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Research Article

Overcoming the Necessity of γ-Substitution in δ-C(sp^3)−H Arylation: Pd-Catalyzed Derivatization of α-Amino Acids

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Cite This: ACS Catal. 2021, 11, 5310−5317

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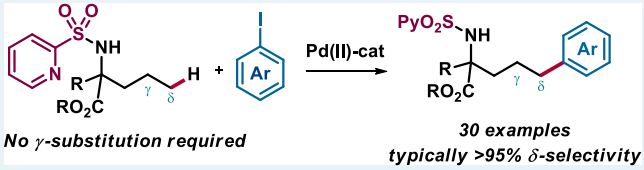
ABSTRACT: Despite the emergence of catalytic C(sp^3)−H arylation at the remote δ-position via challenging six-membered ring cyclometalation, the requirement of blocking the more reactive γ-position represents a restricting limitation. The use of the removable *N*-(2-pyridyl)sulfonyl directing group provides a viable solution to this challenge, expanding the scope of the Pd-catalyzed δ-C−H arylation of α-amino acid and amine derivatives with (hetero)aryl iodides. This method is compatible with complex, multifunctional structures at either reaction partner. Experimental and density functional theory studies provide insights about the underlying factors controlling site selectivity.



KEYWORDS: *remote C(sp^3)−H arylation, palladium-catalysis, α-amino acid, 2-pyridylsulfonyl directing group, late-stage functionalization, peptide*

1. INTRODUCTION

Transition metal-catalyzed C(sp^3)−H derivatization of the side-chains of α-amino acids (αAAs)[1] is a powerful means of generating nonproteinogenic αAAs that can potentially impart improved or novel functions to proteins or peptide mimics.[2] However, this is not an easy task: the weak alkyl−metal bonds, the flexibility of alkyl chains, and the propensity for intermediate species to undergo β-hydride elimination are challenges on top of the problems inherent to C−H activation.[1] The use of bidentate directing groups (DGs) such as the picolinamide (PA), pioneered by Daugulis,[3] typically in combination with palladium catalysis has proven to be an efficient way to circumvent these hurdles. Indeed, this seminal contribution has fueled a significant progress in C(sp^3)−H activation up to the present date.[1,4] In most instances, the strong kinetic and thermodynamic preference for a five-membered metalacycle[5] determines the site selectivity: typically at the β-position, if the DG is installed at the C-terminus of the αAA, or at the γ-position, when the DG is attached at the N-terminus.[1b−d] This trend is so strong that often methylene activation via five-membered cyclometalation occurs in preference over cleavage of available methyl C−H bonds via six-membered metalacycles,[6] even though the activation of primary centers is generally preferred over secondary ones due to increased steric hindrance around the cyclometalation transition state (TS).[6b,7]

This intrinsic selectivity is a restricting limitation when the target C−H bond is at the more remote δ-position. Indeed, only a handful of elegant methods for achieving δ-C(sp^3)−H functionalization via a six-membered ring palladacycle has been recently disclosed by Yu, Maiti, Bannister, Chen, and others.[8] These approaches typically rely on substrates with either high conformational restraint that makes sterically less accessible the more reactive γ-C(sp^3)−H bonds or acyclic substrates having blocked the γ-position with substituents (Scheme 1a).

To our knowledge, only two single procedures have been reported enabling highly selective δ-C(sp^3)−H activation on substrates having unsubstituted γ-CH_2 moieties.[9] Shi recently demonstrated in the PA-assisted Pd-catalyzed C(sp^3)−H functionalization of αAA derivatives that under a Curtin−Hammett scenario where a regime for reversible γ/δ-C−H activation and fast interconversion of five- and six-membered metalacycles is established, high δ-selectivity can be attained if the less favored six-membered palladacycle reacts significantly faster than the five-membered one. However, this strategy was applied only to δ-alkenylation and δ-alkylation via insertion of alkynes[9a] and alkenes,[9b] respectively (Scheme 1b). Therefore, new approaches capable of expanding the scope to other C−C bond forming reactions would be highly appealing. For example, a general and selective method for δ-C(sp^3)−H arylation of γ-unblocked substrates remains undocumented.

