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C-H Activation

Palladium-Catalyzed PIDA-Mediated δ-C(sp^3)–H Acetoxylation of Amino Acid Derivatives: Overriding Competitive Intramolecular Amination

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Abstract: The selective δ-C(sp^3)–H acetoxylation of *N*-(SO_2Py)-protected amino acid derivatives has been accomplished by using palladium-catalysis and PhI-($OAc)_2$ (PIDA) as both terminal oxidant and acetoxy source. The distinct structural and electronic features of the SO_2Py compared to more traditional carbonyl-based directing groups is essential to override the otherwise more favourable competitive intramolecular C–H amination. The δ-site selectivity predominates over traditionally more favorable 5-membered cyclopalladation at competitive γ-CH_2. Experimental and DFT mechanistic studies provide important insights about the mechanism and the underlying factors controlling the chemo- and regioselectivity.

The past decades have witnessed the development of powerful strategies based on transition metal catalyzed direct conversion of C(sp^3)–H bonds into C–C and C–X bonds.[1] Among them, C–H oxygenations, especially acetoxylation, have received substantial attention given the importance of the OAc group in bioactive compounds.[2] Most often, directing group (DG)-assisted metallacycle formation is used as a powerful strategy to lower the energy barrier of C–H activation and ensure regioselectivity.[3]

However, the strong preference for the formation of 5-membered palladacycles[4] has limited the Pd-catalyzed C(sp^3)–H acetoxylation at γ-position to the DG.[5] Achieving more remote site-selectivity through larger palladacycle intermediates remains a significant challenge and only a few examples have been described to date.[6] In fact, previously reported examples of directed δ-oxygenation of aliphatic C–H bonds have been limited to the carboxylate-directed lactonization of benzoic acid derivatives.[7] Methods for intermolecular remote aliphatic C–H oxygenation remain a significant challenge. This transformation becomes arguably even more difficult when several favourable C–H activation pathways are equally accessible. In this field, the increasing demand for more complex amines and amino acid (AA) derivatives in drug discovery platforms[8] has driven the development of methods for their direct functionalisation as an efficient means to rapidly change their properties.[9]

The lack of precedents on δ-C(sp^3)–H oxygenation is likely a consequence of the intrinsic challenge of circumventing the competitive intramolecular C–H amination process, which have demonstrated to be more favourable. For example, under typical conditions for C–H acetoxylation, Chen[10] and Daugulis[11] have independently reported the formation of pyrrolidine derivatives via the Pd-catalyzed intramolecular δ-C–H amination of picolinamide (PA)-protected aliphatic amines using bisacetoxyiodobenzene (PIDA) as stoichimetric oxidant. Similarly, Yao and Zhao have described the PIDA-mediated C–H/N–H cyclization of aliphatic amines employing a *N*,*O*-bidentate oxalyl amide as DG (Scheme 1a).[12]

Recently, the removable *N*-(2-pyridyl)sulfonyl (*N*-SO_2Py) directing group has shown distinct capability for controlling δ-C(sp^3)–H over the traditionally preferred γ-CH_2 selectivity in the arylation of α-AAs.[13] Building on this knowledge, we envisaged that the sp^3 hybridization of the S atom and its lack of conjugation with the bonded N, which are unique features in comparison to the traditionally used DGs, could facilitate δ-C(sp^3)–H acetoxylation and override the otherwise more favourable competitive intramolecular amination (Scheme 1b). Herein we present a versatile protocol for δ-CH_3 acetoxylation of amine and AA derivatives that enables unprecedented chemoselectivity control of intermolecular C–O over intramolecular C–N bond formation. This method also allows the remote δ-selectivity to

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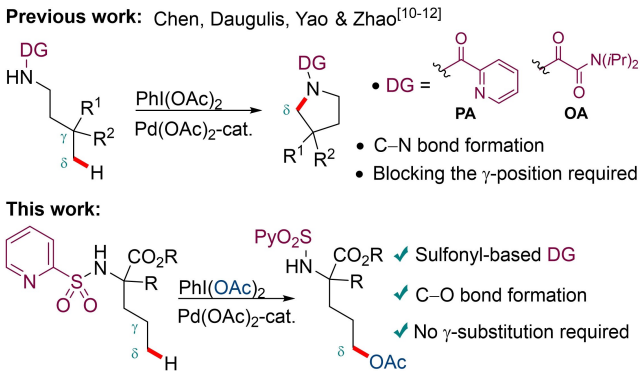


