Thorpe−Ingold effect[2b,20] (or *gem*-dimethyl effect), which improves the outcome of organic cyclization reactions when alkyl substituents are present on the acyclic carbon backbone. Nevertheless the role played by other factors such as $\Delta H^{\ddagger}$ or the hydrogen bond interactions, when acetic acid is used as a solvent, can not be discarded.

Catalytic Results. The great tendency shown by the free amino esters studied to undergo cyclopalladation prompted us to study their palladium-catalyzed NH_2-directed carbonylation at low pressure. Initially palladacycle **4a** was carbonylated to benzolactam **6a** with CO (1 atm) in different solvents at room temperature, thus indicating the feasibility of the process. Then the palladium acetate-catalyzed carbonylation of racemic amino acid **3a**, using $Cu(AcO)_2/O_2$ as the oxidant in toluene, was studied. Unfortunately, only urea **7a** (Table 3) was obtained under different experimental conditions, not the expected benzolactam **6a**. Given the strong accelerating effect of acetic acid in $Pd(AcO)_2$-catalyzed reactions,[21] we swapped to this solvent. Under these conditions, the desired **6a** lactam was obtained although contaminated with acetamide **8a**. The best ratio was **6a**/**8a** = 64:36 in a 91% yield. Since the formation of acetamide may also be favored by the Cu(II) salts, which can enhance the amide bond formation,[22] an alternative oxidant was tried; benzoquinone proved to be the better choice (Table 3). The best results were obtained with a 1.5×10^{-2} M solution of **3a** in refluxing AcOH using 5% molar $Pd(AcO)_2$ and an amino ester/benzoquinone molar ratio of 1:2. Under these conditions the yield was 91% and the benzolactam/acetamide ratio was 90:10 (entry 3).

The catalytic process was successfully expanded to other racemic phenylethylamines and to some lactams substituted at the aromatic ring. The results are shown in Table 4 and Scheme 3, respectively. From the data it is clear that the steric hindrance of the R and R′ groups plays a crucial role in the process. Thus, the carbonylation of methylphenylalaninate produced a rather low benzolactam/acetamide ratio, 46:54 (R′ = H, entry 4), which improved for compound **3a** (Table 3). Even no acetamides were found in the preparation of **6g**, **6f**, and **6h** bearing larger R′ groups (entries 1−3, R′ = propyl, benzyl, and *para*-methoxybenzyl, respectively). An increase in the steric hindrance around the amino group prevents competitive acetylation. Interestingly, the presence of the ester group is not essential for the success of the catalytic carbonylation (entry 6). However, the presence of a neighboring coordinating hydroxymethyl or allyl group erodes or inhibits completely the formation of benzalactam (entries 7 and 5, respectively). It should be also noted that the presence of MeO, CN, or F groups on the aromatic ring (**6f(MeO)** and **6m−o** in Scheme 3) is compatible with the formation of a lactam.

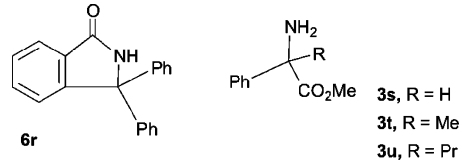
The reaction is also found highly sensitive to the size of the benzolactam formed; no five-membered lactams were detected when the reaction was performed with ligands **3s**, **3t**, and **3u** (Scheme 4). Nevertheless a 57% yield of the five-membered lactam **6r** was obtained from triphenylmethylamine with a total selectivity. It should be noted that, in this last case, the corresponding amino ester presents a larger steric hindrance around the amino group. These results are in sharp contrast with those reported by Orito et al.[8] for the related carbonylation of

Table 4. Carbonylation of Phenylethylamines

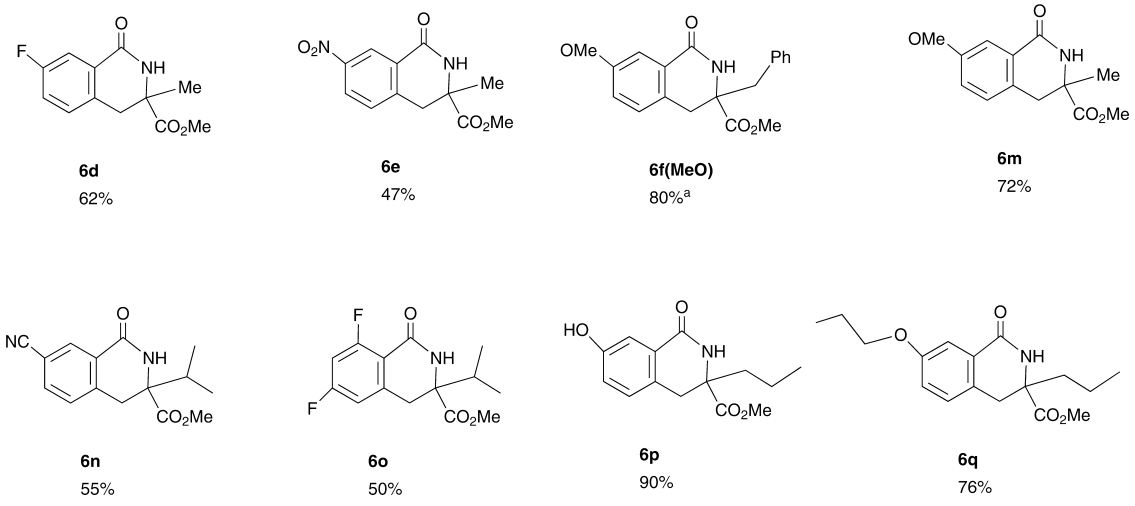
entry	R	R′	lactam	overall yield (%)	lactam/acetamide ratio
1	CO_2Me	propyl	**6g**	98	100:0
2	CO_2Me	Bn	**6h**	93	100:0
3	CO_2Me	*p*-MeO-Bn	**6f**	80[a]	100:0
4	CO_2Me	H	**6i**	91	46:54
5	CO_2Me	allyl	**6j**		[b]
6	Me	Me	**6k**	89	82:18
7	CH_2OH	Bn	**6l**	85	50:50[c]

[a]Mixture of regioisomers (**6f(H)**/**6f(MeO)** = 6:4). [b]Complex mixture of compounds. [c]Lactam **6l** is not acetylated on the hydroxyl group.

Scheme 4. Benzolactam 6r and Methyl Phenylgycinates 3s−u



Scheme 3. Benzolactams Substituted on the Aromatic Ring



[a]Mixture of regioisomers (see Table 4).