In light of these precedents, most of which rely on the use of carbonyl-based directing auxiliaries (mostly PA), we hypothesized that a DG based on a sulfonyl connector (with different geometrical/electronic features in comparison to the carbonyl-

Received: January 18, 2021
Revised: April 2, 2021
Published: April 19, 2021

https://doi.org/10.1021/acscatal.1c00250
ACS Catal. 2021, 11, 5310−5317

Scheme 1. δ-C(sp^3)−H Functionalization of Amine and AA Derivatives

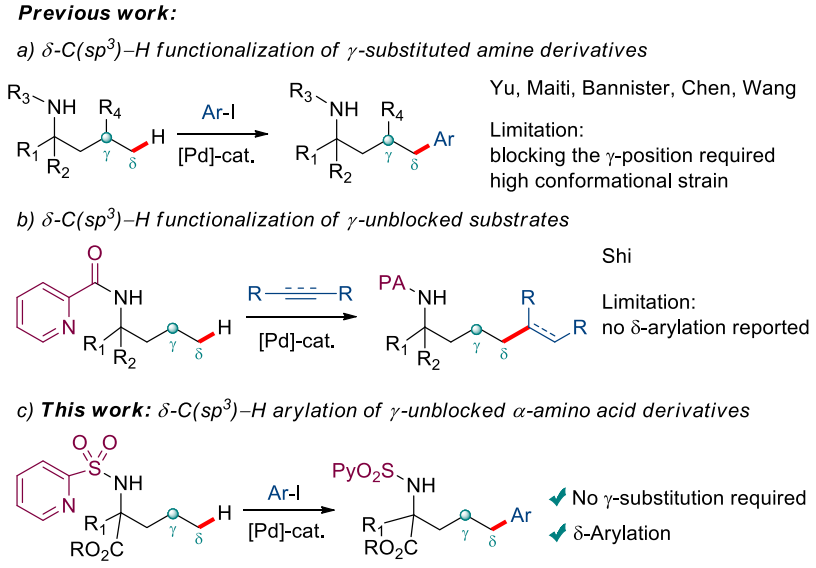
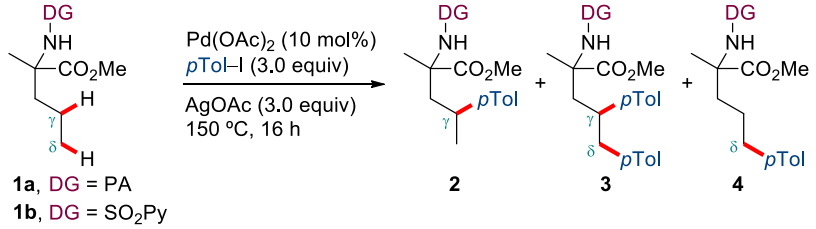


Table 1. Evaluation of the DG in the δ-C(sp^3)−H Arylation of 1[a]



#	*p*Tol-I (equiv)	DG	solvent	**2** (%)[b]	**3** (%)[b]	**4** (%)[b]
1	5.0	PA	HFIP	60	13	
2	5.0	SO_2Py	HFIP			34
3[c]	3.0	PA	1,4-dioxane	51	36	
4[c]	3.0	SO_2Py	1,4-dioxane			58

[a]Reaction conditions: **1** (0.20 mmol), *p*Tol-I (*x* equiv), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), AgOAc (0.60 mmol, 3.00 equiv), solvent (0.20 mL), 150 °C, 16 h. [b]Isolated yields. [c]1,4-Dioxane (0.40 mL).

based PA) could influence the reactivity of metalacyclic intermediates, thereby enabling C−H arylation with a high control of δ-CH_3 over γ-CH_2 site selectivity. Herein, we report a robust solution to this problem that significantly expands the scope of the Pd-catalyzed δ-C(sp^3)−H arylation of αAA derivatives based on the use of the 2-pyridylsulfonyl DG (SO_2Py, Scheme 1c).[10] Density functional theory (DFT) studies, in combination with control and mechanistic experiments, have revealed important insights about the origin of this unique δ-selectivity.

