ACS Catalysis

Research Article

pubs.acs.org/acscatalysis

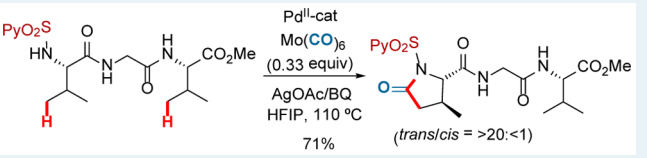
Palladium-Catalyzed Carbonylative Cyclization of Amines via γ-C(sp^3)−H Activation: Late-Stage Diversification of Amino Acids and Peptides

Elier Hernando, Julia Villalva, Ángel Manu Martínez, Inés Alonso, Nuria Rodríguez,* Ramón Gómez Arrayás,* and Juan C. Carretero*

Departamento de Química Orgánica, Universidad Autónoma de Madrid (Uam). Cantoblanco 28049 Madrid, Spain

Supporting Information

ABSTRACT: The selective γ-C(sp^3)−H carbonylation of *N*-(2-pyridyl)sulfonyl (*N*-SO_2Py)-protected amines has been accomplished by using palladium catalysis and $Mo(CO)_6$ as carbonyl source. The reaction provides a powerful approach for derivatization of amine-based moieties, including amino acids, into richly functionalized γ-lactams. Not only methyl groups, but also methylene C−H bonds of cyclopropanes and conformationally biased molecules can be activated to provide ring-fused γ-lactam derivatives. This carbonylation protocol is also amenable to the late-stage diversification of more-complex multifunctional molecules such as dipeptides and tripeptides, demonstrating the key role of the *N*-SO_2Py as directing group and its capacity to override other inherent substrate coordinating elements. In addition to providing an attractive solution to the difficulties in handling hazardous CO gas, the use of $Mo(CO)_6$ as an air-stable solid source of CO in substoichiometric amount (0.33 equiv) ensures Pd^{II}-catalytic activity by preventing its decomposition or deactivation under excess of CO via reduction of Pd^{II} to Pd^0 or saturation of the metal coordination sphere. Indeed, significantly lower efficiency is observed when the reactions are carried out under CO atmosphere (1 atm), or in the presence of increased amounts of $Mo(CO)_6$. A series of experimental and DFT mechanistic studies provide important insights about the reaction mechanism.



KEYWORDS: *C−H carbonylation, palladium catalysis, γ-lactam, amino acid, 2-pyridylsulfonyl, aliphatic amine, peptide*

INTRODUCTION

Despite the direct functionalization of inert C−H bonds being one of the most prevalent technologies for rapidly introducing complexity and diversity on a core molecule,[1] few methods have been demonstrated to be amenable to late-stage diversification of complex multifunctional molecules.[2] This is particularly true in the functionalization of C(sp^3)−H bonds, which, compared to activation of C(sp^2)−H bonds, continues to be highly challenging, because of their lower acidity and the absence of π-orbitals causing stabilizing interaction with the transition metal.[3]

The use of removable (bidentate) directing groups and Pd catalysis has emerged as the preferred strategy to promote both reactivity and selectivity in C(sp^3)−H activation.[4] In 2004, Sanford et al. pioneered the Pd-catalyzed directed functionalization (acetoxylation) of aliphatic C−H bonds using oxime and/or pyridine as directing groups,[5] while Daugulis et al. demonstrated, in 2005, the ability of a removable picolinamide group to facilitate the Pd-catalyzed C−H arylation at remote positions of aliphatic amine derivatives.[6,7] Shortly after, Corey et al. expanded this reactivity to the diastereoselective β-C(sp^3)−H arylation of α-amino acid derivatives.[8] Since these breakthrough reports, the direct functionalization of nitrogen-containing compounds, especially amino acid derivatives, given their prevalence in medicinal chemistry[9] and organic synthesis,[10,11] stands at the forefront in this field.[12]

Among the number of applications in various C−C and C−X bond-forming reactions reported, the direct carbonylation of C(sp^3)−H bonds represents a powerful strategy for derivatization, because it allows the installation of a synthetically valuable carbonyl functional group into the desired target molecule.[13−22] However, the paucity of catalytic direct carbonylation of C(sp^3)−H bonds highlights the challenging nature of this task.

At the turn of the 21st century, long after the proof of concept provided by Fujiwara in 1989,[15] the groups of Yu[16] and Chatani[17] reported the first effective catalytic carbonylations of unactivated C(sp^3)−H bonds.[18,19] Both methods involve β-carbonylation of aliphatic amides, followed by cyclization, to give succinimides under Pd and Ru catalysis, respectively. Gaunt devised a method for the synthesis of β-lactams via carbonylation of β-C(sp^3)−H of secondary amines involving an unusual four-membered ring cyclopalladation.[5h] While the current work was in progress, the groups of Yao and Zhao[20] and Wang[21] independently disclosed a Pd-catalyzed γ-C(sp^3)−H carbonylation of aliphatic amines holding a bidentate picolinamide or oxalyl-amide directing group, respectively, thus providing an efficient access to functionalized γ-lactams.

Received: July 15, 2016
Revised: August 29, 2016

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

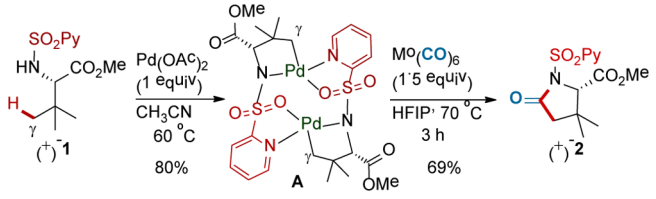
Despite these important recent accomplishments, many challenges remain unsolved. For example, structurally new bidentate directing motifs are needed for improving reactivity and selectivity.[23] Indeed, constraints, in terms of selectivity, have hampered the development of efficient methods for the late-stage functionalization of small peptides, which is highly desirable for peptidomimetic chemistry.[24] On the other hand, carbon monoxide gas is required for most of the reported procedures, in some cases at high pressure. Although the CO represents an ideal carbonylation reagent, in terms of atom efficiency, its hazardous nature limits its application on a laboratory scale. In addition, key obstacles that often limit catalytic C−H carbonylation under an excess of CO stem from the following: (i) the reducing ability of CO might induce the reduction of Pd^{II} species to Pd^0, and (ii) the excess of CO could inhibit the C−H activation event by competitively occupying coordination sites in the Pd^{II} center.[13,16a,25] Consequently, broadly applicable alternative approaches superseding the need for gaseous CO can potentially contribute to further advances.[26] However, to our knowledge, only recently in the literature has the first example of catalytic C(sp^3)−H carbonylation, appeared, relying on the use of CO surrogates. Ge et al. have described β-carbonylation-cyclization of aliphatic amides to succinimides via Ni/Cu synergistic catalysis using DMF as the source of CO.[27]

We report herein the development of a practical and reliable Pd-catalyzed γ-selective C(sp^3)−H carbonylation/cyclization of *N*-SO_2Py-protected aliphatic amines leading to γ-lactams. The use of a substoichiometric amount of $Mo(CO)_6$ (0.33 equiv) as a nonhazardous, air-stable solid source of CO not only avoids the difficulties in handling CO gas, but also enables slow *in situ* release of CO, thus preventing Pd^{II}-catalyst deactivation. Indeed, the *in situ* CO-releasing ability of $Mo(CO)_6$ has been previously demonstrated in a range of Pd^0-catalyzed carbonylations of C(sp^2)−X bonds.[28]

RESULTS AND DISCUSSION

Proof-of-Concept Stoichiometric Experiment. We recently reported the (2-pyridyl)sulfonyl (SO_2Py)-directed Pd-catalyzed arylation of γ-C(sp^3)−H bonds of aliphatic side chains in α-amino esters with iodoarenes.[23e] In our studies, a bimetallic Pd^{II}-complex **A** derived from the *tert*-leucine derivative (+)-**1** was isolated and structurally characterized by X-ray diffraction analysis, thus highlighting the role as bidentate directing group of the *N*-SO_2Py unit (see Scheme 1). We

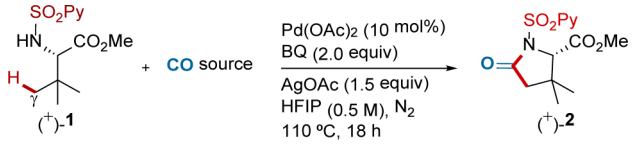
Scheme 1. Proof-of-Concept Experiment



decided to use this complex as an ideal platform to test carbon monoxide insertion, leading to carbonylative cyclization products. The reaction of complex **A** with $Mo(CO)_6$ (1.5 equiv) using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a solvent at 70 °C for 3 h, resulted in the clean formation of the expected γ-lactam (+)-**2**, which was isolated in 69% yield (Scheme 1), along with a significant amount of decomplexated *tert*-leucine derivative (+)-**1** (26%, not shown).

Importance of the Nature and the Amount of the "CO" Source. Encouraged by this proof-of-concept result, we next embarked on the challenging task of developing a catalytic, rather than stoichiometric, version. On the basis of literature precedents on Pd-catalyzed C(sp^3)−H arylation of simple carboxylic acids[29] and our previous work,[23e] we started our investigations by subjecting the *tert*-leucine derivative (+)-**1** to carbonylation with $Mo(CO)_6$ (1.0 equiv) in the presence of a catalytic amount of $Pd(OAc)_2$ (10 mol %) and a combination of AgOAc (1.5 equiv) and 1,4-benzoquinone (BQ, 2.0 equiv)[30] as oxidants in HFIP (0.5 M) at 110 °C for 18 h. Under these reaction conditions, an encouraging 43% conversion toward the expected γ-lactam (+)-**2** was observed, with (+)-**2** being the only detected reaction product by ^{1}H NMR in the crude mixture (Table 1, entry 1).

Table 1. Influence of the Amount of $Mo(CO)_6$ on Reaction Efficiency and Screening of Other Sources of CO[a]



entry	CO source (equiv)	yield[b] (%)
1	$Mo(CO)_6$ (1.00)	43
2	$Mo(CO)_6$ (0.50)	67
3	$Mo(CO)_6$ **(0.33)**	**95** (**93**)[c] (77)[d,e]
4	$Mo(CO)_6$ (0.20)	53
5	$Mo(CO)_6$ (2.00)	42
6	$Mo(CO)_6$ (4.00)	36
7	gaseous CO (1 atm)	37
8	$Cr(CO)_6$ (1.00)	14
9	$Cr(CO)_6$ (0.33)	20
10	$Co_2(CO)_8$ (1.00)	<10
11	$Co_2(CO)_8$ (0.33)	<10
12		n.d.

[a]Reaction conditions: *tert*-leucine derivative (+)-**1** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol), AgOAc (0.15 mmol), BQ (0.20 mmol), CO source (n equiv), HFIP (2 mL), 110 °C, 18 h in a sealed tube. [b]Conversion yield determined by ^{1}H NMR of the crude reaction mixture. [c]Isolated yield. [d]Isolated yield when reaction is scaled-up to gram-scale ((+)-**1**, 1 g, 3.50 mmol). [e]Identical results were obtained when the reaction (at both 0.1 and 3.5 mmol scale) was performed under air.

Speculating that this moderate conversion could be caused by deactivation of the catalytic Pd active species under an excess of CO released from $Mo(CO)_6$, we reasoned that lowering the amount of $Mo(CO)_6$ could be beneficial to the reaction. A study of the dependency of reaction efficiency on the amount of $Mo(CO)_6$ revealed that this was indeed a crucial parameter (Table 1). In accordance with our hypothesis, lowering the amount of $Mo(CO)_6$ positively influenced the reaction outcome, guiding us to a substantial and consistent increase in conversion when decreasing the amount of $Mo(CO)_6$ from 1.0 equiv (43% conversion, entry 1 in Table 1) to 0.5 equiv (67% conversion, entry 2 in Table 1) and 0.33 equiv (95% conversion, entry 3 in Table 1). However, further decrease of the amount of $Mo(CO)_6$ hold a negative impact, with 53% conversion being observed with 0.20 equiv (entry 4 in

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

Table 1). Not unexpectedly, an attenuation of the catalytic activity was consistently observed by increasing the amount of $Mo(CO)_6$ over 1.0 equiv (entries 5 and 6 in Table 1). Moreover, when the reaction of (+)-**1** was carried out under gaseous CO (1 atm, sealed tube), the expected lactam (+)-**2** was obtained in a low 37% conversion (entry 7 in Table 1).

We also explored alternative carbon monoxide sources that could enhance the reactivity. However, a screen of metal−carbonyl complexes different from $Mo(CO)_6$ typically used as carbon monoxide sources[26] led to worse reaction efficiency. For example, the use of $Cr(CO)_6$ (either 1.0 equiv or 0.33 equiv) provided the desired γ-lactam (+)-**2** in a much poorer conversion (≤20%, entries 8 and 9 in Table 1), whereas the $Co_2(CO)_8$ was even less effective, providing only traces of the product (+)-**2** (<10% conversion, entries 10 and 11 in Table 1). Finally, as expected, a control experiment omitting any CO source determined that γ-lactam (+)-**2** is not produced (entry 12 in Table 1).