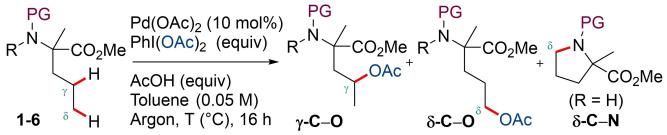
Scheme 1. δ-Functionalization of amine and AA derivatives with PhI(OAc)$_2$.

predominate over the more favorable γ-methylene C–H bonds, thus obviating the need to block that position. Experimental and DFT mechanistic studies have provided insight into the key role of the *N*-SO_2Py in chemoselectivity and regiocontrol.

The α-methyl-norvaline derivative **1** was chosen as model substrate to evaluate the chemoselectivity while also testing the δ-regioselectivity in the presence of an unblocked γ-CH_2 position. Additionally, α,α-disubstituted α-AAs are attractive in medicinal chemistry since they typically confer improved pharmacokinetic properties and stabilize the secondary structure of peptides.[14] When **1** was subjected to the conditions described by Chen for C–H bond amination,[10] clean formation of the δ-acetoxylated product **7** was observed, albeit in low conversion (14 % yield, Table 1, entry 1). Significant increase in reactivity without erosion of chemoselectivity was observed at 130–140 °C (41–47 % yield of **7**, entries 2–3). After systematic screening, optimized conditions were established which entailed the treatment of **1** with 10 mol % $Pd(OAc)_2$, 6 equiv of PhI(OAc)$_2$ and 4 equiv of AcOH in toluene (0.05 M) to afford product **7** in 98 % yield after 16 h at 140 °C (entry 5).[15] Importantly, in no case was the formation of either the γ-acetoxylated product or pyrrolidine detected. This illustrates the distinct ability of the *N*-SO_2Py group to overcome innate tendency of this class of substrates to undergo intramolecular amination. To the best of our knowledge, δ-acetoxylation has only been observed as minor side reaction in Pd-catalyzed directed intramolecular C–N amination.[10] Additionally, a screening of protecting groups revealed that the *N*-SO_2Py-group was uniquely effective for the δ-acetoxylation of α-methyl-norvaline (entries 6–10). In fact, the directing ability of aliphatic free amines was ineffective for this transformation (substrate **2**, entry 6). Moreover, switching to *N*-Ts (**3**) or *N*-SO_2(3-Py) (**4**) led to complete recovery of the starting materials (entry 7 and 8, respectively), emphasizing thus the cooperative directing role of both SO_2 and 2-Py moieties in substrate **1**. On the other hand, the shift to the *N*-COPy coordination group (**5**) provided a complex mixture of products, in which γ-acetoxylated product (**8**) was identified along with pyrrolidine **9** as major products. Finally, we proved that the *N*-alkylation did not fit for this reaction since no reactivity was detected when using the *N*-(Me)(SO_2Py)-derivative (substrate **6**), recovering the starting material unaltered (entry 10).