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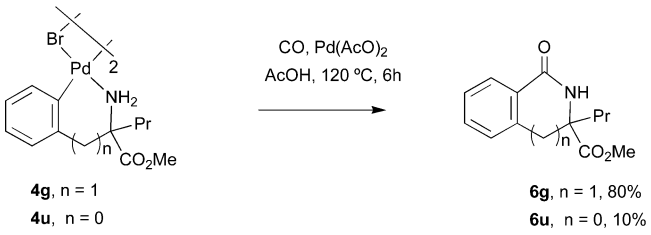
secondary amines using Cu(II) as co-oxidant, in which the five-membered benzolactams were favored over the six-membered analogues.

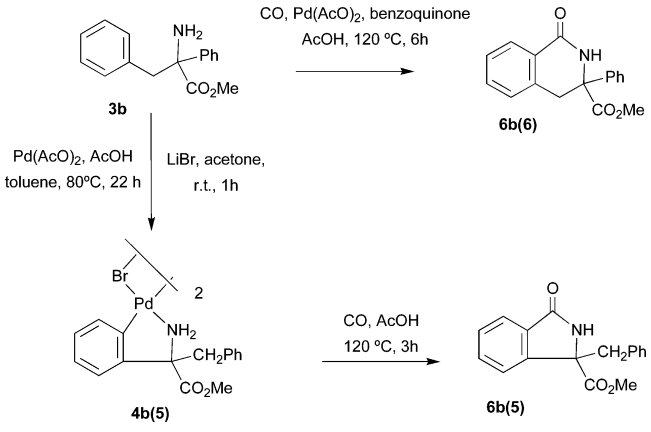
A greater reactivity of the six-membered palladacycles involved could explain this result. To assess this assumption, the reactivity of the six- and five-membered cyclopalladated derivatives **4g** and **4u** (Scheme 5) with CO was studied. Thus, after 1 h of reaction at

Scheme 5. Carbonylation of 4g and 4u



50 °C, the six-membered benzolactam **6g** was obtained in a 80% yield from **4g**, whereas **4u** afforded only a 10% yield of compound **6u**, in full agreement with the catalytic results (Scheme 5). In contrast, the catalytic carbonylation of **3b** produced only lactam **6b(6)**, which originates from the six-membered metallacycle, despite the fact that the stoichiometric cyclometalation of **3b** favors the five-membered palladacycle **4b(5)** as a major product in the **4b** product mixture (Scheme 2). Nevertheless, carbonylation of a pure sample of **4b(5)** in refluxing AcOH afforded the corresponding five-membered lactam **6b(5)** in 86% yield, thus indicating that both benzolactams sizes (six or five) are attainable depending on the carbonylation method (catalytic or stepwise) (Scheme 6).

Scheme 6. Catalytic and Stepwise Carbonylation of 3b



The results indicate that, even though both five-membered and six-membered palladacycles are capable of carbonylation to produce the corresponding lactams, the latter reacts more quickly with CO, affording **6b(6)** as the only isomer.

Conclusions. An adequate selection of the R groups positioned on the acyclic carbon backbone of phenylethylamines and benzylamines allows an unprecedented NH_2-directed catalytic carbonylation with high selectivity and yield. Kinetic results of the cyclometalation process indicate that the formation of the metalated palladium intermediate is much faster than for other systems, even though the presence of protic medium does not favor such a process as for other N-donor ligands. Thus, the studies show that the favorable effect of acetic acid as the solvent in the catalytic process can not be related to the formation of the cyclometalated derivative. The good catalytic results obtained with the palladium acetate/acetic acid system can be explained by the fact that some key steps are assisted by strong hydrogen bonding with AcOH molecules. Finally, the unexpected strong bias toward the six-membered lactams over five-membered analogues can also be explained by the greater reactivity of the six-membered palladacycles formed. Studies designed to expand the process to other organic derivatives of interest are currently under way.

EXPERIMENTAL SECTION

Materials and Methods. Amino esters, aldehydes, benzyl bromide, K_2CO_3, KOH, benzoquinone, $PdCl_2$, $Pd(AcO)_2$, LiCl, LiBr, and PPh_3 were obtained from commercial sources and used as received. Solvents were distilled and dried before use.[23]

Elemental analyses were carried out at the Serveis de Cientifico-Tècnics (Universitat Barcelona). Mass spectra were obtained at the Servei d'Espectrometria de Masses (Universitat de Barcelona). Infrared spectra were obtained with a Nicolet 400FTIR instrument using KBr pellets, and only the most relevant absorptions of the new products are presented in the following sections. High-resolution ^{1}H NMR spectra and the two-dimensional {^{1}H–^{1}H}-NOESY and COSY experiments were registered with a Varian VRX-500 or a Bruker Avance DMX-500 MHz instrument. The solvent used for NMR experiments was $CDCl_3$ (99.9%), and the references were $SiMe_4$ [for ^{1}H NMR] and $P(OMe)_3$ [$\delta(^{31}P)$ = 140.17 ppm, for ^{31}P NMR]. The chemical shifts (δ) are given in ppm, and the coupling constants (J) in Hz. In the characterization section of each product the assignment of signals detected in the ^{1}H NMR spectra refers to the labeling patterns presented in Schemes 1 and 2.

Procedures for synthesis and characterization of organic compounds **3** are giving in the Supporting Information.

Preparation of the Palladium(II) Complexes. *Compounds **4**, Typical Procedure. **4b(5)**.* A mixture of **3b** (500 mg, 1.96 mmol) and palladium acetate (439 mg, 1.96 mmol) in 40 mL of toluene was stirred at 80 °C for 22 h. The solvent was removed under vacuum, and the residue was treated with lithium bromide (213 mg, 2.45 mmol) in acetone (40 mL) for 1 h at rt. The suspension was filtered to obtain 783 mg (91%) of a 6:1 mixture of five-membered and six-membered palladacycles (^{1}H NMR of the crude). The crude was purified by flash chromatography (hexane/EtAcO, 8:2) to afford five-membered palladacycle **4b(5)** (625 mg, 72%). Compound **4b(5)**: brownish solid; mp 212–214 °C; R_f (hexane/EtAcO, 8:2) 0.32; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.44 (3H, m, ArH), 7.33 (3H, m, ArH), 7.18 (1H, dd, J = 7.7, 1.2 Hz, ArH), 7.04 (1H, m, ArH), 6.94 (1H, m, ArH), 4.75 (1H, br d, J = 10.3, NHH), 3.86 (3H, s, OCH_3), 3.72 (1H, d, J = 14.1 Hz, CHH), 3.61 (1H, d, J = 14.1 Hz, CHH), 3.67 (1H, br d, J = 10.3, NHH); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.1, 136.2, 133,9, 130.2, 130.0, 129.5, 129.4, 128.3, 127.2, 125.0, 123.0, 74.9 (q), 53.3 (OCH_3), 47.4 (CH_2); IR (KBr) ν_{max} 3296, 3256, 1730; HRMS (MALDI-TOF) calcd for $C_{32}H_{32}BrN_2O_4Pd_2$ $(M - Br)^+$ 798.9609, found 798.9626. Anal. Calcd for $C_{32}H_{32}Br_2N_2O_4Pd_2$: C, 43.61; H, 3.66; N, 3.18. Found: C, 43.7; H, 3.5; N, 3.3.