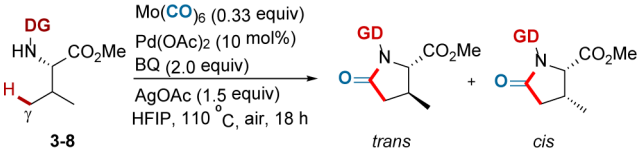
Importantly, simply adjusting the amount of $Mo(CO)_6$ to 0.33 equiv led us to find conditions for the efficient transformation of *tert*-leucine derivative (+)-**1** into the pyroglutamic acid derivative (+)-**2**, which could be isolated in 93% yield after purification by column chromatography (entry 3 in Table 1). These results seem to indicate that each molecule of $Mo(CO)_6$ releases three molecules of CO under the reaction conditions.[28c,d] Furthermore, we successfully performed an experiment on a larger gram-scale to demonstrate the practicality of this methodology, which afforded product (+)-**2** in 77% isolated yield after an extended reaction time of 24 h (entry 3 in Table 1). Finally, it was found that performing the reaction under air had no influence on the reaction (virtually the same results were obtained at both 0.1 and 3.5 mmol scale), thus eliminating the need for inert atmosphere (entry 3).

Carbonylation of L-Valine Derivative and Confirmation of the Directing Role of the SO_2Py Group. Our attention was shifted to the Pd-catalyzed carbonylative cyclization of the derivative of the natural amino acid L-valine ((+)-**3**), having a kinetically less favorable isopropyl group (rather than a *tert*-butyl group). In addition, since the isopropyl unit contains two diastereotopic methyl groups, this substrate would also allow testing the diastereoselectivity of the reaction.

To our delight, the reaction of (+)-**3** with $Mo(CO)_6$ (0.33 equiv) proceeded smoothly under the optimized conditions, affording the expected amidocarbonylation product (−)-**9** as an 5.7:1 mixture of *trans*/*cis* diastereoisomers (Table 2, entry 1). This good *trans*-diastereoselectivity is remarkable, revealing a marked preference for C−H activation of the pro-*S* methyl group of (+)-**3**.[23e] Importantly, the major (−)-*trans*-**9** diastereomer could be isolated in 75% yield with no appreciable loss of enantiopurity (97% *ee*) upon standard chromatography.

Although the structure of the bimetallic complex of γ-cyclopalladation of *tert*-leucine derivative (+)-**1** (complex **A**) strongly suggested that the NH−SO_2Py directing group is crucial for this transformation, we were interested in confirming this issue by screening other potentially coordinating *N*-protecting groups. For this purpose, a set of L-valine derivatives (substrates **4**−**8**) were examined in the carbonylation reaction under the optimized conditions, and the results are summarized in Table 2. While L-valine methyl ester hydrochloride decomposed under the reaction conditions (entry 2 in Table 2), the NH-Ts derivative **5** and the NH-(2-thienyl)sulfonyl derivative **6** were recovered unaltered without detecting any

Table 2. Carbonylative Cyclization of Valine Derivatives: Effect of the Protecting/Directing Group[a]



entry	DG (substrate)	yield[b] (%)	trans/cis[c] (product)	ee (%)[d]
1	(2-pyridyl)SO_2 ((+)-**3**)	87 (75)[e]	5.7:1 (**9**)	97
2	−(**4**)[f]			
3	(*p*-Tol)SO_2 (**5**)			
4	(2-thienyl)SO_2 (**6**)			
5	(8-quinolyl)SO_2 (**7**)	<10		
6	(2-pyridyl)CO (**8**)	<10		

[a]Reaction conditions are identical to those given in Table 1 (under air). [b]Conversion yield determined by ^{1}H NMR of the crude reaction mixture. [c]Determined by ^{1}H NMR. [d]Enantiomeric excess of the major product *trans*-**9**. [e]Isolated yield of the major product (−)-*trans*-**9**. [f]L-valine methyl ester hydrochloride was used as substrate, adding 1.0 equiv of Et_3N to the reaction.

carbonylation product (entries 3 and 4, respectively, in Table 2). The reaction of the (8-quinolyl)sulfonyl and (2-pyridyl)-carbonyl derivatives (**7** and **8**, respectively) led to a complex mixture of products in low conversion (<10%) (entries 5 and 6 in Table 2). Interestingly, the lack of reaction efficiency observed for the NH−COPy-protected substrate **8** emphasizes the cooperative directing role of both the sulfonyl-tethering group and the 2-pyridyl moiety in the C−H activation process.

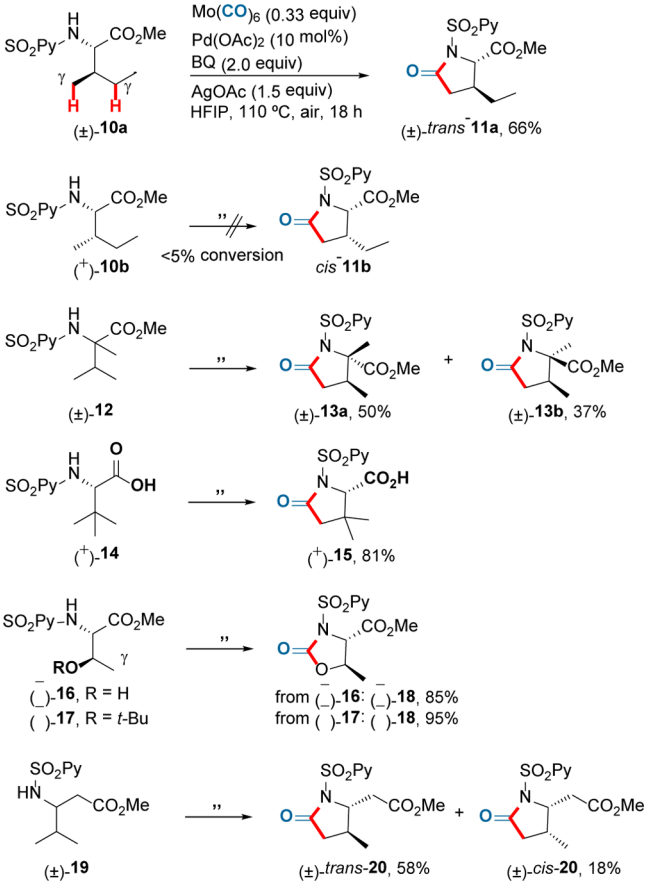
Screening of a handful of other reaction parameters (see Supporting Information) revealed the superiority of $Pd(OAc)_2$ over other Pd sources (no product was detected in the absence of Pd) and that the combination of AgOAc and benzoquinone was also essential to reach high catalytic activity. HFIP and CH_3CN were identified as the optimal solvents.

Structural Versatility: γ-Carbonylation of Amino Acid Derivatives. We next set out to investigate the versatility of the reaction, with regard to structural modifications in the amino acid moiety (see Scheme 2). The reaction of the allo-isoleucine derivative (±)-**10a**, having two sterically distinct primary and secondary γ-C(sp^3)−H bonds, selectively produced the cyclized product (±)-**11a** (66%), indicating that primary (methyl) γ-C(sp^3)−H bonds are more reactive in comparison with secondary (methylene) ones. In contrast, the isoleucine diastereomer (+)-**10b** was unreactive when exposed to identical catalytic conditions, with no *cis*-**11b** detected. This result is in agreement with the previously observed preference for C−H activation of the pro-*S* methyl group of the L-valine derivative (+)-**3**.[23e] Derivative (±)-**12** bearing a quaternary center at the α-position did also participate in the reaction, yielding the expected cyclized compound (±)-**13** as a separable 1.5:1 mixture of diastereoisomers in good yield (87% overall yield).

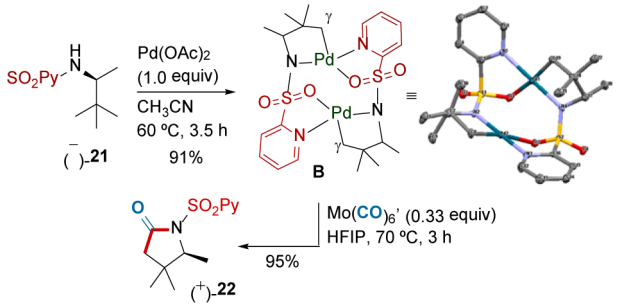
The *tert*-leucine derivative (+)-**14**, bearing a free COOH group, proved also to be suitable, thus expanding the functional group tolerance. The 5-oxopyrrolidinone-2-carboxylic acid derivative (+)-**15** was obtained in good yield (81%). However, the threonine derivative (−)-**16**, having a free hydroxyl group at the β-position, failed to provide the C−H carbonylation product, affording instead the cyclic carbamate (−)-**18** (85% yield), as a result of a hydrocarboxylation process. More

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

Scheme 2. Carbonylative Cyclization of Amino Acid Derivatives

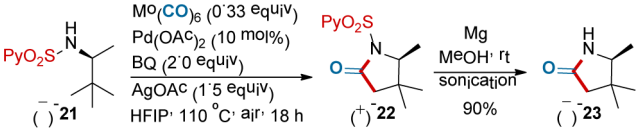


Scheme 3. Stoichiometric γ-C(sp³)−H Cyclopalladation and Carbonylation of Aliphatic Amine Derivative (−)-21



To our delight, when (−)-**21** was subjected to the optimized catalytic reaction conditions, the pyrrolidinone (+)-**22** was cleanly obtained in 89% yield. Moreover, the reaction can be scaled up to 10 times (1.0 g scale) in a similarly yield (85%), thus emphasizing the robustness of this method (Scheme 4). s4

Scheme 4. Catalytic Carbonylative Cyclization of Amine (−)-21 and Subsequent *N*-Deprotection



mmol	time (h)	Yield (%)
0.10	18	89
3.73 (*1.0 gram*)	24	85

Also important to take full advantage of the preparative potential of this method is the facile removal of the directing functionality. This was demonstrated upon treatment of (+)-**22** with magnesium turnings in MeOH at room temperature (rt) under sonication overnight, which afforded the unprotected γ-lactam derivative (−)-**23** in 90% yield.[32]

An examination of the scope of carbonylation of various simple aliphatic amine derivatives was undertaken to test the versatility of the reaction, with regard to steric modifications of the reactive γ-C(sp³)−H bond (see Scheme 5). The product of *trans* configuration was again formed predominantly (trans/cis = 5.6:1) in the reaction of (−)-**24**, possessing two diastereotopic β-methyl groups, allowing the isolation of (+)-*trans*-**26** in 78% yield. In sharp contrast, the 2-butanamide derivative (±)-**25**, without branching at the β-position, was recovered unaltered even when increasing the catalyst loading to 20 mol % of $Pd(OAc)_2$. When the achiral substrate **27** was tested, the corresponding pyrrolidinone derivative (±)-*trans*-**28**, having two contiguous stereogenic centers, was obtained in good yield (71%) as a single diastereoisomer. These results suggest that branching at the β-position is an essential biasing structural element for the reaction to proceed.

However, we were pleased to find that branching at the α-position was not a required structural feature for this transformation (substrates **29** and **31**), even though this type of substitution is often necessary as turning elements maximizing the conformation that leads to C−H activation. Nevertheless, the reaction proved to be more difficult, requiring an increased catalyst loading of 20 mol % to achieve synthetically useful yields (Scheme 5). For instance, the carbonylative cyclization of the 2,2-dimethylpropanamine

Extension of the Method to Simple Aliphatic Amines. The broad substrate scope displayed by this reaction with α-amino acid derivatives prompted us to explore the extension of this method to simple aliphatic amine derivatives. We first tested if compound (−)-**21**, analogue to *tert*-leucine derivative **1** but lacking the methyl ester moiety, could undergo γ-cyclometalation. The stoichiometric reaction of (−)-**21** with $Pd(OAc)_2$ (1.0 equiv) in acetonitrile at 60 °C for 3.5 h, cleanly provided, after simple recrystallization, the expected bimetallic complex **B** in 91% yield (unambiguously determined by single-crystal X-ray diffraction (XRD) analysis; see Scheme 3), which s3 presents an analogous structure to complex **A**.[31]

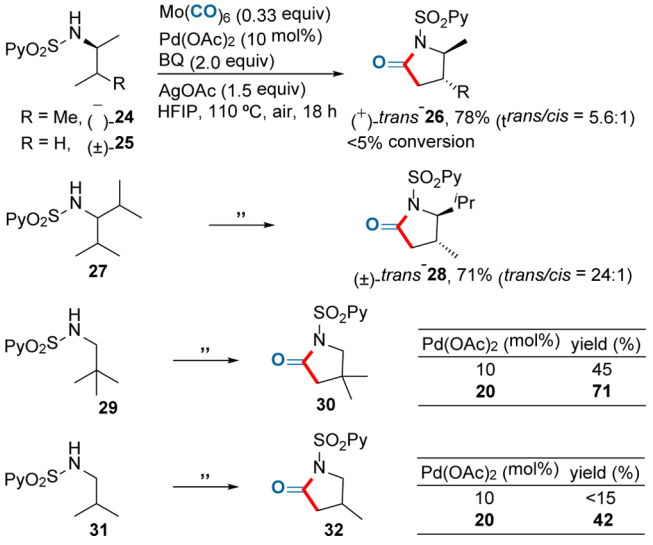
This result demonstrated that the ester group at the α-position of the previously studied α-amino ester derivatives was not essential for the C−H activation step. Furthermore, the reaction of this complex with 1.5 equiv of $Mo(CO)_6$ at 70 °C in HFIP for 3 h afforded the expected γ-lactam product (+)-**22** in 95% yield, evidencing that simple *N*-(2-pyridyl)sulfonyl-protected aliphatic amines are suitable substrates for the γ-C(sp³)−H carbonylative cyclization protocol (see Scheme 3).

unexpected was that the protected *O*-*tert*-butyl threonine derivative (−)-**17** led to the same carbamate (−)-**18** under identical reaction conditions (95% yield).