2. RESULTS AND DISCUSSION

2.1. Optimization Studies. We first examined the effect of the DG (PA vs SO_2Py) on reactivity and site selectivity in the arylation of the α-methyl-norvaline derivative **1** with *p*-iodotoluene using $Pd(OAc)_2$ as the catalyst (10 mol %) and AgOAc as the oxidant (Table 1, see the Supporting Information for full optimization studies). A dramatic effect on selectivity was observed by just replacing the carbonyl connector of PA (**1a**) by a sulfonyl moiety (**1b**). Whereas the reaction of **1a** in hexafluoroisopropanol (HFIP) (1 M) afforded a 4.6:1 mixture of the γ-arylation product **2a** and the γ,δ-diarylated product **3a** (entry 1), the *N*-(2-pyridyl)-sulfonyl (*N*-SO_2Py)-protected **1b** provided **4b** as the only product under identical reaction conditions (34% isolated yield, entry 2). The reaction in 1,4-dioxane at lower concentration (0.5 M) offered better reactivity, providing **4b** in a synthetically useful 58% yield (entry 4). It is important to note that despite incomplete conversion, the reaction was very clean, with 42% of starting **1b** being recovered unaltered. Unfortunately, reducing the amount of either $Pd(OAc)_2$, AgOAc, or *p*-tolyl iodide resulted in reduced yields (not shown). It should be also noted that, to the best of our knowledge, direct δ-C−H arylation of the simple α-methyl norvaline has not been reported to date.

2.2. Reaction Scope. Upon completion of our optimization studies, the results of an examination of the scope of various αAA derivatives having unblocked γ-CH_2 are presented in Scheme 2. Structurally diverse γ-CH_2-unblocked αAA derivatives were surveyed in the reaction with *p*-iodotoluene under optimized conditions (Scheme 2). Substrates possessing α-quaternary carbon centers without further branching provided δ-arylation products with complete site selectivity in useful yields (**15**−**17**, 42−56% yield), except for **16**, possessing two *n*Pr chains, which was obtained as a mixture of δ- and γ'-monoarylation derivatives (δ/γ' = 1.7:1). Decreased

https://doi.org/10.1021/acscatal.1c00250
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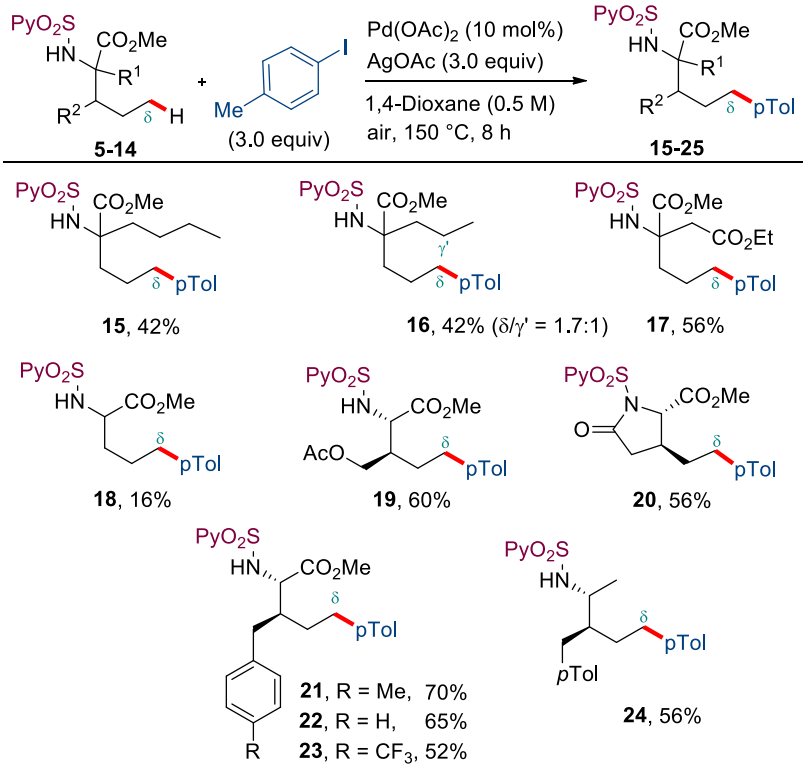
Scheme 2. δ-Arylation of γ-Methyl Groups in αAA Derivatives