***4g*.** **4g** was obtained using the same procedure as that described above from 191 mg (0.87 mmol) of amine **3g** as a brownish solid: yield 305 mg (87%); mp 110–112 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.38 (1H, d, J = 7.8 Hz), 6.90 (1H, m), 6.83 (1H, m), 6.75 (1H, dd, J = 7.3, 1.8 Hz), 4.46 (1H, br d, J = 11.3 Hz, NHH), 3.68 (3H, s, OCH_3), 3.59 (1H, d, J = 13.8 Hz, CHH), 3.25 (1H, d, J = 13.8 Hz, CHH), 3.14 (1H, br d, J = 11.3 Hz, NHH), 1.98 (1H, m), 1.84 (1H, m), 1.43 (1H, m), 1.24 (1H, m), 0.95 (3H, t, J = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.9 (COO), 136.8, 135.0, 127.5, 127.4, 125.6, 124.6, 59.7 (q), 53.2 (OCH_3), 51.5 (CH_2), 40.0 (CH_2), 17.7 (CH_2), 14.0 (CH_3); IR (KBr) ν_{max} 3302, 3237, 1726, 1571, 1558, 1435, 1230; HRMS (MALDI-TOF) calcd for $C_{26}H_{36}BrN_2O_4Pd_2$ $(M - Br)^+$ 730.9928, found 730.9899. Anal. Calcd for $C_{26}H_{36}Br_2N_2O_4Pd_2$: C, 38.40; H, 4.46; N, 3.44. Found: C, 38.67; H, 4.33; N, 3.60.

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***4u*.** **4u** was obtained using the same procedure as that described above from 100 mg (0.48 mmol) of amine **3u** as a brownish solid: yield 305 mg (87%); mp 122−124 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.38 (1H, d, J = 7.8 Hz), 6.98 (2H, m), 6.88 (1H, m), 5.10 (1H, br d, J = 10.3 Hz, NH*H*), 3.83 (3H, s, OCH_3), 3.63 (1H, br d, J = 10.3 Hz, N*H*H), 2.18 (2H, m), 1.45 (1H, m, CH*H*), 1.34 (1H, m, C*H*H), 0.99 (3H, t, J = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.4 (*C*OO), 150.6, 144.9, 135.6, 127.1, 124.8, 123.9, 74.7 (q), 53.5 (O*C*H$_3$), 42.7 (*C*H$_2$), 17.3 (*C*H$_3$), 14.0; IR (KBr) ν_{max} 3296, 3252, 1729, 1571, 1433, 1210; HRMS (MALDI-TOF) calcd for $C_{24}H_{32}BrN_2O_4Pd_2$ (M − Br)$^+$ 702.9615, found 702.9609. Anal. Calcd for $C_{24}H_{32}Br_2N_2O_4Pd_2$: C, 36.71; H, 4.11; N, 3.57. Found: C, 36.65; H, 4.05; N, 3.75.

*Compounds **5**, Typical Procedure. **5a**.* A suspension of **3a** (318 mg, 1.64 mmol) and palladium acetate (358 mg, 1.59 mmol) in toluene (25 mL) was stirred at 80 °C for 22 h. The reaction mixture was cooled, and volatiles were removed under vacuum to obtain a solid. This solid was dissolved in acetone, LiCl (180 mg, 4.24 mmol) and PPh_3 (442 mg, 1.69 mmol) were added to the solution, and the resulting mixture was stirred at room temperature for 1 h. The solution was filtered and concentrated to afford, after addition of ethyl ether, a solid, which was purified by chromatography, using $CHCl_3$/MeOH (98:2) as eluent, to afford **5a** (532 mg, 50%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.59−7.50 (6H, m, PPh_3), 7.41−7.29 (9H, m, PPh_3), 6.70 (2H, d, J = 4.2 Hz, H^3, H^4), 6.46 (1H, dd, J = 7.5, 4.9 Hz, H^1), 6.34 (1H, m, H^2), 4.21 (2H, m, NH_2), 3.67 (3H, s, OCH_3), 3.59 (1H, d, J = 13.3 Hz, C*H*H), 3.30 (1H, d, J = 13.2 Hz, C*H*H), 1.76 (3H, s, CH_3); ^{31}P{^{1}H}NMR (250 MHz, $CDCl_3$) δ 34.16; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 136.93, 134.78 (d, J = 11.7 Hz, PPh_3), 130.34 (s, PPh_3), 128.07 (d, J = 10.8 Hz, PPh_3), 126.53, 125.63, 123.58, 54.15 (*C*H$_2$), 53.07 (*C*H$_3$O), 25.68 (*C*H$_3$); ESI-MS (+) {H_2O:CH_3CN}, m/z [M − Cl]$^+$ = 560.10, [2M − Cl]$^+$ = 1157.17. Anal. Calcd for $C_{29}H_{29}ClNO_2PPd$: C, 58.40; H, 4.90; N, 2.35. Found: C, 58.6; H, 5.1; N, 2.5.