This method was extended to β-amino acid derivatives, as exemplified by the clean cyclocarbonylation of β-amino ester (±)-**19**, affording the product (±)-**20** as a separable 3.8:1 mixture of trans/cis diastereoisomers in good overall yield (76%).

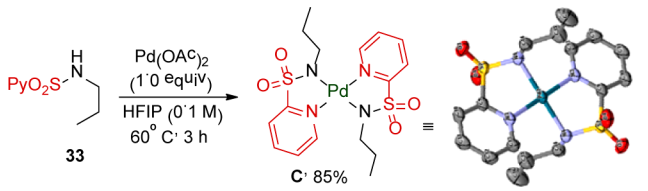
DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

Scheme 5. Effect of Branching at the α- and β-Position in Aliphatic Amine Derivatives



derivative **29** afforded the 2-pyrrolidinone derivative **30** in good yield (71%). On the other hand, the less conformationally restrained derivative **31** was found to be significantly less reactive, providing the corresponding 4-methyl-2-pyrrolidinone **32** in an acceptable 42% yield under identical reaction conditions. In accordance with these observations, the linear *N*-(SO_2Py)sulfonyl propanamine derivative **33** (see structure in Scheme 6), having unbranched both α- and β-positions, was unreactive toward the C−H carbonylation (not shown).

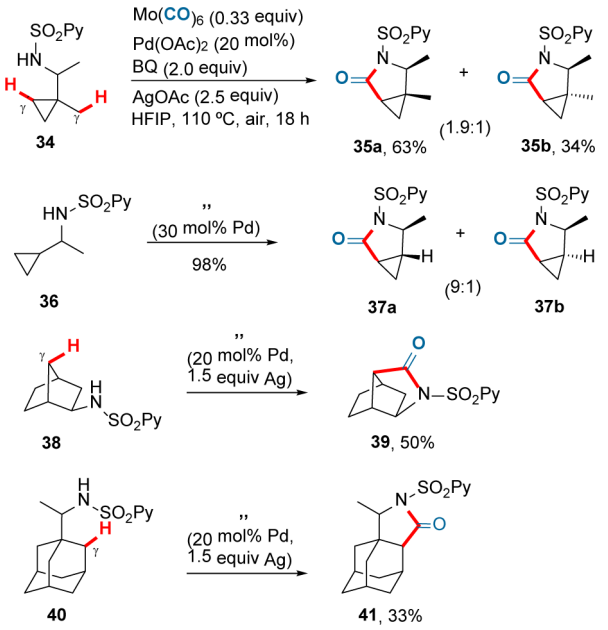
Scheme 6. Formation of Bis-Amide Pd-Complex C from Linear Sulfonamide 33



Intrigued by the strong dependence of the reactivity on the steric properties imposed by the substitution pattern of the substrates and the appearance of an unknown product in the reaction of amine derivatives lacking any substituent at the β-position (starting compounds **25** and **33**), we decided to study the cause behind this effect in more detail. In a recent report by Gaunt on Pd-catalyzed C−H activation of unprotected aliphatic amines to give strained nitrogen heterocycles, hindered secondary amines were used to overcome the propensity of these amines to form very stable, coordinatively saturated and catalytically inactive, square-planar bis-amine palladium(II) complexes.[5h] It was suggested by the authors that the steric hindrance around the Pd^{II} center should facilitate dissociation of an amine ligand to create the essential vacant coordination site required for the C−H activation to occur. In fact, this could be a primary reason for the scarcity of studies involving aliphatic amines in C−H bond functionalization.

Accordingly, we found reasonable to assume the formation of this type of bis-amine complexes in the reaction of the secondary sulfonamides. In the present case, the *N*,*N*-bidentate nature of these substrates imparted by the *N*-SO_2Py directing group should strengthen the interaction of the substrate to the metal, thereby compensating the weakened coordination ability of a sulfonamide compared to amine ligands, leading to more stable complexes. To test this hypothesis, the linear propanamide derivative **33** was treated with a stoichiometric amount of $Pd(OAc)_2$. After 3 h of reaction in HFIP at 60 °C, we observed by ^{1}H NMR the clean formation of the mononuclear air-stable palladium complex **C**, which was isolated in 85% yield (Scheme 7). XRD analysis of suitable

Scheme 7. Carbonylation at γ-Methylene Groups



crystals revealed a slightly distorted square-planar *N*,*N*,*N*,*N*-tetracoordinated palladium complex in which the Pd^{II} atom coordinates two molecules of **33** through the deprotonated amide and the pyridyl nitrogen atoms.[31] The formation of this type of stable Pd-complex provides a reasonable explanation for the strong dependence of reactivity on the degree of substitution (branching) of the substrate.

Carbonylation at γ-Methylene Groups of Aliphatic Amine Derivatives. At this point, we wondered whether it might enable activation at the more challenging (less reactive) γ-methylene C−H bonds.[33] In particular, cyclopropane derivatives are attractive because of their prominence in natural products and pharmaceuticals,[34] along with the relative scarcity of methods enabling their C−H activation.[35] In addition, the rigidity of the cyclopropyl ring and the more sp^2-like character for its carbon atom should facilitate C−H functionalization processes.

As shown in Scheme 7, compound **34** could be smoothly transformed into the expected cyclopropane-fused pyrrolidinone[36] derivative **35** in 97% yield as a 1.9:1 mixture of diastereoisomers, although it required increased catalyst loading (20 mol %). This result not only shows that this method is effective for the carbonylation of methylene C−H bonds in cyclopropylmethylamine derivatives, but it also reveals that cyclopropyl C(sp^3)−H methylene groups can be selectively carbonylated over a methyl γ-C(sp^3)−H bond. The less conformationally biased substrate **36**, lacking the β-methyl substituent, also participated in the reaction, providing the corresponding bicyclic lactam with increased diastereoselectiv-

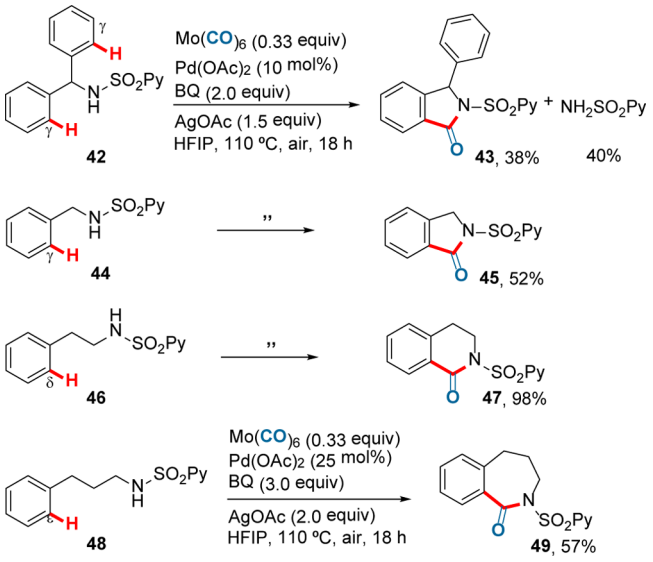
DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

ity (**37**, 98% yield, cis/trans = 9:1), although a higher 30 mol % of Pd-catalyst was needed to achieve complete conversion.

The conformationally biased *exo*-norbornylamine derivative **38**, lacking a marked sp^2 character, afforded the expected lactam **39** with 75% conversion (50% yield) when subjected to the general catalytic reaction conditions using 20 mol % of $Pd(OAc)_2$ (Scheme 7). Similarly, the functionalization of the 1-[adamantan-1-yl)ethanamine derivative **40** under similar conditions turned out to be viable, albeit with a lower yield (**41**, 33%). Despite the modest yield, the result is remarkable considering the scarcity of C−H activation reactions in nonactivated methylene groups.[33,37]

C(sp^2)−H Carbonylation−Cyclization Reactions. To test whether this method would be also effective for the C(sp^2)−H carbonylation, the dibenzylic sulfonamide derivative **42**, having four C(sp^2)−H bonds at the γ-position, was submitted to the carbonylation reaction. Unfortunately, however, only 38% of the corresponding 3-phenylisoindolinone **43** was isolated, along with the (2-pyridyl)sulfonamide in 40% yield (see Scheme 8).[38] In fact, the *N*-SO_2Py-benzylamine

Scheme 8. C(sp^2)−H Carbonylation of Amine Derivatives

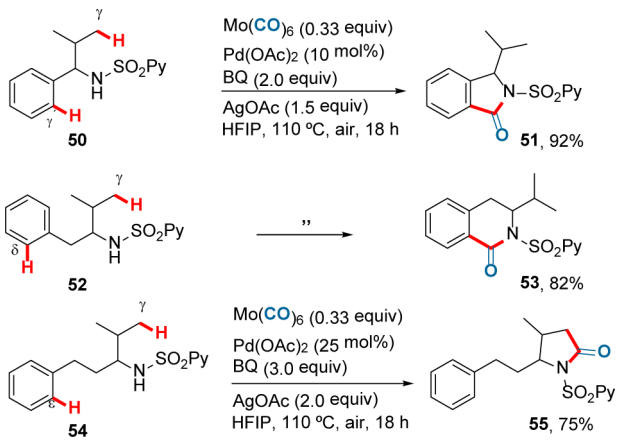


derivative **44**, which is less prone to benzylic elimination, underwent cyclocarbonylation to afford the corresponding isoindolinone derivative **45** in a synthetically useful yield (52% isolated).[39]

Importantly, this method can be extended to phenethylamine derivatives. For example, the δ-carbonylation of the phenethylamine derivative **46** afforded the 3,4-dihydroisoquinolin-1(2H)-one **47** in very high yield. This result suggests the participation of a seven-membered palladacycle intermediate prior to CO insertion.[40] Even the direct functionalization of the ε-C(sp^2)−H bond of the 3-phenylpropylamine derivative **48** turned out to be viable, yet using customized reaction conditions with increased catalyst loading and oxidants [$Pd(OAc)_2$ (25 mol %), AgOAc (2.0 equiv), and BQ (3.0 equiv)], providing the benzo[c]azepine-1-one derivative **49** in 57% yield. This structural flexibility is remarkable since very often the precise tether length of the directing group is found to be crucial for reactivity in C−H activation.[41] A further point to note is that, compared to the plethora of methods for the construction of five- or six-membered *N*-heterocyclic systems, there are very few reports on the direct synthesis of seven-membered rings by Pd-catalyzed oxidative cyclization.[42]

C(sp^2)−H versus C(sp^3)−H Carbonylation Selectivity. The suitability of this method for both C(sp^3)−H and C(sp^2)−H bond activation led us to examine site selectivity in substrates containing both types bonds. For this purpose, the 2-methyl-1-phenylpropanamine derivative **50**, containing both γ-C(sp^2)−H and γ-C(sp^3)−H bonds, was tested next (see Scheme 9). Not