yield was observed in substrates having an α-tertiary carbon as the only branching (**18**, 16%), suggesting that the Thorpe–Ingold effect may play a crucial role in the reactivity. Gratifyingly, the reactivity was restored without affecting δ-selectivity in α-tertiary substrates when additional branching at the β-position was present (**19**–**23**, 52–70% yield). When the β-substituent is a (methoxycarbonyl)methyl group, the δ-arylation product undergoes lactamization (**20**, 56%).

Interestingly, benzyl substituents at the β-position are also tolerated. These are more challenging substrates because they contain an additional set of even more acidic benzylic γ-CH_2 bond moiety in addition to ε-C(sp^2)–H.[10a] In spite of these additional complications, the δ-functionalization took place cleanly to afford exclusively the desired products **21**–**23** in satisfactory yields (52–70%). Interestingly, better reactivity was observed on increasing the electron density of the aryl ring. Finally, the α-ester group is not essential, but it does, however, improve the efficiency of the reaction, as demonstrated in the arylation of an analogous simple aliphatic amine derivative (**24**, 56%). It is worth noting that no epimerization was observed in the arylation of substrates containing two stereogenic centers (**19**–**24**), thereby demonstrating the configurational stability of the relatively labile C2 stereocenter under the reaction conditions. This method is also tolerant of αAAs having γ-substitution, although diarylation selectivity was observed for those with equivalent δ-Me groups, complementing previous described protocols[8a,c] (see Scheme S1 in the Supporting Information).

Next, we examined the scope of the iodoarene coupling partner on substrates with either α-quaternary or α-tertiary-β-branched substitution (Scheme 3). A range of para- and metasubstituted aryl, as well as O-, S-, and N-based heteroaromatic systems, with diverse steric and electronic properties (ethers, esters, and aldehyde groups) can be readily exploited in this protocol (**26**–**42**, 20–74%). Furthermore, aryl chloro (**28**, 71%), bromo (**29**, 46%), or iodo (**34**, 74%) substituents were also compatible, thus providing flexible handles for further orthogonal functionalization. In all cases, complete δ-selective arylation was observed despite the presence of a γ-CH_2 moiety, which remained intact after the transformation. Although clean formation of the δ-arylation product was generally observed, incomplete conversions often result in modest yield. In those cases, the unreacted starting material was recovered by standard chromatography (see Supporting Information). Remarkably, this method is compatible with aryl iodides of higher structural and functional complexity, thereby enabling the incorporation of natural product and drug derivatives into the αAA skeleton (**40**–**42**).

To the best of our knowledge, only two isolated examples have been demonstrated on the activation of δ-CH_2 bonds.[8c,d] Given that this remote activation has never been harnessed to functionalize αAA systems, we questioned whether this method could enable activation of the more challenging methylene C–H bonds. As shown in Scheme 4, the cyclopropyl derivative **43** reacted smoothly under these conditions, affording the monoarylation product in good yield with good diastereoselectivity (**44**, 60%, dr = 80:20). Unfortunately, the reaction of other cycloalkyl derivatives with lower sp^2-like character was less regioselective (cyclobutyl; not shown; see the Supporting Information).

The robustness of this method was further demonstrated by the postsynthetic modification of a small peptide (Scheme 5). The reaction occurred with complete site selectivity control to provide dipeptide **46** with modest yield (33%).