***5b(5)*.** **5b(5)** was obtained using the same procedure as that described above from 311 mg (1.22 mmol) of amino ester **3b**. Yield: 833 mg (75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.70 (6H, m, PPh_3), 7.50−7.27 (17H, m), 6.89 (1H, m), 6.45 (2H, m), 4.76 (1H, dd, J = 3.9, 10.5 Hz, *H*NH), 4.16 (1H, dd, J = 3.1, 3.8 Hz, *H*NH), 3.82 (3H, s, CH_3O), 3.62 (1H, d, J = 13.9 Hz, *H*CH), 3.79 (1H, d, J = 14.3 Hz, *H*CH); ^{31}P{^{1}H} NMR (250 MHz, $CDCl_3$): δ 41.24; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 139.00, 135.27 (d, J = 12.0 Hz, PPh_3), 130.68 (PPh_3), 128.13 (d, J = 10.8 Hz, PPh_3), 126.38, 124.20, 123.00, 53.06 (*C*H$_3$O), 48.03 (*C*H$_2$); ESI-MS (+) {H_2O:CH_3CN}, m/z [M − Cl]$^+$ = 622.12. Anal. Calcd for $C_{34}H_{31}ClNO_2PPd$: C, 62.02; H, 4.75; N, 2.13. Found: C, 62.3; H, 5.0; N, 1.9.

***5c*.** **5c** was obtained using the same procedure as that described above from 255 mg (1.15 mmol) of amino ester **3c**. Yield: 344 mg (45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.51 (6H, m, PPh_3), 7.40−7.34 (3H, m, PPh_3), 7.31−7.27 (6H, m, PPh_3), 6.70−6.65 (2H, m, H^3, H^4), 6.46 (1H, dd, J = 7.6, 5.0 Hz, H^1), 6.35−6.25 (1H, m, H^2), 3.75 (1H, d, J = 12.7 Hz, *H*CH), 3.60 (3H, s, CH_3O), 3.13 (1H, d, J = 12.8 Hz, *H*CH), 2.44 (1H, m, C*H*CH$_3$), 1.34 (3H, d, J = 6.9 Hz, CH_3CH), 1.03 (3H, d, J = 6.9 Hz, CH_3CH); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 33.85; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.03, 134.75 (d, J = 11.6 Hz, PPh_3), 130.28 (s, PPh_3), 127.96 (d, J = 10.7 Hz, PPh_3), 126.31, 125.45, 123.45, 52.79 (*C*H$_3$O), 51.36 (*C*H$_2$), 34.678 (*C*HCH$_3$), 18.26 (*C*H$_3$CH), 17.18 (*C*H$_3$CH); ESI-MS (+) {H_2O:CH_3CN}, m/z [M − Br]$^+$ = 588.13; [M − Br + CH_3CN]$^+$ = 629.15. Anal. Calcd for $C_{31}H_{33}BrNO_2PPd$: C, 55.66; H, 4.97; N, 2.09. Found: C, 55.7; H, 4.8; N, 1.9.

***5d*.** **5d** was obtained using the same procedure as that described above from 110 mg (0.52 mmol) of amino ester **3d**. Yield: 170 mg (50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.53 (6H, m, PPh_3), 7.43−7.38 (3H, m, PPh_3), 7.34−7.30 (6H, m, PPh_3), 6.64 (1H, dd, J = 8.1, 5.7 Hz, H^4), 6.38 (1H, td, J = 8.3, 2.3 Hz, H^3), 6.08 (1H, ddd, J = 2.6, 4.8, 9.2 Hz, H^1), 3.67 (3H, s, CH_3O), 3.55 (1H, d, J = 13.3 Hz, *H*CH), 3.28 (1H, d, J = 13.3 Hz, *H*CH), 1.74 (3H, s, CH_3C); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 33.84 (br); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −115.4 (d, J = 105.9 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.75 (d, J = 11.5 Hz, PPh_3), 130.56 (PPh_3), 128.14 (d, J = 10.9 Hz, PPh_3), 126.75 (d, J = 7.33 Hz, C^4), 123.02, 110.16 (d, J = 21.9 Hz, C^3), 53.31 (*C*H$_2$), 53.15 (s, *C*H$_3$O), 25.51 (s, *C*H$_3$C); ESI-MS (+) {H_2O:CH_3CN}, m/z [M − Br]$^+$ = 578.09. Anal. Calcd for $C_{29}H_{28}BrFNO_2PPd$: C, 52.87; H, 4.28; N, 2.13. Found: C, 52.9; H, 4.2; N, 1.9.

***5e*.** **5e** was obtained using the same procedure as that described above from 189 mg (0.79 mmol) of amino ester **3e**. Yield: 160 mg (35%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62−7.55 (6H, m, PPh_3), 7.41−7.36 (3H, m, PPh_3), 7.34−7.29 (6H, m, PPh_3), 7.53 (1H, dd, J = 2.3, 8.2 Hz, H^3), 7.24 (1H, dd, J = 2.3, 4.2 Hz, H^1), 6.80 (1H, d, J = 8.2 Hz, H^4), 3.66 (3H, s, CH_3O), 3.63 (1H, d, J = 13.3 Hz, *H*CH), 3.37 (1H, d, J = 13.2 Hz, *H*CH), 1.76 (3H, s, CH_3C); ^{31}P{^{1}H} NMR (250 MHz, $CDCl_3$) δ 34.37; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.53, 144.85, 134.80 (d, J = 11.5 Hz, PPh_3), 131.75, 130.88 (PPh_3), 130.09 (PPh_3), 128.43 (d, J = 10.9 Hz, PPh_3), 126.25, 118.89, 56.72 (*C*H$_3$C), 53.87 (*C*H$_2$), 53.47 (*C*H$_3$O), 25.88 (*C*H$_3$C); ESI-MS (+) {H_2O:CH_3CN}, m/z [M − Cl]$^+$ = 605.07. Anal. Calcd for $C_{29}H_{28}ClN_2O_4PPd$: C, 54.31; H, 4.40; N, 4.37. Found: C, 54.4; H, 4.5; N, 3.9.

***5f*.** **5f** was obtained, as a 1:1 mixture of compounds, using the same procedure as that described above from 257 mg (0.86 mmol) of amino ester **3f**. Yield: 477 mg (75%). **5f(MeO):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.53 (6H, m, PPh_3), 7.41−7.36 (3H, m, PPh_3), 7.33−7.28 (6H, m, PPh_3), 6.66 (1H, d, J = 8.1 Hz, H^4), 6.27 (1H, dd, J = 2.5, 8.1 Hz, H^3), 5.98 (1H, dd, J = 2.5, 5.3 Hz, H^1), 3.77 (3H, s, CH_3O), 3.65 (3H, s, CH_3OCO); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 34.47; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.90 (d, J = 11.5 Hz, PPh_3), 130.35 (PPh_3), 128.06 (d, J = 10.6 Hz, PPh_3), 126.60, 120.78, 110.43, 55.21 (*C*H$_3$O), 52.81 (*C*H$_3$OCO). **5f(H):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.53 (6H, m, PPh_3), 7.36−7.41 (3H, m, PPh_3), 7.28−7.33 (6H, m, PPh_3), 6.72−6.33 (4H, m, H^1−H^4), 3.65 (3H, s, CH_3OCO), 3.18 (s, 3H, CH_3O); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 34.13; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 139.39, 134.90 (d, J = 11.5 Hz, PPh_3), 130.35 (PPh_3), 128.06 (d, J = 10.6 Hz, PPh_3), 126.33, 114.39, 54.53 (*C*H$_3$O), 52.81 (*C*H$_3$OCO); ESI-MS (+) {H_2O:CH_3CN}, m/z [M − Br]$^+$ = 666.14; [M − Br + CH_3CN]$^+$ = 707.17. Anal. Calcd for $C_{36}H_{35}BrNO_3PPd$: C, 57.89; H, 4.72; N, 1.88. Found: C, 57.8; H, 4.9; N, 1.7.