Scheme 9. C(sp^3)−H vs C(sp^2)−H Selectivity

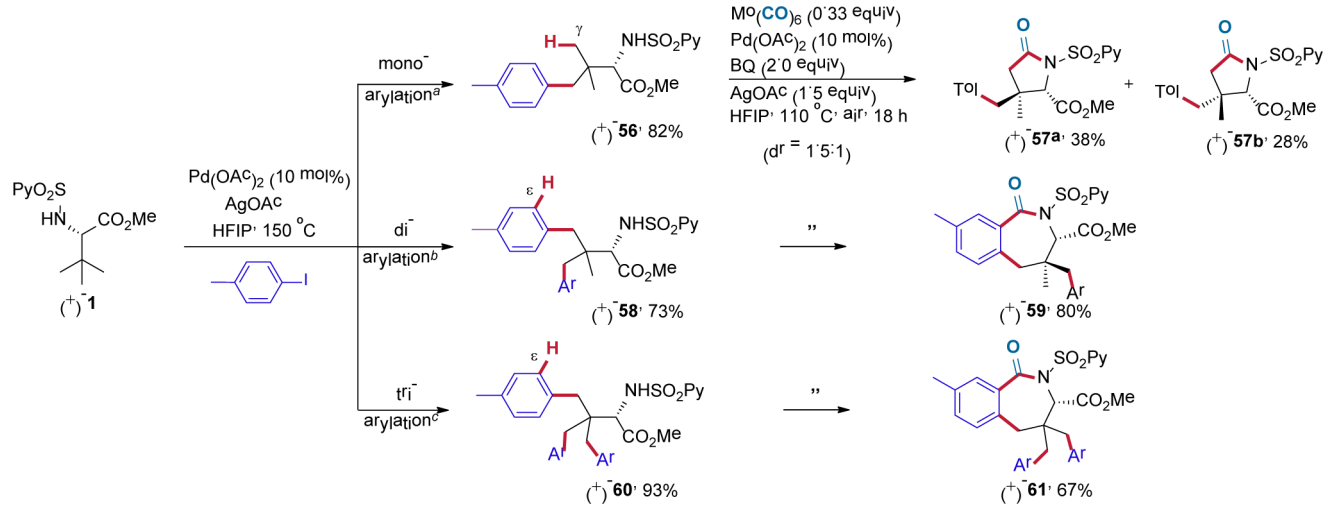


unexpectedly, the carbonylation reaction occurred at the site of the more acidic C(sp^2)−H, leading to the isoindolinone derivative **51** in 92% yield. The same preference for aryl activation was still remained even when the C(sp^2)−H bond was located at the δ-position, as demonstrated in the reaction of derivative **52**, which afforded exclusively the 3,4-dihydroisoquinolinone **53** in 82% isolated yield. Interestingly, opposite site selectivity (i.e., complete preference for γ-C(sp^3)−H activation) was attained in the case of the derivative **54** having the phenyl group one bond further away from the directing group [ε-C(sp^2)−H bond], even though the same customized conditions previously optimized for the ε-C(sp^2)−H carbonylation/cyclization of derivative **48** were employed. In this case, the selective formation of the γ-lactam **55** (75% yield) over the corresponding benzo[c]azepine-1-one product is likely caused by the much more kinetically disfavored seven-membered ring formation, compared with a five-membered ring, thereby overriding the higher reactivity of the aromatic C−H bond.

On the basis of these results, and taking advantage of our previously reported Pd-catalyzed γ-C−H arylation of α-amino acid derivatives with iodoarenes,[23e] we envisaged that two sequential C−H functionalization processes (i.e., arylation, followed by carbonylative cyclization) could provide an efficient strategy for rapidly introducing complexity and diversity on a core amine molecule. We chose the *tert*-leucine derivative (+)-**1** as an ideal platform to test this possibility. As shown in Scheme 10, our previously developed C−H arylation method[23e] enabled the selective preparation of the monoarylated, diarylated, and triarylated derivatives (+)-**56**, (+)-**58**, and (+)-**60**, respectively, in good yields (73%−93%) by simply adjusting the excess of iodoarene and oxidant. Subsequently, each of these *tert*-leucine derivatization products was subjected to the optimized conditions for the Pd-catalyzed carbonylative cyclization. The reaction outcome proved to be strongly dependent on the substitution pattern at the starting amine derivative. For instance, the γ-monoarylated compound (+)-**56** smoothly

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

Scheme 10. Sequential C−H Arylation and Carbonylative Cyclization for Introducing Structural Diversity and Complexity on *tert*-Leucine Derivative (+)-1

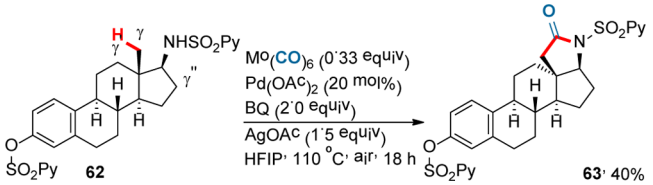


[a]Monoarylation conditions: AgOAc (1.5 equiv), 4-iodotoluene (1.5 equiv). [b]Diarylation: AgOAc (1.5 equiv), 4-iodotoluene (2.5 equiv). [c]Triarylation: AgOAc (3.5 equiv), 4-iodotoluene (3.5 equiv). Ar = *p*-Tol. SO_2Py = 2-$PySO_2$. For further details, see the Supporting Information.

reacted with complete γ-C(sp^3)−H site selectivity but low stereocontrol (dr = 1.5:1) to afford the γ-lactam (+)-**57a** in 38% yield, accompanied by (+)-**57b** in 28% yield. In contrast, the diarylated compound (+)-**58** delivered exclusively the corresponding benzazepine-1-one derivative (+)-**59** in 80% yield and high diastereoselectivity (no other diasteromer was detected). The γ-lactam product was not detected by ^{1}H NMR of the crude reaction mixture, revealing that the presence of two aryl substituents (four *ortho*-C−H bonds against three γ-C(sp^3)−H bonds) kinetically favors aryl activation. Not unexpectedly, the triarylated derivative (+)-**60**, having six equivalent *ortho*-C−H bonds, provided the benzo[c]azepine-3-carboxylate (+)-**61** in good yield (67%). It is important to note that up to four new C−C bonds and one new C−N bond are formed in this two-step derivatization protocol.

Late-Stage Diversification of Functional Molecules. *Derivatization of a Derivative of the Steroid Strone.* In addition, to further demonstrate the potential of this method to induce site-specific reactivity on complex molecules at otherwise unreactive sites, the estrone derivative **62**,[43] having a variety of sterically distinct primary and secondary C−H bonds, as well as a potentially reactive aryl sulfonate, was chosen (see Scheme 11). We were delighted to find that the C−H carbonylation/cyclization reaction of **62** afforded cleanly the pentacyclic γ-lactam product **63**, resulting from γ-functionalization at the methyl group, in 40% yield. This result also illustrates the capacity of the bidentate *N*-SO_2Py directing group to act in the presence of the potentially coordinating *O*-SO_2Py unit.

Scheme 11. Late-Stage Carbonylation of the Estrone Derivative

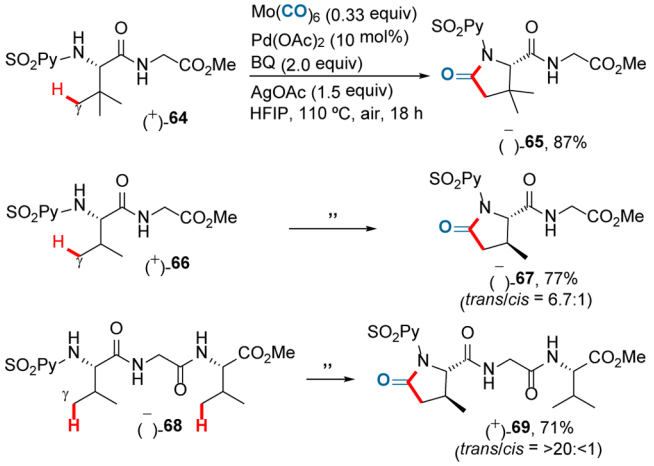


Carbonylation/Cyclization of Dipeptides and Tripeptides. Motivated by the great significance of post-synthetic modification of small peptides as a means of optimizing their molecular function or discovering new biologically active candidates, we sought to expand the substrate scope of this reaction to dipeptides and tripeptides. The increased complexity of this class of molecules represents a demanding test due to the possible formation of competing *N*,*N*- or *N*,*O*-bis-coordinated complexes with Pd^{II} that could either inhibit the reaction or compromise the desired pathway, in terms of selectivity. Indeed, Yu has recently demonstrated that the native amino acid moiety of peptides can coordinate with Pd^{II} via *N*,*N*- or *N*,*O*-bidentate coordination and promote the functionalization of proximate C(sp^3)−H bonds such as arylation or acetoxylation reactions.[5i]

We were delighted to see that the carbonylative cyclization of both *tert*-leucine-glycine ((+)-**64**) and valine-glycine [(+)-**66**] dipeptide derivatives occurred efficiently, providing the corresponding modified dipeptides (−)-**65** and (−)-**67** in good yields (87% and 77%, respectively) and complete site-selectivity control (see Scheme 12). In the case of the valine-containing dipeptide, the product (−)-**67** was obtained with good *trans*-diastereoselectivity (trans/cis = 6.7:1). Encouraged by this outstanding reactivity, we questioned whether this carbonylation protocol could be applied to the more challenging tripeptide derivatives. We chose the valine-glycine-valine derivative (−)-**68** as the substrate because it contains two valine moieties—one at the *N*-terminus and another one at the C-terminus—thus it is well-suited to test the capability of the *N*-SO_2Py directing group in controlling site selectivity. To our delight, the carbonylation of tripeptide (−)-**68** under the optimized reaction conditions proceeded smoothly to afford the expected modified tripeptide (+)-**69** as the only isolated product in 71% yield after chromatographic purification. Importantly, the C−H activation occurred with complete site-selectivity control at the *N*-terminus, thus highlighting the capacity of the bidentate *N*-SO_2Py directing group to override other inherent substrate coordinating elements. Also remarkable is the fact that the reaction occurred with almost-complete trans-diastereoselectivity (trans/cis =

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

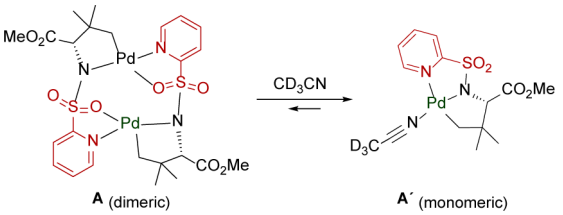
Scheme 12. Late-Stage Carbonylation of Dipeptides and Tripeptides



>20:<1), presumably due to the bulky peptide chain attached to C(5) of the 2-pyrrolidinone cyclic system (Scheme 12).

Mechanistic Insights. *Nuclearity of Complex A in Solution.* In order to gain insights into the reaction mechanism, we first sought to identify the catalytically active species. Previous studies performed in our group suggested that the dimer is not the predominant species in solution of CD_3CN,[44] but rather this complex is mainly present as a monomer (most likely **Á**), in which the weakly coordinating CD_3CN reversibly coordinates the active catalyst (**A′**) (see Scheme 13).

Scheme 13. Behavior of Complex A in a CD_3CN Solution



This assumption was initially based on the fact that the one-dimension (1D)-selective NOE spectrum in CD_3CN obtained by inversion of the signal corresponding to the proton ortho to the nitrogen of the pyridine ring (H^1, 8.38 ppm) showed a weak NOE interaction (<0.05%) with the methylene protons (H^2 and $H^{2'}$, 2.12 and 1.94 ppm, respectively; see Figure 1). In fact, a similar 1D-selective NOE spectrum of **A** in DCE-d_4 (an apolar noncoordinating solvent) shows an important NOE interaction (4.7% and 5%).[45]

To shed more light on this hypothesis, we performed an analysis by positive electrospray high-resolution mass spectroscopy (ESI-HRMS) of two separate solutions of complex **A**: one in the weakly coordinating CH_3CN as solvent and another one in the noncoordinating solvent CH_2Cl_2. The ESI-HRMS spectrum of complex **A** in MeCN is shown in Figure 2. The main feature of this spectrum is that it shows intense peaks corresponding to monomeric Pd^{II} complexes. In fact, the monomeric complex **A′** was detected as the most intense peak [m/z (M+H)$^+$: 432.0198], while the corresponding monomeric complex **A′′**, resulting from **A′** by loss of CH_3CN ligand, was detected in lower abundance [m/z (M+H)$^+$: 390.9872]. Instead, the dimeric form of this complex (complex **A**), easily

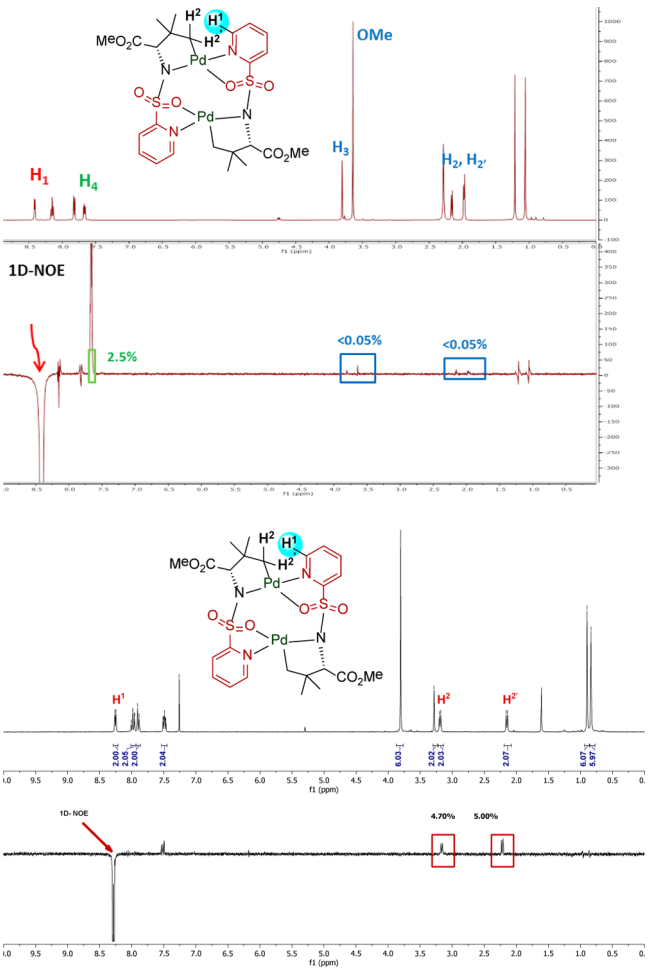


Figure 1. 1D-selective NOE spectrum of **A** in two solvents with different coordinating ability. Upper panel shows the 1D-selective NOE spectrum of **A** in CD_3CN at 5 °C; lower panel shows the 1D-selective NOE spectrum of **A** in DCE-d_4.