2.3. Mechanistic Experiments. To gain preliminary mechanistic data, we carried out a series of H/D scrambling experiments. Substrate **11** was selected because it contains four different types of reactive C–H bonds: primary δ-CH_3,

https://doi.org/10.1021/acscatal.1c00250
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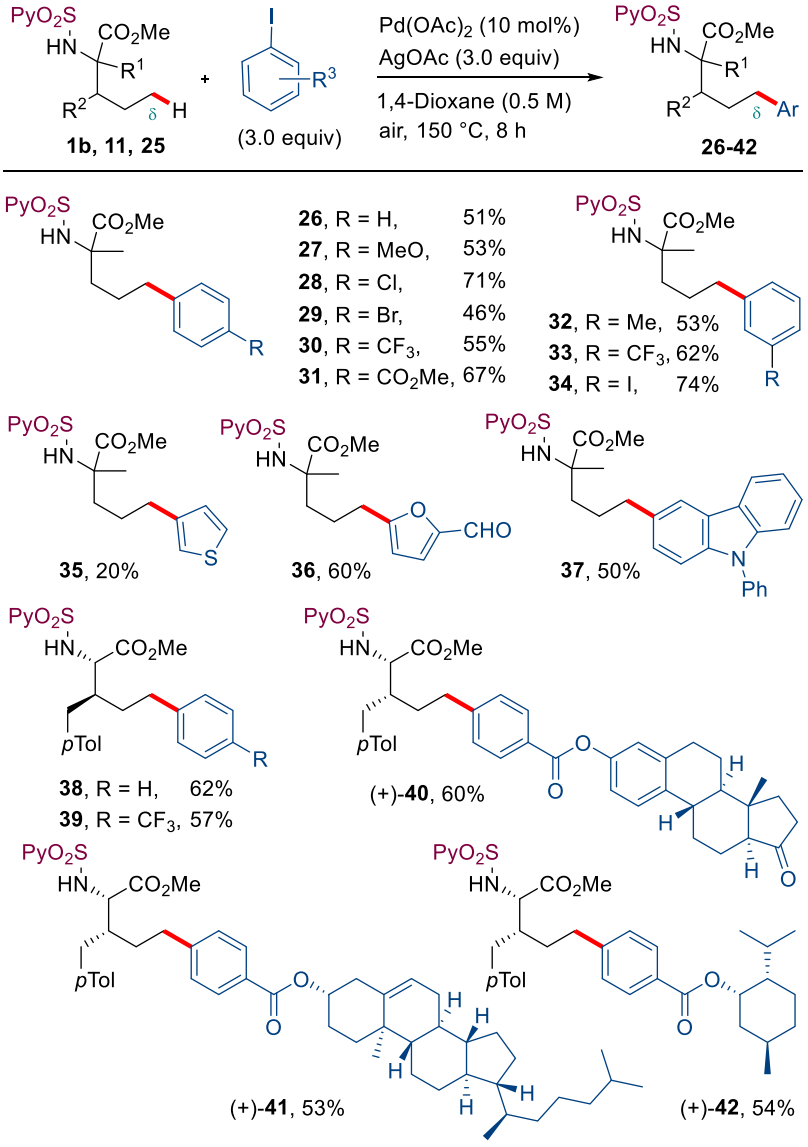
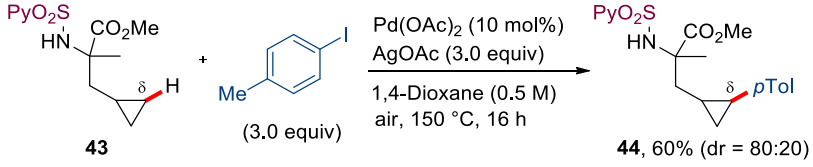
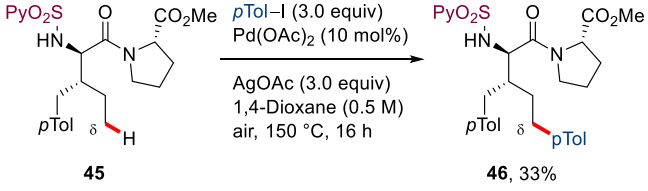
Scheme 3. Scope of Aryl Iodide