*Synthesis of **6a** by Stoichiometric Carbonylation of **4a**.* A suspension of **4a(X= Br)** (120 mg, 0.16 mmol) in methanol (25 mL) was stirred at room temperature in an atmosphere of nitrogen containing carbon monoxide delivered from a toy balloon (∼200 mL) for 24 h. The reaction mixture was filtered, washed with 10% aqueous $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was removed in a rotatory evaporator to obtain **6a** in 93% yield (65 mg).

***6a*:** mp 180−182 °C (lit.[24] 181−183 °C); R_f (CH_2Cl_2/MeOH, 98:2) 0.31; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.07 (1H, d, J = 7.7 Hz, Ar*H*), 7.46 (1H, m, Ar*H*), 7.36 (1H, m, Ar*H*), 7.22 (1H, d, J = 7.5 Hz, Ar*H*), 6.58 (1H, br s, NH), 3.69 (3H, s, OCH_3), 3.40 (1H, d, J = 15.7 Hz, C*H*H), 3.11 (1H, d, J = 15.7 Hz, CH*H*), 1.56 (3H, s, CCH_3); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.6 (*C*OO), 165.5 (*C*ONH), 136.1 (q), 132.8, 128.3, 127.9, 127.8, 127.6, 59.0 (q), 53.1 (O*C*H$_3$), 37.9 (*C*H$_2$), 25.9 (*C*H$_3$); IR (ATR) ν_{max} 3195, 1737, 1665; HRMS (ESI$^+$) calcd for $C_{12}H_{14}NO_3$ (M + H)$^+$ 220.0968, found 220.0968.

*Stepwise Preparation of Lactam **6b(5)**.* A stirred solution of palladacycle **4b(5)** (110 mg, 0.125 mmol) in AcOH (25 mL) was gently refluxed in an oil bath at 120 °C in an atmosphere of nitrogen containing carbon monoxide delivered from a toy balloon (∼200 mL) for 3 h. The reaction mixture was cooled and filtered through a thin pad of Celite. The volatiles were removed under vacuum, and the solid obtained was purified by flash chromatography to afford **6b(5)** (61 mg, 86%).

*Methyl 1-benzyl-3-oxoisoindoline-1-carboxylate, **6b(5)**:* white solid; mp 140−142 °C; R_f (hexane/EtAcO, 8:2) 0.32; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.82 (1H, d, J = 7.7 Hz, Ar*H*), 7.79 (1H, d, J = 7.5 Hz, Ar*H*), 7.64 (1H, m, Ar*H*), 7.52 (1H, m, Ar*H*), 7.27 (3H, m, Ar*H*), 7.12 (2H, m, Ar*H*), 6.53 (1H, br s, NH), 3.77 (1H, d, J = 13.4 Hz, C*H*H), 3.71 (3H, s, OCH_3), 2.96 (1H, d, J = 13.4 Hz, CH*H*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.6 (CO), 169.5 (CO), 144.9 (q), 134.5, 132.5, 130.8, 129.8, 129.5, 128.7, 127.7, 124.0, 123.3, 68.8 (q), 53.0 (O*C*H$_3$), 45.0 (*C*H$_2$); IR (ATR) ν_{max} 3219, 1733, 1695, 1611, 1250; HRMS (ESI$^+$) calcd for $C_{17}H_{16}NO_3$ (M + H)$^+$ 282.1130, found 282.1128.

Catalytic Synthesis of Benzolactams. Typical Procedure. A stirred suspension of methyl 2-amino-2-benzyl-3-phenylpropanoate (**3h**) (100 mg, 0.38 mmol), benzoquinone (83 mg, 0.76 mmol), and palladium acetate

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(4.5 mg, 0.02 mmol) in AcOH (25 mL) was gently refluxed in an oil bath at 120 °C in an atmosphere of nitrogen containing carbon monoxide delivered from a toy balloon (~200 mL) for 6 h. The reaction mixture was cooled and filtered through a thin pad of Celite. The volatiles were removed under vacuum to obtain a solid corresponding to almost pure benzolactam **6h**. The residue was purified by flash chromatography to afford **6h** (105 mg, 93%).

Methyl 1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, ***6b(6)****:* R_f (hexane/EtAcO, 7:3) 0.43; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.04 (1H, d, J = 7.7 Hz, Ar*H*), 7.48−7.25 (7H, m, Ar*H*), 7.20 (1H, d, J = 7.6 Hz, Ar*H*), 6.84 (1H, br s, NH), 3.75 (3H, s, OCH_3), 3.71 (1H, d, J = 15.6, C*H*H), 3.63 (1H, d, J = 15.6, CH*H*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.5 (*C*OO), 165.5 (*C*ONH), 139.1, 135.6, 132.9, 128.9, 128.5, 128.2, 128.0, 127.8, 127.7, 127.5, 125.3, 64.3 (*C*NH), 53.3 (O*C*H$_3$), 38.0 (*C*H$_2$); IR (ATR) ν_{max} 3174, 1733, 1661, 1602, 1446, 1377; HRMS (ESI$^+$) calcd for $C_{17}H_{16}NO_3$ (M + H)$^+$ 282.1130, found 282.1144.