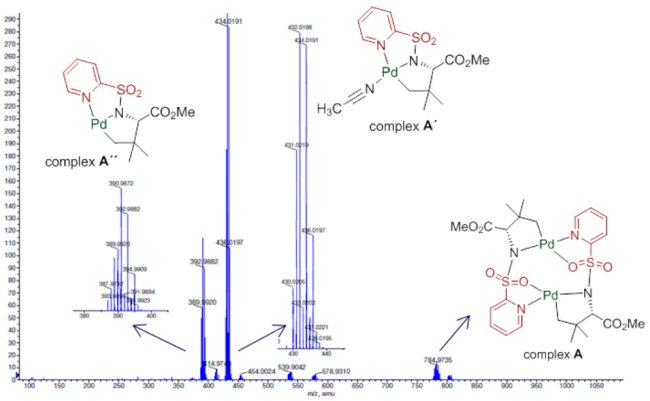


Figure 2. HRMS spectrum of complex **A** in CH_3CN.

attributable to the peak at m/z (M+H)$^+$: 780.9782, was detected with a very low intensity. In comparison with the previous results, the ESI-HRMS analysis of a solution of complex **A** in CH_2Cl_2 showed the dinuclear species (**A**) with the highest intensity, clearly indicating that this complex becomes predominant in noncoordinating solvents (Figure 3). No mononuclear species associated with this complex was detected in this case.

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

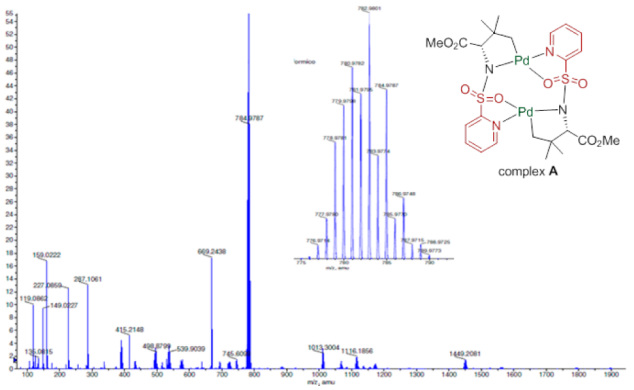


Figure 3. HRMS spectrum of complex **A** in CH_2Cl_2.

These observations are in accordance with the much higher catalyst activity encountered in coordinating solvents such as HFIP or CH_3CN (≥87% conversion in the model reaction of **3** → **9**), compared to the low outcome when using the noncoordinating DCE (17% conversion, see the Supporting Information for solvent screening studies).

Monitoring Stoichiometric Carbonylation of Complex A. Next, using ^1H NMR in CD_3CN as a solvent (much less expensive than deuterated-HFIP), we monitored the stoichiometric reaction of complex **A** with $Mo(CO)_6$ (0.33 equiv) at rt. This experiment led us to find a fast and clean formation of an intermediate (**D**), which reached its highest concentration after 2.5 h (roughly complex **A**/intermediate **D** ratio = 1:1), as shown in Figure 4 (*vide infra* for the characterization of intermediate **D**). The resulting mixture remained almost unaltered for a period of an additional 2.0−2.5 h and, suddenly, a relatively fast conversion of intermediate **D** into the final γ-lactam (+)-**2** was observed, with a complete disappearance of characteristics signals of intermediate **D** upon 7.5 h. Remarkably, a 60% conversion toward (+)-**2** was achieved after 9.5 h of reaction. Nevertheless, full conversion of complex **A** into the γ-lactam **2** was reached under extended reaction times (24 h). Figure 5 shows the complete reaction kinetic profile from a measure of conversion (%) versus time (hours).

Structural Characterization of Intermediate D. The ^1H NMR spectra of intermediate **D** in CD_3CN was very similar to that of complex **A**, providing little structural information (just very small differences in chemical shifts). However, the ^{13}C NMR spectrum in CD_3CN (at −20 °C to minimize decomposition) showed two extra peaks, compared to the ^{13}C NMR spectrum of complex **A**. While one of them, at 179.0 ppm, was assigned to a CO bonded to the Pd center,[46] the other one, at 125.4 ppm, with a very low intensity, was tentatively assigned to the nitrile carbon of the CD_3CN ligand

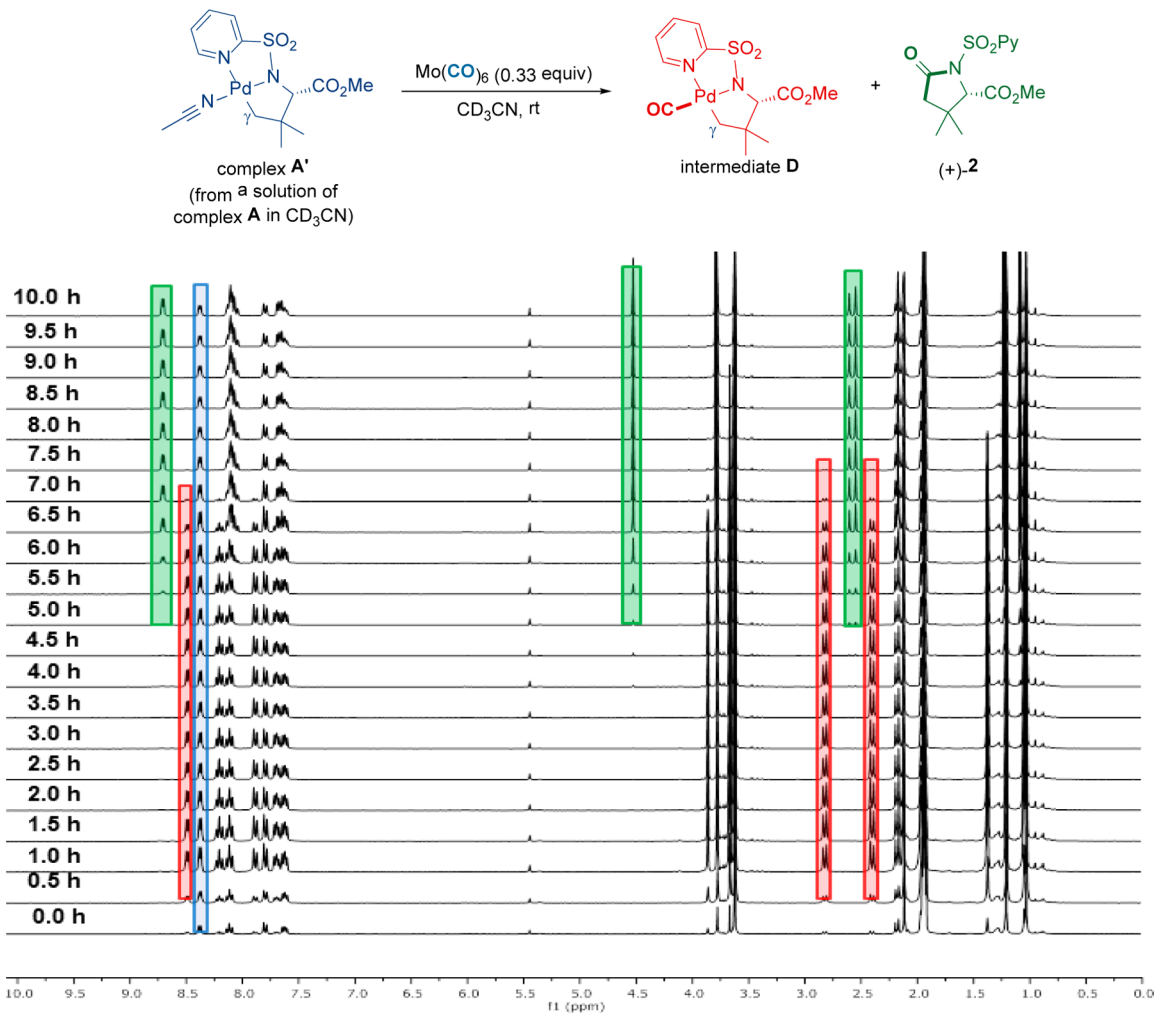


Figure 4. ^1H NMR monitoring the reaction of complex **A** with $Mo(CO)_6$ (0.33 equiv) in CD_3CN at room temperature (rt).

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

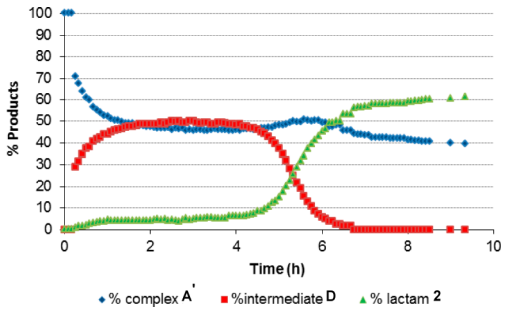


Figure 5. Complete kinetic reaction profile of complex **A** with $Mo(CO)_6$ (0.33 equiv) in CD_3CN at rt.

bonded to the Pd center in the monomeric complex **A′**, which is slowly formed by decomposition of intermediate **D**, likely through CO ligand displacement by CD_3CN (the signal for the CD_3 group of this CD_3CN ligand would appear overlapped with the signal of the solvent).[47]

Importantly, monomeric intermediate **D** was detected as the highest intensity peak upon analysis by ESI-HRMS of a CD_2Cl_2 solution [*m*/*z* $(M+CO+H)^+$: 418.9893] accompanied by the corresponding C−H activation complex **A′′** after loss of CO [*m*/*z* $(M-CO+H)^+$: 390.9943] (see Figure 6).[48]

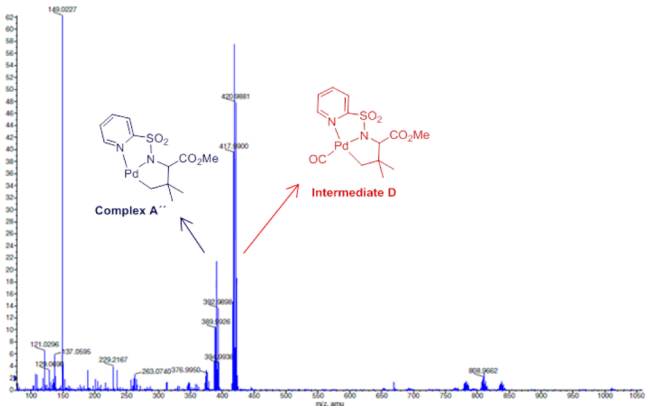


Figure 6. HRMS spectrum of intermediate **D** in CD_2Cl_2.

Finally, the presence of a CO molecule as an external ligand in the structure of intermediate **D** was corroborated by infrared (IR) spectroscopy. A very representative peak at 2095 cm^{-1} (observed both in CD_3CN and CD_2Cl_2) was very characteristic and perfectly matches with previously reported data for similar palladium−carbonyl complexes (typically in the range of 1900−2100 cm^{-1}).[46] The stretch vibration corresponding to the carbonyl group of the methyl ester moiety appeared, as expected, at 1742 cm^{-1} (see the Supporting Information).

Computational Studies. To shed more light on the carbonylation/cyclization reaction mechanism, a complete energy profile for the reaction of the *N*-(2-pyridyl)sulfonyl-*tert*-leucine derivative **1** was calculated (see Figure 7). The first considered step was the C−H activation. It may occur by several potential mechanisms. Among them, a concerted metalation−deprotonation (CDM) pathway has often been found to be the most favorable.[49] Based on our previous studies,[44] model complex **I** was used as the starting point.[50] A change in the conformation of this complex affords complex **II**, which shows an agostic interaction between the Pd atom and the C−H bond that is going to be cleaved. The most stable transition state found for this C−H activation was **TS(II−III)**, in which the six-membered cycle formed by Pd, N, and the rest of the amino acid moiety, including the C−H bond being cleaved, adopts a distorted chairlike conformation. After the C−H activation process, a bicyclic five−five-membered palladium intermediate **III** is formed, which could suffer a ligand exchange between the acetic acid and an acetonitrile solvent molecule, thus generating intermediate **IV** [model structure of the proposed intermediate **D**, − 1.2(−7.1) kcal mol^{-1}] as a stable palladium(II) complex stabilized by the pyridine ring and the acetonitrile molecule. In the presence of CO ligands, another ligand exchange can occur between the acetonitrile and the CO ligand, generating an even more stable intermediate **V** [−10.2(−15.4) kcal mol^{-1}], in which the sulfonamide nitrogen and the CO adopt a trans arrangement.