Scheme 4. δ-Arylation of Cyclopropyl Derivative 43



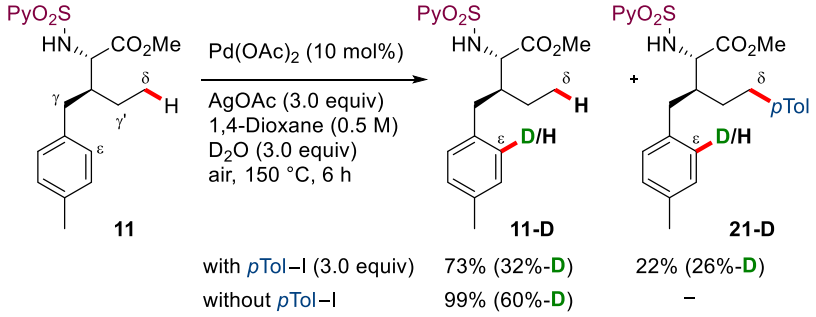
Scheme 5. δ-Arylation of a Dipeptide Derivative



benzylic secondary γ-CH_2, unactivated secondary γ'-CH_2, and ε-C(sp^2)−H bonds (Scheme 6). Thus, the arylation of **11** with *p*-iodotoluene in the presence of D_2O (3.0 equiv), stopped at early stages (6 h), provided the product **21-D** in 22% yield. The exclusive D-incorporation at the aryl ε-position (26%-D), which was also observed in the recovered starting material **11-D** (73% yield, 32%-D), supports the reversibility of the ε-C(sp^2)−H cleavage. The absence of D-incorporation at the γ- or γ'-position seems to indicate that either their activation is not favored or they lead to highly stable five-membered palladacycles that do not evolve further (see the Supporting Information for additional experiments). On the other hand, the lack of D-scrambling at the δ-position suggests that either the δ-C(sp^3)−H activation step is irreversible or the subsequent C−Ar bond formation from the six-membered cyclopalladation intermediate is sufficiently fast to outcompete the reversibility of the δ-C−H bond activation. To gain more