Methyl 7-fluoro-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, ***6d****:* white solid; mp 123−127 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.75 (1H, dd, J = 8.8, 2.4 Hz, Ar*H*), 7.22−7.13 (2H, m, Ar*H*), 6.26 (1H, br s, NH), 3.71 (3H, s, OCH_3), 3.37 (1H, d, J = 14.8 Hz, C*H*H), 3.07 (1H, d, J = 15.9 Hz, CH*H*), 1.54 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.5, 173.9, 162.7 (d, J_{CF} = 245 Hz), 131.4 (d, J_{CF} = 8 Hz), 120.9 (d, J_{CF} = 22 Hz), 115.3 (d, J_{CF} = 21 Hz), 114.9 (d, J_{CF} = 23 Hz), 59.1, 53.3, 40.2, 37.3, 25.8, 23.5; IR (ATR) ν_{max} 3201, 1734, 1668, 1443, 1199; HRMS (ESI$^+$) calcd for $C_{12}H_{13}FNO_3$ (M + H)$^+$ 238.0874, found 238.0870.

Methyl 3-methyl-7-nitro-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, ***6e****:* reddish solid; mp 104−108 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.91 (1H, d, J = 2.4 Hz, Ar*H*), 8.31 (1H, dd, J = 8.4, 2.4 Hz, Ar*H*), 7.44 (1H, d, J = 8.4 Hz, Ar*H*), 6.51 (1H, br s, NH), 3.85 (1H, d, J = 16.4 Hz, C*H*H), 3.71 (3H, s, OCH_3), 3.11 (1H, d, J = 16.4 Hz, CH*H*), 1.59 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.9, 164.5, 164.4, 145.4, 144.2, 135.4, 129.1, 127.4, 121.1, 54.7, 52.3, 41.2, 22.8; IR (ATR) ν_{max} 3338, 1737, 1671, 1516, 1343, 1206; HRMS (ESI$^+$) calcd for $C_{12}H_{13}N_2O_5$ (M + H)$^+$ 265.0819, found 265.0798.

Mixture of methyl 3-(4-methoxybenzyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, ***6f(OMe)****, and methyl 3-benzyl-6-methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate,* ***6f(H)****:* white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (1H, d, J = 7.5 Hz, Ar*H*), 7.48 (1H, td, J = 7.5, 1.5 Hz, Ar*H*), 7.37 (1H, t, J = 7.5 Hz, Ar*H*), 7.24 (1H, d, J = 7.5 Hz, Ar*H*), 7.33−7.02 (4H, m, Ar*H*), 6.25 (1H, br s, N*H*), 3.79 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.43 (1H, d, J = 13.6 Hz, C*H*H), 3.23 (1H, d, J = 13.6 Hz, C*H*H) 3.17 (1H, d, J = 13.6 Hz, C*H*H), 2.96 (1H, d, J = 13.6 Hz, C*H*H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 165.1, 135.6, 111.3, 62.9, 55.2, 52.7, 43.8, 36.8; IR (ATR) ν_{max} 3189, 1734, 1666, 1610, 1513; HRMS (ESI$^+$) calcd for $C_{19}H_{20}NO_4$ (M + H)$^+$ 326.1387, found 326.1412.

Methyl 1-oxo-3-propyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, ***6g****:* white solid; mp 120−121 °C; R_f (hexane/EtAcO, 1:1) 0.48; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.06 (1H, d, J = 7.6 Hz, Ar*H*), 7.46 (1H, m, Ar*H*), 7.36 (1H, m, Ar*H*), 7.22 (1H, d, J = 7.5 Hz, Ar*H*), 6.43 (1H, br s, NH), 3.71 (3H, s, OCH_3), 3.37 (1H, d, J = 15.7 Hz, C*H*H), 3.13 (1H, d, J = 15.7 Hz, CH*H*), 1.79 (2H, m), 1.40 (1H, m), 1.25 (1H, m), 0.90 (3H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.3 (*C*OO), 165.1 (*C*ONH), 135.9, 132.6, 128.1, 127.9, 127.8, 127.4, 61.9 (*C*NH), 52.8 (OCH_3), 40.7, 36.6 (*C*H$_2$), 17.0 (*C*H$_2$), 13.9 (*C*H$_3$); IR (ATR) ν_{max} 3209, 1727, 1664, 1606, 1578, 1390; HRMS (ESI$^+$) calcd for $C_{14}H_{18}NO_3$ (M + H)$^+$ 248.1287, found 248.1294.

Methyl 3-benzyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, ***6h****:* white solid; mp 128−129 °C; R_f (hexane/EtAcO, 7:3) 0.30; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.09 (1H, d, J = 7.6 Hz, Ar*H*), 7.49 (1H, m, Ar*H*), 7.38 (1H, m, Ar*H*), 7.31−7.23 (4H, m, Ar*H*), 7.06 (2H, m, Ar*H*), 6.26 (1H, br s, NH), 3.63 (3H, s, OCH_3), 3.44 (1H, d, J = 15.8 Hz, CH_2), 3.24 (1H, d, J = 13.4 Hz, CH_2), 3.23 (1H, d, J = 15.8 Hz, CH_2), 3.03 (1H, d, J = 13.4 Hz CH_2); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.6 (*C*OO), 165.0 (*C*ONH), 135.5 (q), 134.0 (q), 132.7, 129.7, 128.7, 128.2, 127.8, 127.6, 127.5, 62.8 (*C*NH), 52.7 (OCH_3), 44.6, 36.8; IR (ATR) ν_{max} 3191, 1731, 1663, 1603, 1384; HRMS (ESI$^+$) calcd for $C_{18}H_{18}NO_3$ (M + H)$^+$ 296.1281, found 296.1283.

Methyl 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, ***6i****:* oil; lit.[25] ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.04 (1H, d, J = 7.5 Hz, Ar*H*), 7.47 (1H, m, Ar*H*), 7.37 (1H, m, Ar*H*), 7.25 (1H, m, Ar*H*), 6.48 (1H, br s, NH), 4.41 (1H, ddd, J = 9.9, 5.4, 2.1 Hz, NHC*H*), 3.79 (3H, s, OCH_3), 3.33 (1H, dd, J = 15.7, 5.2 Hz, C*H*H), 3.22 (1H, dd, J = 15.7, 9.9 Hz, CH*H*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.8 (*C*OO), 165.1 (*C*ONH), 136.1, 132.5, 129.3, 128.1, 127.5, 127.4, 53.0 (O*C*H$_3$), 52.8 (NH*C*H), 31.1 (*C*H$_2$); IR (ATR) ν_{max} 3271, 1737, 1656, 1546, 1536, 1215, 1176; HRMS (ESI$^+$) calcd for $C_{11}H_{12}NO_3$ (M + H)$^+$ 206.0817, found 206.0803.