If the Pd atom coordinates with another molecule of solvent or CO, the pyridine ring could be displaced out of the coordination plane achieving different intermediates **VI** from which two similar routes **a** (L = CH_3CN) and **b** (L = CO) have been studied. While **VIa** and **VIb** differ in the nature of the ligand (L) but both keep the sulfonamide nitrogen and one CO ligand in a *trans*-arrangement, in **VI′a**, these groups show a cis configuration.

We first studied route **a**. The CO insertion could just be achieved from **VIa** via a high energetic transition state **TS(VI−VII)a** [19.1(16.4) kcal mol^{-1}], which shows a pentacoordinated palladium structure. In this transition state, the Pd−C bond is being cleaved while the C−CO−Pd bond is being formed (insertion) by a three-membered ring in a concerted way, yielding **VIIa** as a bicyclic six-five-membered palladium(II) intermediate in which the other vacancies are occupied by an acetonitrile ligand and the pyridine ring. All the attempts to find an analogous insertion transition state from **VI′a** failed, probably due to an important electronic repulsion between CO and SO_2 groups as they get closer. These results finally suggest that the CO insertion probably occurs into the C−Pd bond (via intermediate C−CO−Pd), dismissing other alternative hypotheses which proceeded via the CO insertion on the N−Pd bond (intermediate, N−CO−Pd). Complex **VIIa** evolves through a reductive elimination transition state, where the N−CO bond is being formed as the Pd−CO bond is being cleaved [**TS(VII−VIII)a**, 10.4(6.9) kcal mol^{-1})] yielding the cyclized intermediate **VIIIa** [−10.2(−14.3) kcal mol^{-1})], where the ester moiety adopts a pseudo-ecuatorial conformation. However, a more stabilized intermediate was found in which the ester group presents a pseudo-axial conformation, **IXa** [−13.4(−17.7) kcal mol^{-1})]. In this first route, both C−H activation and the CO insertion steps present transition states very similar in energy (19.7 and 19.1 kcal mol^{-1}, respectively) and thus both could act as reaction limiting steps (with the C−H activation step having a slightly higher energy barrier).

This energy profile did not provide an explanation for the observed negative role of an excess of CO in the reaction medium since a more energy-demanding insertion step would be expected in this case. Thus, in order to evaluate the effect of CO as a ligand in these intermediates, route **b** was also studied. However, as shown in Figure 7, all the intermediates and transition states found were much more stable, indicating that the C−H activation step could be the reaction-limiting step and once the required energy to overcome this step is available, the process should be favorable. Therefore, the possible influence of CO before the C−H activation step was explored (Figure 8). The coordination of a CO molecule in complex **I** afforded a

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

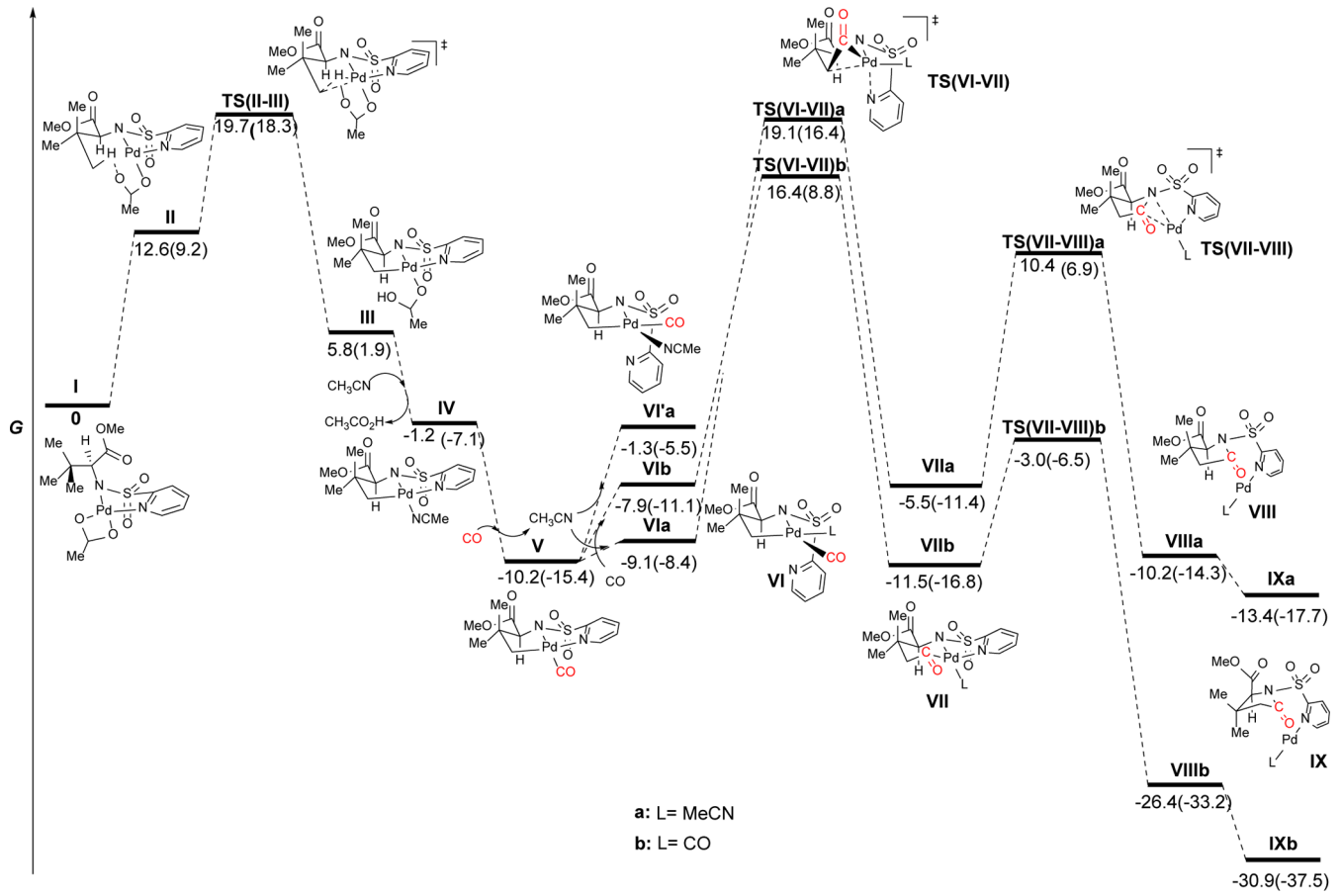


Figure 7. Complete energy profile for the reaction of the *N*-(2-pyridyl)sulfonyl-*tert*-leucine derivative **1** in the gas phase. Relative *G* values are reported at 298 K (kcal mol^{-1}). Single-point solvation energy corrections (CH_3CN, CPCM model) are indicated in parentheses.

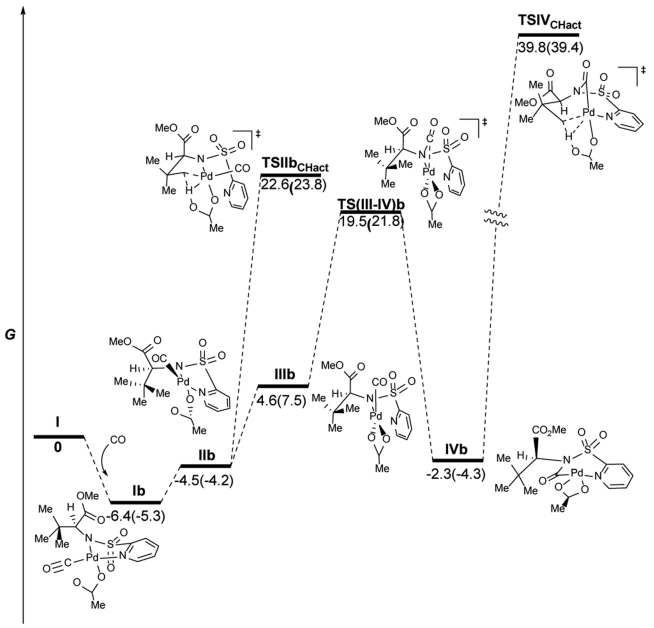


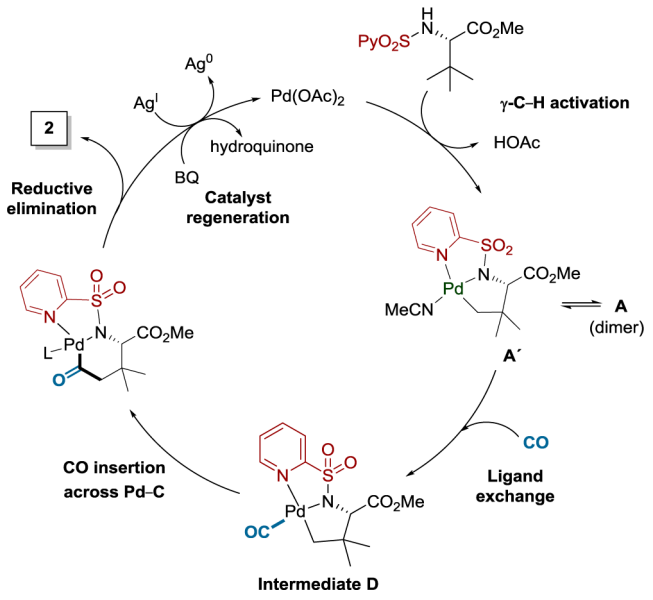
Figure 8. Possible competitive route in the presence of an excess of carbon monoxide. Relative *G* values are reported at 298 K (kcal mol^{-1}). Single-point solvation energy corrections (CH_3CN, CPCM model) are indicated in parentheses.

much more stable complex **Ib**. A conformational change on this complex gave rise to complex **IIb**, from which the located transition state for the C−H activation step [**TSIIb**$_{CHact}$, 22.8 (23.8) kcal mol^{-1}] was less stable than that proposed without coordination of CO [Figure 7, **TSII-III**, 19.7 (18.3) kcal mol^{-1}]. This suggests that the limiting C−H activation step becomes more difficult when an excess of CO is present. In addition, from complex **IIb** a more favorable pathway for the insertion of CO into the Pd−N bond was found. A change in the coordination mode of the acetate ligand promotes the displacement of the pyridine one, affording complex **IIIb** from which the insertion process occurs [**TS(III−IV)b**, 19.5 (21.8) kcal mol^{-1}] to give a quite stable six-membered amide-type complex **IVb**. From this intermediate, the C−H activation process would be extremely difficult [**TSIVb**$_{CHact}$, 39.8 (39.4) kcal mol^{-1}], promoting the entire catalytic cycle to stop. This competitive off-cycle nonproductive pathway could explain the empirically observed negative role of an excess of CO.

Working Mechanistic Hypothesis. Based on these mechanistic insights gained from both experimental and theoretical studies, we propose the simplified catalytic cycle presented in Scheme 14. We reasoned that the reaction might proceed through initial Pd^{II}-catalyzed γ-C−H activation via a concerted metalation-deprotonation (CMD) mechanism assisted by the acetate ion, thus leading to the bimetallic complex **A**, which is in equilibrium with an active monomeric complex **A′**. The latter might undergo solvent ligand displacement by CO to afford intermediate **D**. Carbonyl insertion across the Pd−C bond (intermediate **VII**), which is energetically favored over the insertion across the Pd−N bond), followed by reductive elimination would yield the carbonylative cyclization

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

Scheme 14. Tentative Mechanistic Rationalization



product. The so-formed reduced Pd^0 species would then reoxidize back to the active Pd^{II} species via the combined action of BQ and AgOAc.[51]

CONCLUSIONS

In conclusion, a practical and reliable Pd-catalyzed procedure for the site-selective γ-C(sp^3)−H carbonylation/cyclization of aliphatic amine derivatives, including α- and β-amino acid derivatives, has been developed, thus leading to the corresponding γ-lactams in good yields through a 2-fold carbonylation [at both C(γ)−H and N−H bonds]. This protocol strongly relies on the excellent directing ability displayed by the *N*-SO_2Py protecting group, which also proved to be easily removed under mild conditions. In addition to γ-methyl groups, the reaction proved to be also effective for the activation of γ-methylene C−H bonds of cyclopropanes and conformationally biased molecules. This carbonylation protocol also allows late-stage modifications of more-complex, functional compounds such as dipeptides or tripeptides, thereby illustrating the capacity of the bidentate *N*-SO_2Py directing group to override other inherent substrate coordinating elements, as well as broad functional group tolerance. Importantly, the use of a substoichiometric amount of $Mo(CO)_6$ (0.33 equiv) as a solid source of CO circumvents the problem of handling toxic gaseous CO and also enables slow *in situ* generation of CO, thus preventing Pd^{II} catalyst deactivation under excess of CO, as suggested by both experimental and computational studies.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out in anhydrous solvents taken from the PureSolv MD purification system. Palladium precatalysts, metal carbonyls, and silver salts were purchased from commercial sources and used without further purification.