https://doi.org/10.1021/acscatal.1c00250
ACS Catal. 2021, 11, 5310−5317

Scheme 6. H/D Scrambling Experiments in Substrate 11



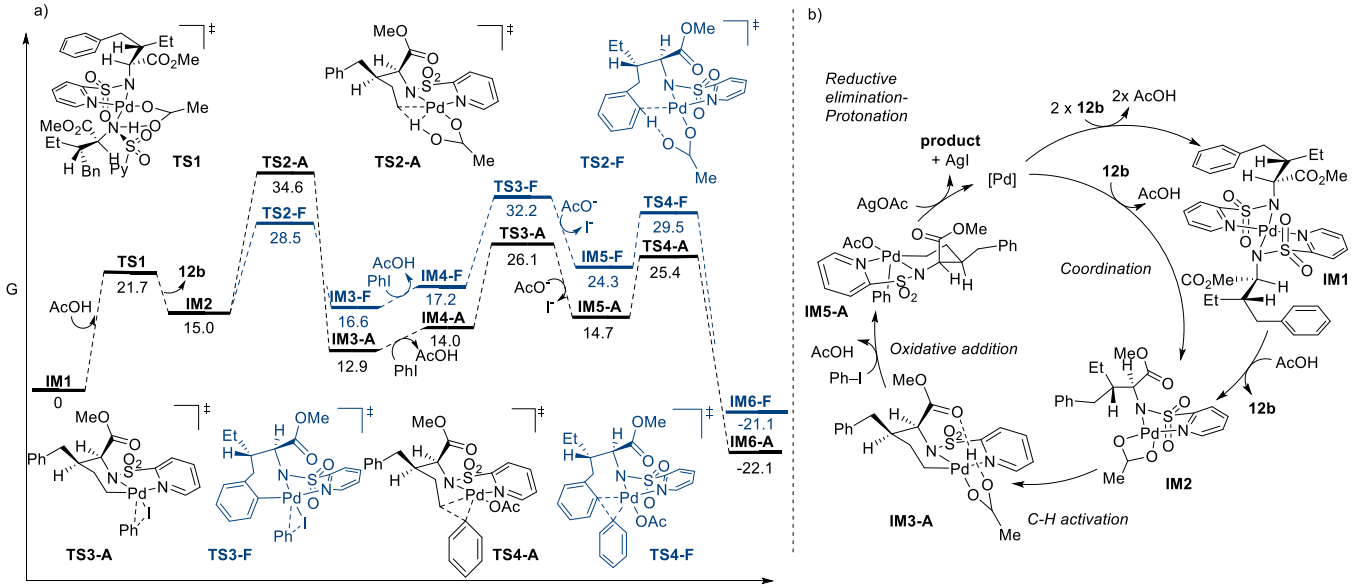


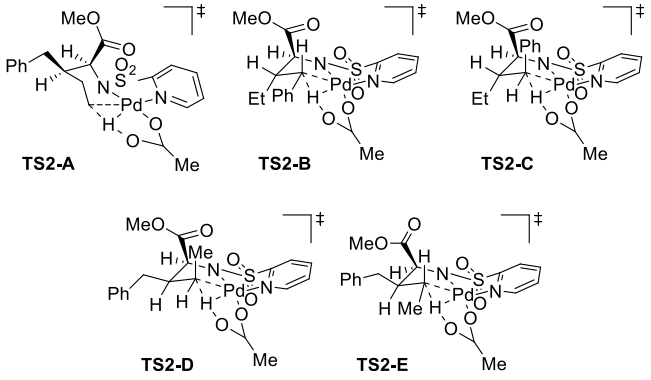
Figure 1. (a) Computed free-energy profile (kcal mol^{-1}) at 298 K in 1,4-dioxane, M06$_{SMD}$/6-311++G(d,p) (C, H, N, O, S), SDD (Pd, I)//B3LYP-D3/6-31G(d) (C,H,N,O,S), LANL2DZ(f) (Pd), LANL2DZ(d) (I) for the δ-C(sp^3)−H arylation of substrate **12b** (black pathway) vs the ε-C(sp^2)−H (blue pathway). (b) Proposed catalytic cycle.

insight into this aspect, the same H/D scrambling experiment was performed in the absence of the iodoarene coupling partner showing exclusive deuteration at the ε-position. This result supports the notion that the δ-C−H activation step can be irreversible under the reaction conditions.

2.4. DFT Studies. Next, we undertook DFT investigations of the arylation of **12b**, a simpler analogue of **11**, to shed some light on the factors that govern selectivity of competing functionalization pathways (Figure 1). These studies suggest that the δ-C−H activation step might occur via an acetate-assisted concerted metalation−deprotonation mechanism, leading to a six-membered cyclopalladated intermediate (**IM3-A**) which, upon AcOH/Ph-I ligand exchange (**IM4-A**), undergoes subsequent oxidative addition of PhI to give the Pd(IV) intermediate **IM5-A**, followed by reductive elimination (black pathway).

According to the energy profile shown in Figure 1, the highest energy barrier was found to be the substrate displacement from **IM1** by AcOH to give **IM2** (21.7 kcal·mol^{-1}), whereas the subsequent C−H activation step showed the highest TS energy (**TS2-A**, 34.6 kcal·mol^{-1}). A comparison of the relative stabilities of the TSs found for the δ- and γ-activation (**TS2-A** and **TS2-B-E**, respectively) revealed that the δ-C−H cleavage is kinetically favored (Table 2). Additionally, the intermediate resulting from δ-activation is the most stable

Table 2. Relative *G* Values (kcal mol^{-1}, at 298 K in 1,4-Dioxane) Respect to IM1 for the C−H Activation Step in the Different δ- vs γ-Positions



	δ-CH$_3$	γ-(Bn)-CH$_2$		γ-CH$_2$	
	A	(Pro *S*) **B**	(Pro *R*) **C**	(Pro *S*) **D**	(Pro *R*) **E**
TS2	34.6	36.3	37.5	37.5	39.4
IM3	12.9	17.1	16.8	20.2	17.8

(compare **IM3-A** with **IM3-B-E** in Table 2) and the δ-C−H cleavage was found to be irreversible, unlike any γ-C−H activation step. These data are consistent with the lack of γ-

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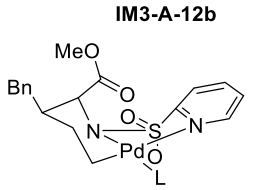

bond angle	IM3-12b	IM3-12a
N-Pd-N	85.2	79.8
N-Pd-O	94.7	99.1
O-Pd-C	91.4	89.4
C-Pd-N	87.5	94.2
	358.8	362.5

Figure 2. Structure and bond angles of *N*-SO_2Py and *N*-PA six-membered palladacycles **IM3-A-12a** and **IM3-A-12b**.

and γ'-D-incorporation observed experimentally in either the starting material or the δ-arylated product, as well as the absence of D-scrambling at the δ-position in the starting substrate (vide supra).