3,3-Dimethyl-3,4-dihydroisoquinolin-1(2H)-one, ***6k****:* white solid; mp 146−147 °C (lit.[26] 146−147); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.06 (1H, d, J = 7.6 Hz, Ar*H*), 7.45 (1H, m), 7.36−7.13 (2H, m, Ar*H*), 6.37 (1H, br s, NH), 2.92 (2H, s, CH_2), 1.32 (6H, s, CH_3); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 165.5 (*C*ONH), 137.5, 132.2, 130.4, 127.8, 126.9, 126.2, 52.0 (*C*NH), 41.6 (*C*H$_2$), 28.8 (*C*H$_3$); IR (KBr) ν_{max} 3395, 1660; HRMS (ESI$^+$) calcd for $C_{11}H_{14}NO$ (M + H)$^+$ 176.1075, found 176.1069.

3-Benzyl-3-(hydroxymethyl)-3,4-dihydroisoquinolin-1(2H)-one, ***6l****:* brownish oil; R_f (hexane/EtAcO, 1:1) 0.20; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.05 (1H, d, J = 7.6 Hz, Ar*H*), 7.50 (1H, m, Ar*H*), 7.36 (1H, m, Ar*H*), 7.32−7.15 (6H, m, Ar*H*), 6.91 (1H, br s, N*H*, Ar*H*), 3.60 (1H, d, J = 11.2 Hz, C*H*H), 3.52 (1H, d, J = 11.2 Hz, CH*H*), 3.06 (1H, J = 13.6 Hz), 2.95−2.80 (4H, m); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 165.8 (*C*ONH), 136.7, 135.9, 132.8, 130.4, 128.5, 128.1, 128.0, 127.1, 126.9, 65.7 (*C*NH), 58.4, 33.7, 30.9; IR (ATR) ν_{max} 3383, 2927, 1651, 1387, 1253, 1094; HRMS (ESI$^+$) calcd for $C_{17}H_{18}NO_2$ (M + H)$^+$ 268.1338, found 268.1345.

Methyl 7-methoxy-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, ***6m****:* white solid; mp 171−174 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.58 (1H, d, J = 2.8 Hz, Ar*H*), 7.11 (1H, d, J = 8.4 Hz, Ar*H*), 7.01 (1H, dd, J = 8.4, 2.8 Hz, Ar*H*), 6.27 (1H, br s, NH), 3.84 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.33 (1H, d, J = 15.6 Hz, C*H*H), 3.03 (1H, d, J = 15.6 Hz, CH*H*), 1.53 (3H, s, CCH_3); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.0 (*C*OO), 165.4 (*C*ONH), 158.9, 130.7, 128.8, 127.9, 120.1, 111.2, 58.9 (*C*NH), 55.4 (O*C*H$_3$), 52.7 (O*C*H$_3$), 37.0 (*C*H$_2$), 25.5 (*C*H$_3$); IR (KBr) ν_{max} 3195, 3075, 2951, 1736, 1668, 1493, 1451, 1437, 1382; HRMS (ESI$^+$) calcd for $C_{13}H_{16}NO_4$ (M + H)$^+$ 250.1079, found 250.1068.

Methyl 7-cyano-3-isopropyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, ***6n****:* white solid; mp 176−178 °C; R_f (hexane/EtAcO, 1:1) 0.43; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.44 (1H, d, J = 1.6 Hz, Ar*H*), 7.72 (1H, dd, J = 8.0, 1.6 Hz, Ar*H*), 7.36 (1H, d, J = 8.0 Hz, Ar*H*), 6.29 (1H, br s, NH), 3.68 (3H, s, OCH_3), 3.38 (1H, d, J = 16.4 Hz, C*H*H), 3.26 (1H, d, J = 16.4 Hz, CH*H*), 2.18 (1H, m, C*H*CH$_3$), 1.00 (3H, d, J = 6.8 Hz, C*H*CH$_3$), 0.98 (3H, d, J = 6.8 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.7 (*C*OO), 163.7 (*C*ONH), 141.5, 135.4, 132.8, 128.9, 128.7, 117.9 (*C*N), 111.5, 65.3 (*C*NH), 52.8 (OCH_3), 35.0, 33.5, 17.1 (*C*H$_3$), 16.8 (*C*H$_3$); IR (ATR) ν_{max} 3205, 2963, 2229, 1670, 1610, 1433, 1330, 1277, 1189; HRMS (ESI$^+$) calcd for $C_{15}H_{17}N_2O_3$ (M + H)$^+$ 273.1239, found 273.1230.

Methyl 6,8-difluoro-3-isopropyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, ***6o****:* white solid; mp 138−140 °C; R_f (hexane/EtAcO, 1:1) 0.45; ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.77 (2H, m, Ar*H*), 6.29 (1H, br s, NH), 3.68 (3H, s, OCH_3), 3.27 (1H, d, J = 15.8 Hz, C*H*H), 3.17 (1H, d, J = 15.8 Hz, CH*H*), 2.12 (1H, hept, J = 6.9 Hz, C*H*CH$_3$), 0.99 (3H, d, J = 6.9 Hz, C*H*CH$_3$), 0.96 (3H, d, J = 6.9 Hz, C*H*CH$_3$); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.5 (*C*OO), 166.0 (*C*ONH), 164.7, 165.0 (dd, J_{CF} = 251.2, 13.3 Hz), 163.3 (dd, J_{CF} = 274.2, 8.0 Hz), 141.3 (d, J_{CF} = 10.4 Hz), 110.9 (dd, J_{CF} = 21.9, 4.0 Hz), 104.4 (t, J_{CF} = 25.5 Hz), 64.9 (*C*NH), 52.7 (OCH_3), 34.9, 29.7, 17.2 (*C*H$_3$), 16.9 (*C*H$_3$); IR (ATR) ν_{max} 3226, 3090, 2960, 1724, 1667, 1615, 1307, 1228, 1122; HRMS (ESI$^+$) calcd for $C_{14}H_{16}F_2NO_3$ (M + H)$^+$ 284.1098, found 284.1085.