Computational Methodology. Geometries were optimized with B3LYP and the SDD basis set for Pd and the 6-31G(d) basis set for other atoms. Single-point energies were calculated at the M06/SDD-6-311+G(2df, 2p) level. The reported free energies include zero-point energies and thermal corrections calculated at 298 K with B3LYP/SDD-6-31G(d). All calculations were performed with Gaussian 09.[52]

*Typical Procedure for the Pd-Catalyzed Carbonylative Cyclization of Aliphatic Amines: Synthesis of (S)-methyl-3,3-dimethyl-5-oxo-1-(pyridin-2-ylsulfonyl)-pyrroledine-2-carboxylate [(+)-**2**].* An oven-dried pressure tube was charged with $Pd(OAc)_2$ (2.33 mg, 0.010 mmol), AgOAc (26.04 mg, 0.156 mmol), benzoquinone (22.48 mg, 0.208 mmol), $Mo(CO)_6$ (9.06 mg, 0.034 mmol), *tert*-leucine derivative (+)-**1** (29.78 mg, 0.104 mmol), and HFIP (0.2 mL). The pressure tube was then sealed with a screw cap and the reaction was placed in a preheated oil bath at 110 °C for 18 h. The mixture then was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was then diluted with EtOAc, filtered through a pad of Celite and concentrated. The residue was purified by flash chromatography (cyclohexane/EtOAc 6:1 to 3:1) to afford γ-lactam (+)-**2** as a yellow oil; yield: 26.96 mg (83%), $[\alpha]_D^{298}$= +5 (*c* = 0.2, CH_2Cl_2).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b01987.

Experimental and computational details, as well as optimization studies, and spectroscopic and analytical data for new compounds (PDF)

Crystallographic data (ZIP)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: n.rodriguez@uam.es (N. Rodríguez).

*E-mail: ramon.gomez@uam.es (R. Gómez Arrayás).

*E-mail: juancarlos.carretero@uam.es (J. C. Carretero).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the Spanish Ministerio de Economía y Competitividad (MINECO, Project No. CTQ2012-35790), and MINECO/FEDER, UE (Project No. CTQ2015-66954-P) for financial support. E.H. thanks the Gobierno Vasco for a predoctoral fellowship. N.R. thanks the MICINN for a Ramón y Cajal contract and the European Commission for a Marie Curie Foundation (CIG: CHAAS-304085). We also thank the Centro de Computación Científica de la UAM for their generous allocation of computer time.

REFERENCES

(1) For selected general reviews on C−H functionalization, see (a) Bergman, R. G. *Nature* **2007**, *446*, 391−393. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115. (c) Daugulis, O. *Top. Curr. Chem.* **2009**, *292*, 57−84. (d) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362−3374. (e) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788−802. (f) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236−10254. (g) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879−5918. (h) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Tetrahedron* **2012**, *68*, 5130−5136. (i) Mousseau, J. J.; Charette, A. B. *Acc. Chem. Res.* **2013**, *46*, 412−424. (j) Sharma, A.; Vacchani, D.; Van der Eycken, E. *Chem.—Eur. J.* **2013**, *19*, 1158−1168. (k) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281−295. (l) Miura, M.; Satoh, T.; Hirano, K. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751−764. (m) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74−100. (n) Kuhl, N.; Schroder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443−1460. (o) Tani, S.; Uehara, T. N.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2014**, *5*, 123−135. (p) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29−39.

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

(2) For reviews on the use of C−H activation in late stage diversification of functional molecules, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67−72. (b) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885−1898. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960−9009. (d) Bruckl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826−839. (e) Chen, D. Y.-K.; Youn, S. W. *Chem.—Eur. J.* **2012**, *18*, 9452−9474. (f) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369−375. (g) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546−576. For selected recent examples, see: (h) Simmons, E. M.; Hartwig, J. F. *Nature* **2012**, *483*, 70−73. (i) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129−133. (j) Gong, W.; Zhang, G.; Liu, T.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 16940−16946. (k) Zhang, L.-S.; Chen, G.; Wang, X.; Guo, Q.-Y.; Zhang, X.-S.; Pan, F.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3899−3903. (l) Xu, Y.; Yan, G.; Ren, Z.; Dong, G. *Nat. Chem.* **2015**, *7*, 829−834. (m) He, J.; Hamann, L. G.; Davies, H. M. L.; Beckwith, R. E. J. *Nat. Commun.* **2015**, *6*, 5943−5951. (n) Huang, X.; Bergsten, T. M.; Groves, J. T. *J. Am. Chem. Soc.* **2015**, *137*, 5300−5303. (o) Durak, L. J.; Payne, J. T.; Lewis, J. C. *ACS Catal.* **2016**, *6*, 1451−1454. (p) Peng, J.; Chen, C.; Xi, C. *Chem. Sci.* **2016**, *7*, 1383−1387.

(3) For reviews on Pd-catalyzed C(sp^3)−H activation, see: (a) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654−2672. (b) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191−206. (c) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902−4911. (d) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588−5598. (e) Dastbaravardeh, N.; Christakakou, M.; Haider, M.; Schnürch, M. *Synthesis* **2014**, *46*, 1421−1439.

(4) For reviews on the functionalization of C−H bonds utilizing *N,N*-bidentate directing group, see: (a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−11743. (b) Castro, L. C. M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 410−421. (c) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053−1064. (d) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450−4459. (e) Yadav, M. R.; Rit, R. K.; Shankar, M.; Sahoo, A. K. *Asian J. Org. Chem.* **2015**, *4*, 846−864. For general reviews on directing group strategy in C−H activation, see: (f) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450−2494. (g) Wang, C.; Huang, Y. *Synlett* **2013**, *24*, 145−149. (h) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front.* **2014**, *1*, 843−895. (i) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107−1295.

(5) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542−9543.

(6) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155. Also see: (b) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657−3659.

(7) For reviews on remote C−H functionalization, see: (a) Franzoni, I.; Mazet, C. *Org. Biomol. Chem.* **2014**, *12*, 233−241. (b) Schranck, J.; Tlili, A.; Beller, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 9426−9428. (c) Qiu, G.; Wu, J. *Org. Chem. Front.* **2015**, *2*, 169−178.

(8) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391−3394.

(9) (a) Albericio, F.; Kruger, H. G. *Future Med. Chem.* **2012**, *4*, 1527−1531. (b) Craik, D. J.; Fairlie, D. P.; Liras, S.; Price, D. *Chem. Biol. Drug Des.* **2013**, *81*, 136−147. (c) Kaspar, A. A.; Reichert, J. M. *Drug Discovery Today* **2013**, *18*, 807−817. (d) Bunch, L., Krogsgaard-Larsen, P. In *Amino Acids, Peptides and Proteins in Organic Chemistry*, Vol. *4*; Hughes, A. B., Ed.; Wiley−VCH: Weinheim, Germany, 2011; p 151.

(10) For amino acids as versatile chiral building blocks in total synthesis and ligand design for chiral catalysis, see : Coppola, G. M., Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987.

(11) For the synthesis of amino acids, see: Blaskovich, M. A. *Handbook on Syntheses of Amino Acids: General Routes for the Syntheses of Amino Acids*, 1st Edition; Oxford University Press: New York, 2010.

(12) For general reviews on C−H functionalization of amino acids and peptides, see: (a) Noisier, A. F. M.; Brimble, M. A. *Chem. Rev.* **2014**, *114*, 8775−8806. (b) He, G.; Wang, B.; Nack, W. A.; Chen, G. *Acc. Chem. Res.* **2016**, *49*, 635−645. (c) Lu, X.; Xiao, B.; Shang, R.; Liu, L. *Chin. Chem. Lett.* **2016**, *27*, 305−311. For selected recent examples of C(sp^3)−H functionalization on amino acid derivatives, see: (d) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124−2127. (e) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J.-Q. *Nat. Chem.* **2014**, *6*, 146−150. (f) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216−1220. (g) Chen, K.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 11950−11954. (h) Zhu, R.-Y.; He, J.; Wang, X.-C.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 13194−13197. (i) Zhang, Q.; Yin, X.-S.; Chen, K.; Zhang, S.-Q.; Shi, B.-F. *J. Am. Chem. Soc.* **2015**, *137*, 8219−8226. (j) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 2042−2046. (k) Chen, G.; Shigenari, T.; Jain, P.; Zhang, Z.; Jin, Z.; He, J.; Li, S.; Mapelli, C.; Miller, M. M.; Poss, M. A.; Scola, P. M.; Yeung, K.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 3338−3351 (also see refs 5h and 5i.).

(13) For selected recent reviews, see: (a) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788−10799. (b) Wu, X.-F.; Neumann, H.; Beller, M. *ChemSusChem* **2013**, *6*, 229−241. (c) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1−35. (d) Gadge, S. T.; Bhanage, B. M. *RSC Adv.* **2014**, *4*, 10367−10389. (e) Fukuyama, T.; Totoki, T.; Ryu, I. *Green Chem.* **2014**, *16*, 2042−2050. (f) Wu, X.-F.; Fang, X.; Wu, L.; Jackstell, R.; Neumann, H.; Beller, M. *Acc. Chem. Res.* **2014**, *47*, 1041−1053. (g) Liu, B.; Hu, F.; Shi, B.-F. *ACS Catal.* **2015**, *5*, 1863−1881.

(14) For selected recent examples of carbonylative C(sp^2)−H functionalization, see: (a) Tlili, A.; Schranck, J.; Pospech, J.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6293−6297. (b) Luo, S.; Luo, F.-X.; Zhang, X.-S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 10598−10601. (c) Liang, D.; Hu, Z.; Peng, J.; Huang, J.; Zhu, Q. *Chem. Commun.* **2013**, *49*, 173−175. (d) Lee, T.-H.; Jayakumar, J.; Cheng, C.-H.; Chuang, S.-C. *Chem. Commun.* **2013**, *49*, 11797−11799. (e) Zeng, F.; Alper, H. *Org. Lett.* **2013**, *15*, 2034−2037. (f) Rajeshkumar, V.; Lee, T.-H.; Chuang, S.-C. *Org. Lett.* **2013**, *15*, 1468−1471. (g) Inamoto, K.; Kadokawa, J.; Kondo, Y. *Org. Lett.* **2013**, *15*, 3962−3965. (h) Chen, J.; Natte, K.; Spannenberg, A.; Neumann, H.; Beller, M.; Wu, X.-F. *Chem.—Eur. J.* **2014**, *20*, 14189−14193. (i) Liang, D.; He, Y.; Zhu, Q. *Org. Lett.* **2014**, *16*, 2748−2751. (j) Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2014**, *136*, 834−837. (k) Wang, L.; Wang, Y.; Liu, C.; Lei, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 5657−5661. (l) Li, W.; Liu, C.; Zhang, H.; Ye, K.; Zhang, G.; Zhang, W.; Duan, Z.; You, S.; Lei, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 2443−2446. (m) Li, X.; Li, X.; Jiao, N. *J. Am. Chem. Soc.* **2015**, *137*, 9246−9249. (n) Tjutrins, J.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2015**, *137*, 12050−12054. (o) Li, W.; Duan, Z.; Zhang, X.; Zhang, H.; Wang, M.; Jiang, R.; Zeng, H.; Liu, C.; Lei, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 1893−1896. (p) Li, W.; Duan, Z.; Jiang, R.; Lei, A. *Org. Lett.* **2015**, *17*, 1397−1400. (q) Shin, Y.; Yoo, C.; Moon, Y.; Lee, Y.; Hong, S. *Chem.—Asian J.* **2015**, *10*, 878−881. (r) Wang, P.-L.; Li, Y.; Ma, L.; Luo, C.-G.; Wang, Z.-Y.; Lan, Q.; Wang, X.-S. *Adv. Synth. Catal.* **2016**, *358*, 1048−1053.

(15) Fujiwara, Y.; Takaki, K.; Watanabe, J.; Uchida, Y.; Taniguchi, H. *Chem. Lett.* **1989**, *18*, 1687−1688.

(16) (a) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378−17380. The Yu group further extended this reactivity profile to the γ-C−H carbonylation of amides to enable the access to six-membered imides. See: (b) Li, S.; Chen, G.; Feng, C.-G.; Gong, W.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 5267−5270.

(17) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070−8073.

(18) For a remarkable example of directed C(sp^3)−H carbonylation under stoichiometric amount of Pd, see: Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856−11857.

(19) For catalytic carbonylation of benzylic C(sp^3)−H bonds or in the α-position to a heteroatom, see: (a) Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882−12883. (b) Xie, P.; Xie, Y.; Qian, B.; Zhou, H.;

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 9902−9905. (c) Liu, H.; Laurenczy, G.; Yan, N.; Dyson, P. J. *Chem. Commun.* **2014**, *50*, 341−343.

(20) Wang, C.; Zhang, L.; Chen, C.; Han, J.; Yao, Y.; Zhao, Y. *Chem. Sci.* **2015**, *6*, 4610−4614.

(21) Wang, P.-L.; Li, Y.; Wu, Y.; Li, C.; Lan, Q.; Wang, X.-S. *Org. Lett.* **2015**, *17*, 3698−3701.