The ε-C(sp^2)−H arylation through **TS2-F** was also studied (blue pathway in Figure 1). If we compare the δ- and ε-activation pathways, the DFT calculations reveal that the ε-C(sp^2)−H activation step is reversible and kinetically much more favored (28.5 kcal·mol^{-1}) than the δ-cleavage (34.6 kcal·mol^{-1}), which appears to be irreversible. Moreover, the energy profile of the ε-functionalization pathway indicates that from the seven-membered palladacycle **IM3-F**, the oxidative addition of phenyl iodide is slower (**IM4-F** → **IM5-F**, 15.0 kcal·mol^{-1}) than the back reaction (**IM3-F** → **IM2**, 11.9 kcal·mol^{-1}). Therefore, it seems reasonable to assume that **IM3-F** would favorably evolve back to **IM2** and follow the thermodynamically favored δ-activation pathway. These computational results and the underlying hypothesis are supported by the deuterium incorporation at the ε-position observed experimentally in the H/D scrambling studies (Scheme 6).

To rationalize the unique role of SO_2Py as DG compared to PA, we studied computationally the C−H activation step for PA-containing substrate **12a**. The similar stability found for the γ- and δ-C−H activation TSs, as well as the reversible character of both cyclopalladation pathways, account for the poor γ/δ-selectivity observed experimentally for **12a** (see Supporting Information) and **1a** (Table 1). The higher stability of **IM3-A-12b** intermediate compared to **IM3-A-12a**, which is responsible for the irreversibility of the δ-activation step in **12b**, can be ascribed to the different size and electronic properties of the SO_2 moiety compared to CO (Figure 2). Conjugation of the carbonyl with nitrogen makes the five-membered ring completely flat, whereas the lack of conjugation with SO_2 imposes an envelope conformation orienting the sulfur atom out of the plane. This latter arrangement allows the six-membered ring palladacycle **IM3-A-12b** to adopt a chair-like conformation with a smaller distortion of the coordination plane of Pd(II), whereas the sp^2 hybridization of nitrogen in the PA-intermediate **IM3-A-12a** leads to a conformation with reduced flexibility that results in a more distorted square planar geometry. Finally, the higher reactivity observed for αAA substrates compared to simple amines could be related to a stabilizing interaction between the carbonyl oxygen of the α-ester moiety and the metal that stabilizes the catalytically active species **IM2** (see the Supporting Information).

3. CONCLUSIONS

In summary, we have developed a Pd-catalyzed δ-C(sp^3)−H arylation that circumvents the need for blocking the more reactive γ-position. This strategy enables the derivatization of a variety of γ-CH_2-containing αAA derivatives with high δ-selectivity and is compatible with complex structures at both coupling partners. DFT studies suggest that the sp^3 hybridization of the sulfonyl moiety and its lack of conjugation with nitrogen, which are distinct elements compared to widely used carbonyl-based DGs, play an important role in the unique efficiency of the SO_2Py DG.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c00250.

Experimental procedures, spectral data, and complete DFT studies (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Ministerio de Economía, Industria y Competitividad (MINECO) and Fondo Europeo de Desar-

rollo Regional (FEDER, UE) (Project CTQ2015-66954-P) and Ministerio de Ciencia e Innovación (MICINN)/FEDER, UE (Agencia Estatal de Investigación/Project PGC2018-098660-B-I00) for the financial support. M.M.-M. thanks MINECO for a FPI predoctoral fellowship. We also thank the Centro de Computación Científica at the Universidad Autónoma de Madrid for their generous allocation of computer time.

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