Methyl 7-hydroxy-1-oxo-3-propyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, ***6p****:* white solid; mp 169−173 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.73 (1H, d, J = 2.8 Hz, Ar*H*), 7.08 (1H, d, J = 7.6 Hz, Ar*H*), 7.00 (1H, dd, J = 8.4, 2.8 Hz, Ar*H*), 6.32 (1H, br s, NH), 3.71 (3H, s, OCH_3), 3.28 (1H, d, J = 15.6 Hz, C*H*H), 3.04 (1H, d, J = 15.9 Hz, CH*H*), 1.78 (2H, t, J = 9.2 Hz, CH_2CH$_2$CH$_3$), 1.42−1.16 (2H, m, CH$_2$CH_2CH$_3$), 1.02 (3H, t, J = 7.2 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.3, 165.5, 156.0, 129.1, 127.2, 120.5, 114.8, 62.3, 52.8, 40.5, 35.8, 17.1, 13.9; IR (ATR) ν_{max} 3124, 1723, 1658, 1383,

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1260; HRMS (ESI$^+$) calcd for $C_{28}H_{35}N_2O_8$ $(2M + H)^+$ 527.2388, found 527.2381.

Methyl 1-oxo-7-propoxy-3-propyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, ***6q:*** white solid; mp 119−123 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.56 (1H, d, J = 2.8 Hz, Ar*H*), 7.10 (1H, d, J = 8.4 Hz, Ar*H*), 7.00 (1H, dd, J = 8.4, 2.8 Hz, Ar*H*), 6.32 (1H, br s, NH), 3.95 (2H, t, J = 6.8 Hz, OCH_2), 3.71 (3H, s, OCH_3), 3.29 (1H, d, J = 15.6 Hz, C*H*H), 3.04 (1H, d, J = 15.9 Hz, CH*H*), 1.84−1.74 (2H, m, $OCH_2CH_2CH_3$), 1.42−1.17 (2H, m, $CH_2CH_2CH_3$), 1.02 (3H, t, J = 7.6 Hz, $CH_2CH_2CH_3$), 0.89 (3H, t, J = 7.6 Hz, $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.9, 164.7, 154.7, 135.2, 130.3, 128.7, 117.2, 115.4, 71.5, 55.7, 53.1, 39.0, 29.6, 23.1, 14.8, 14.1, 10.4; IR (ATR) ν_{max} 3195, 1738, 1663, 1451, 1378, 1066; HRMS (ESI$^+$) calcd for $C_{14}H_{18}NO_4$ $(M + H)^+$ 306.1700, found 306.1695.

3,3-Diphenylisoindolin-1-one, ***6r:*** white solid; mp 208−210 °C (lit.[27] 210−211 °C); ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.88 (1H, d, J = 7.5 Hz, Ar*H*), 7.56 (1H, m, Ar*H*), 7.31−7.51 (2H, m, Ar*H*), 7.35−7.20 (9H, m, Ar*H*), 7.15 (1H, m, Ar*H*), 6.65 (1H, br s, N*H*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.7 (CONH), 150.1, 142.7, 138.1, 132.4, 130.5, 128.7, 128.5, 128.0, 127.9, 127.0, 126.3, 124.5, 124.3, 71.1 (CNH); IR (ATR) ν_{max} 291, 1692, 1651, 1446, 1258, HRMS (ESI$^+$) calcd for $C_{20}H_{16}NO$ $(M + H)^+$ 286.1232, found 286.1256.

Crystallography. A prismatic crystal of **5a**, **5c**, or **5b(6)** (Table S1) was selected and mounted on a MAR345 diffractometer and image plate detector. Unit-cell parameters were determined from 332 (for **5a**), 1574 (for **5c**), and 719 (for **5b(6)**) reflections, in the range $3° < \theta < 31°$, and refined by least-squares methods. Intensities were collected with graphite-monochromatized Mo Kα radiation. The number of reflections collected were 11 514 (for **5a**), 15 530 (for **5c**), and 13 074 (for **5b(6)**), in the ranges $1.65° \le \theta \le 30.65°$, $1.65° < \theta < 32.32°$, and $1.57° \le \theta \le 30.67°$ for **5a**, **5c**, and **5b(6)**, respectively, of which 6314 (for **5a**), 8579 (for **5c**), and 7050 (for **5b(6)**) were nonequivalent by symmetry. The number of reflections assumed as observed applying the condition $I > 2\sigma(I)$ were 5492, 6203, and 6874 (for **5a**, **5c**, and **5b(6)**, respectively). Lorentz−polarization corrections were made.

The structures were solved by direct methods, using the SHELXS computer program,[28] and refined by full-matrix least-squares method with the SHELX97 computer program[29] using 11 514, 15 530, and 13 074 reflections for **5a**, **5c**, and **5b(6)**, respectively (very negative intensities were not assumed). The function minimized was $\sum w||F_o|^2 - |F_c|^2|^2$, where $w = [\sigma^2(I) + (0.0494P)^2 + 0.2769P]^{-1}$ (for **5a**), $w = [\sigma^2(I) + (0.1182P)^2 + 0.5077P]^{-1}$ (for **5c**), and $w = [\sigma^2(I) + (0.0607P)^2 + 1.4868P]^{-1}$ (for **5b(6)**) and $P = (|F_o|^2 + 2|F_c|^2)/3$; f, f', and f'' were taken from the bibliography.[30] The final R(on F) factor was 0.0357, 0.0660, and 0.0313 for **5a**, **5c**, and **5b(6)**, respectively, and the goodness of fit values were equal to 1.127 (for **5a**), 1.050 (for **5c**), and 1.195 (for **5b(6)**). Further details concerning the resolution and refinement of these crystal structures are given in Table S1. CCDC nos. 905213−905215 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Kinetics. The kinetic profiles for the reactions were followed by UV−vis spectroscopy in the 700−300 nm range. Atmospheric pressure runs were recorded on HP8452A or Cary50 instruments equipped with thermostated multicell transports. Observed rate constants were derived from absorbance versus time traces at the wavelengths where a maximum increase and/or decrease of absorbance was observed. For runs at variable pressure, a previously described pressurizing system and pill-box cell were used;[31] the system was connected to a J&M TIDAS spectrophotometer, which was used for the absorbance measurements. The calculation of the observed rate constants from the absorbance versus time monitoring of reactions, studied under second- or first-order concentration conditions, was carried out using the SPECFIT software.[32] The general kinetic technique is that previously described.[32] The solutions for the kinetic runs were prepared by mixing the calculated amounts of stock solutions of the palladium compounds and the metalating ligands in the desired solvent. In all cases no dependence on the concentration of palladium was detected, and it was kept in the $(2-5) \times 10^{-4}$ M margin. Table S2 collects all the obtained k_{obs} values for all the systems studied as a function of the metalating ligand, solvent, temperature, and pressure. All postrun fittings were carried out by the standard available commercial programs.

■ ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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