(22) For nondirected C(sp^3)−H carbonylation, see: (a) Ryu, I.; Tani, A.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1869−1872. (b) Li, Y.; Dong, K.; Zhu, F.; Wang, Z.; Wu, X.-F. *Angew. Chem., Int. Ed.* **2016**, *55*, 7227−7230 (also see ref 19c)..

(23) For other innovative contributions to the design of auxiliaries for C(sp^3)−H activation (a) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192−5196. (b) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124−11128. (c) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724−3727. (d) Rodríguez, N.; Romero-Revilla, J. A.; Fernández-Ibáñez, M. A.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175−179. (e) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187−4192. (f) Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Chem. Sci.* **2013**, *4*, 3712−3716. (g) Fan, M.; Ma, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 12152−12155. (h) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3868−3871. (i) Wang, C.; Chen, C.; Zhang, J.; Han, J.; Wang, Q.; Guo, K.; Liu, P.; Guan, M.; Yao, Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 9884−9888. (j) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Shankar, M.; Sahoo, A. K. *Org. Lett.* **2014**, *16*, 5258−5261. (k) Chen, K.; Li, Z.-W.; Shen, P.-X.; Zhao, H.-W.; Shi, Z.-J. *Chem.—Eur. J.* **2015**, *21*, 7389−7393 See also ref 17..

(24) For the late stage C(sp^3)−H functionalization of di-, tri- and tetrapeptides, see ref 2j. See also ref 23e. For late stage C(sp^2)−H functionalization of small peptides, see: Zhu, Y.; Bauer, M.; Ploog, J.; Ackermann, L. *Chem.—Eur. J.* **2014**, *20*, 13099−13102.

(25) (a) Li, H.; Cai, G.-X.; Shi, Z.-J. *Dalton Trans* **2010**, *39*, 10442−10446. (b) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686−693 and references cited therein..

(26) For reviews on the use of CO surrogates, see: (a) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580−5588. (b) Wu, L.; Liu, Q.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 6310−6320. For recent reports, see: (c) Friis, S. D.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 18114−18117. (d) Natte, K.; Dumrath, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10090−10094. (e) Hansen, S. V. F.; Ulven, T. *Org. Lett.* **2015**, *17*, 2832−2835. (f) Nageswar Rao, D.; Rasheed, S.; Das, P. *Org. Lett.* **2016**, *18*, 3142−3145 and references cited therein..

(27) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2015**, *137*, 4924−4927.

(28) For examples on the use of $Mo(CO)_6$ as CO surrogate in Pd^0-catalyzed carbonylation of haloarenes, see: (a) Nordeman, P.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2012**, *77*, 11393−11398. (b) Kaiser, N. F. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109−111 and references cited therein. (Upon refluxing in a high boiling solvent or in the presence of a coordinating ligand, $Mo(CO)_6$ is smoothly transformed into trisubstitued molybdenum carbonyls. For instance, on refluxing $Mo(CO)_6$ in excess acetonitrile under nitrogen, an almost-quantitive yield of $[Mo(CO)_3(MeCN)_3]$ is obtained with evolution of 3 mol of gas.). (c) Abel, E. W.; Bennett, M. A.; Wilkinson, G. *J. Chem. Soc.* **1959**, 2323−2327. (d) Tate, D. P.; Knipple, W. R.; Augl, J. M. *Inorg. Chem.* **1962**, *1*, 433−434.

(29) Giri, R.; Maugel, N.; Li, J.−J.; Wang, D.−H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.−Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510−3511.

(30) For mechanistic studies on the key role of BQ in Pd-catalyzed oxidative cross-coupling reactions, see: (a) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651−9653. (b) Pattillo, C. C.; Strambeanu, I. I.; Calleja, P.; Vermeulen, N. A.; Mizuno, T.; White, M. C. *J. Am. Chem. Soc.* **2016**, *138*, 1265−1272. For the use of benzoquinone as oxidant in C−H functionalization reactions, see: (c) Popp, B. V.; Stahl, S. S. *Top. Organomet. Chem.* **2007**, *22*, 149−190.

(31) For X-ray crystallographic data of this compound, see the SI. CCDC 1485593−1485594 (for complex B) and 1485578 (for complex C) contains 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.

(32) For further examples on the use of the N-SO_2Py directing group in C−H functionalization showing its easy removal, see: (a) García-Rubia, A.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511−6515. (b) García-Rubia, A.; Urones, B.; Gómez Arrayás, R.; Carretero, J. C. *Chem.—Eur. J.* **2010**, *16*, 9676−9685. (c) García-Rubia, A.; Urones, B.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10927−10931. (d) Urones, B.; Gómez Arrayás, R.; Carretero, J. C. *Org. Lett.* **2013**, *15*, 1120−1123. (e) Urones, B.; Martínez, A. M.; Rodríguez, N.; Gómez Arrayás, R.; Carretero, J. C. *Chem. Commun.* **2013**, *49*, 11044−11046. (f) Mei, T.-S.; Leow, D.; Xiao, H.; Laforteza, B. N.; Yu, J.-Q. *Org. Lett.* **2013**, *15*, 3058−3061. (g) Yan, Z.-L.; Chen, W.-L.; Gao, Y.-R.; Mao, S.; Zhang, Y.-L.; Wang, Y.-Q. *Adv. Synth. Catal.* **2014**, *356*, 1085−1092. (h) Legarda, P. D.; García Rubia, A.; Gómez Arrayás, R.; Carretero, J. C. *Adv. Synth. Catal.* **2016**, *358*, 1065−1072.

(33) For examples of methylene C(sp^3)−H functionalization, see: (a) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570−18572. (b) Chen, K.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 11950−11954. (c) Ling, P.-X.; Fang, S.-L.; Yin, X.-S.; Chen, K.; Sun, B.-Z.; Shi, B.-F. *Chem.—Eur. J.* **2015**, *21*, 17503−17507.

(34) For the medicinal chemistry of biologically active cyclopropane derivatives, see: (a) Kumar, K. A. *Int. J. Pharm. Pharm. Sci.* **2013**, *5* (1), 467−472. (b) Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511−542. For a review on the use of cyclopropanes and their derivatives in organic synthesis, see: (c) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165−198.

(35) For examples on the C(sp^3)−H functionalization of cyclopropane derivatives, see: (a) Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 4394−4397. (b) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15*, 3238−3241. (c) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598−19601. (d) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 2042−2046.

(36) For the synthesis of cyclopropane-fused γ-lactams by intramolecular alkylation of cyclopropyl C(sp^3)−H bonds, see: (a) Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 9064−9067. For the synthesis of strained α-alkylidene-γ-lactams via intramolecular C(sp^3)−H alkenylation, see: (b) Holstein, P. M.; Dailler, D.; Vantourout, J.; Shaya, J.; Millet, A.; Baudoin, O. *Angew. Chem., Int. Ed.* **2016**, *55*, 2805−2809.

(37) For Pd-catalyzed methylene activation of the adamantyl scaffold, see: Lao, Y.-X.; Wu, J.-Q.; Chen, Y.; Zhang, S.-S.; Li, Q.; Wang, H. *Org. Chem. Front.* **2015**, *2*, 1374−1378.

(38) This outcome can be explained by competitive dehydrogenation of substrate **42** at the benzylic position leading to the corresponding diphenylmethanimine, whose hydrolysis would generate the (2-pyridyl)sulfonamide (see, for instance: (a) Kim, D.−S.; Park, J. −W.; Jun, C.−H. *Adv. Synth. Catal.* **2013**, *355*, 2667−2679. (b) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2011**, *40*, 600−602. Alternatively, direct 2-pyridylsulfonamide displacement leading to theformation of the highly stabilized carbocation intermediate could also take place under the harsh reaction conditions (see, for instance: (c) Alonso, I.; Esquivias, J.; Gómez Arrayás, R.; Carretero, J. C. *J. Org. Chem.* **2008**, *73*, 6401−6404. (d) Esquivias, J.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 629−633.

(39) Yu and co-workers have reported the intramolecular C−H amidation of *N*-(2-pyridyl)sulfonyl phenethylamines leading to indoline derivatives; see ref 32f.

(40) The proposal of seven-membered cyclopalladation intermediates is unusual. See, for example: (a) Wang, G.-W.; Yuan, T.-T.; Li, D.-D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1380−1383. (b) Wang, H.-L.; Hu,

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX

R.-B.; Zhang, H.; Zhou, A.-X.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 5302−5305.

(41) For examples of Pd^{II}-catalyzed olefination protocols featuring tolerance with regard to the tether length, see: (a) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676−17677. (b) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315−319. (c) Li, G.; Wan, L.; Zhang, G.; Leow, D.; Spangler, J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 4391−4397. (d) Also see refs 32c and 32h.

(42) For examples of construction of benzazepine skeleton through C-H activation, see: (a) Wang, L.; Huang, J.; Peng, S.; Liu, H.; Jiang, X.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1768−1772. (b) Sustac Roman, D.; Charette, A. B. *Top. Organomet. Chem.* **2015**, *56*, 91−113.

(43) Compound **62** was setereoselectively prepared from commercially available estrone following a reported procedure. See: Zhang, L.-S.; Chen, G.; Wang, X.; Guo, Q.-Y.; Zhang, X.-S.; Pan, F.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3899−3903.

(44) Poveda, A.; Alonso, I.; Fernández-Ibáñez, M. A. *Chem. Sci.* **2014**, *5*, 3873−3882.

(45) In accordance with the different behaviour of complex **A** in CD_2Cl_2, a marked difference in the reactivity profile was noticed when monitoring by ^1H NMR the stoichiometric carbonylation of complex **A** with $Mo(CO)_6$ (0.33 equiv) using CD_2Cl_2 as solvent (see the Supporting Information).

(46) This chemical shift is consistent with values previously reported for similar Pd-carbonyl complexes (160−180 ppm). For selected publications on the characterization of palladium carbonyl complexes, see: (a) García-López, J.-A.; Oliva-Madrid, M.-J.; Saura-Llamas, I.; Bautista, D.; Vicente, J. *Organometallics* **2013**, *32*, 1094−1105. (b) Trebbe, R.; Goddard, R.; Rufinska, A.; Seevogel, K.; Pörschke, K.-P. *Organometallics* **1999**, *18*, 2466−2472. For a review on palladium carbonyl complexes, see: (c) Stromnova, T. A.; Moiseev, I. I. *Russ. Chem. Rev.* **1998**, *67*, 485−514. For a selected textbook for the synthesis of transition-metal complexes, see: (d) Angelici, R. J. *Reagents for Transition Metal Complex and Organometallic Syntheses*; Wiley & Sons: New York, 1990.

(47) A very similar result was achieved in CD_3CN: Intermediate **D**; [*m*/*z* $(M+CO+Na)^+$: 440.9712] and complex **Á**; [*m*/*z* $(M-CO+Na)^+$: 412.9762] (see the Supporting Information for details).

(48) Diffusion-ordered NMR spectroscopy (DOSY) experiments carried out on a 58:42 mixture of monomeric complex **A′** (monomeric) and intermediate **D** (in CD_3CN at 5 °C) and on a 40:60 mixture of complex **A** (dimeric) and intermediate **D** (in CD_2Cl_2 at rt) further supported the monomeric nature of the intermediate **D** (see the Supporting Information for details).

(49) (a) Sanhueza, I. A.; Wagner, A. M.; Sanford, M. S.; Schoenebeck, F. *Chem. Sci.* **2013**, *4*, 2767−2775. (b) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880−6886. (c) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848−10849.

(50) The model structures **I**, **TS(II-III)**, **III**, and **IV** were also proposed to be involved in the C−H activation step during the γ-arylation process (see ref 45 for details).

(51) Since in the stoichiometric reaction, the formation of complex **I** and its reaction with $Mo(CO)_6$ occur without AgOAc, providing cleanly the carbonylation product **2**, we might intuitively rule out that the Ag salt is necessary for the C−H activation step to take place. Instead, the Ag salt is likely acting as an oxidant for the palladium center. However, silver salts could also be involved in the formation of heterobimetallic Pd-Ag species, which could participate in the C−H activation step. See (a) Yang, Y.-F.; Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, Y.-Q.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344−355. (b) Anand, M.; Sunoj, R. B.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **2014**, *136*, 5535−5538. (c) Anand, M.; Sunoj, R. B.; Schaefer, H. F., III. *ACS Catal.* **2016**, *6*, 696−708. We have also tried to shed light on this point by calculating the possible heterobimetallic Pd-Ag intermediates and transition states that could be involved in our C−H activation process but we could not find any more favorable pathway (see the Supporting Information for details). For a recent investigation of the role of silver carboxylate salts in Pd-catalyzed arene C−H functionalization, see: (d) Lotz, M. D.; Camasso, N. M.; Canty, A. J.; Sanford, M. S. *Organometallics* **2016**, DOI: 10.1021/acs.organomet.6b00437.

(52) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Rev. E.01*; Gaussian, Inc.: Wallingford, CT, 2009.

DOI: 10.1021/acscatal.6b01987
ACS Catal. XXXX, XXX, XXX−XXX