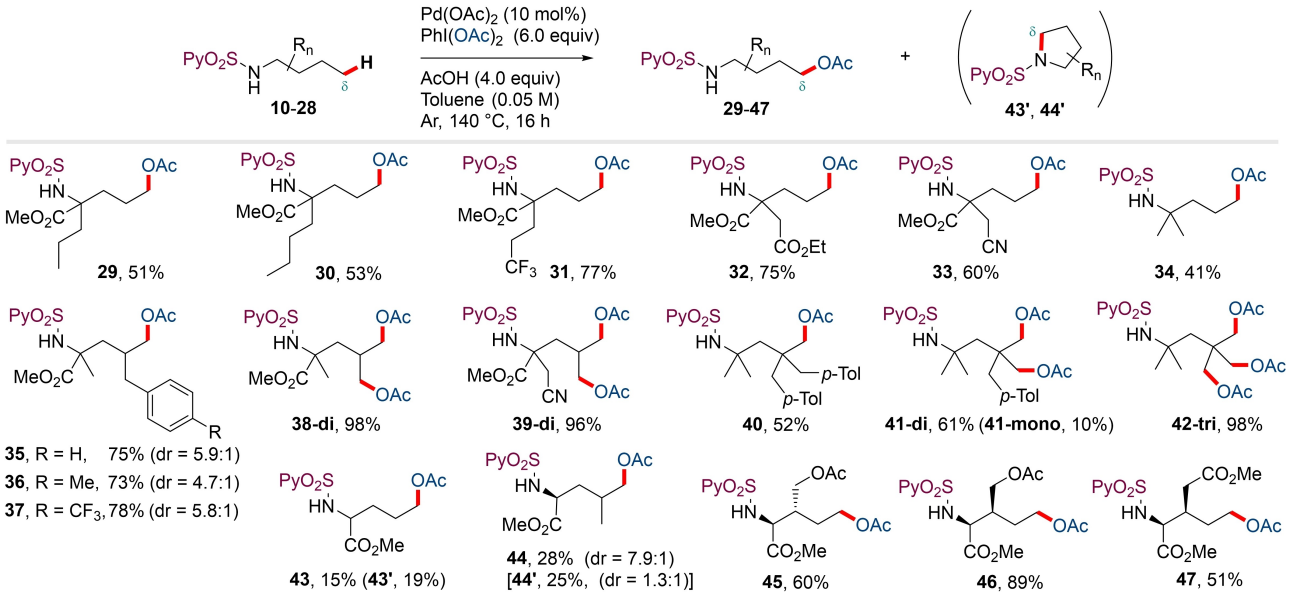
An examination of the scope of the δ-CH_3 acetoxylation is shown in Scheme 2.[16] A variety of α,α-disubstituted α-AAs with no further branching provided cleanly the δ-acetoxylation products with complete site and chemoselectivity in useful yields regardless of the nature of the α-alkyl chain (**29**–**33**, 51–77 % yield). Importantly, the non-reacted starting material can be recovered unaltered. However, α-alkyl chains containing strong electron withdrawing groups resulted in improved catalytic activity (**31**–**33**, 60–77 %). This effect can be ascribed to the more acidic character of

Table 1: δ-C(sp^3)–H functionalization of α-methyl-norvaline.



Entry[a]	PG/R	PIDA (equiv)	AcOH (equiv)	T [°C]	γ-C–O [%][b]	δ-C–O [%][b]	δ-C–N [%][b]
1	$PySO_2$/H (**1**)	2.5	10	110	n.d.	14 (**7**)	n.d.
2	$PySO_2$/H (**1**)	2.5	10	130	n.d.	41 (**7**)	n.d.
3	$PySO_2$/H (**1**)	2.5	10	140	n.d.	47 (**7**)	n.d.
4	$PySO_2$/H (**1**)	2.5	4	140	n.d.	39 (**7**)	n.d.
5	$PySO_2$/H (**1**)	6	4	140	n.d.	>98 (98)[c] (**7**)	n.d.
6	– (**2**)[d]	6	4	140	n.d.	n.d.	n.d.
7[e]	*p*-TolSO_2/H (**3**)	6	4	140	n.d.	n.d.	n.d.
8[e]	(3-Py)SO_2/H (**4**)	6	4	140	n.d.	n.d.	n.d.
9	PyCO/H (**5**)	6	4	140	34 (**8**)	n.d.	40 (**9**)
10[e]	$PySO_2$/Me (**6**)	6	4	140	n.d.	n.d.	n.d.

[a] *Reaction conditions:* amino acid derivative (0.10 mmol), PhI(OAc)$_2$ (equiv), $Pd(OAc)_2$ (0.01 mmol, 10 mol %), AcOH (equiv), Toluene (0.05 M), T(°C), argon, 16 h. [b] Determined by ^{1}H NMR of the crude mixture. [c] Isolated yield. [d] α-Methyl-norvaline methyl ester hydrochloride was used as substrate, adding 1.0 equiv of Et_3N to the reaction. [e] The starting material was recovered unaltered.



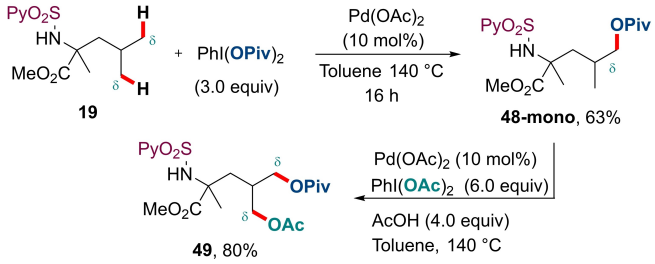
Scheme 2. Evaluation of the scope of δ-CH_3 acetoxylation.

the NH group, thus facilitating its directing role. In fact, the α,α-dimethyl amine derivative **34**, which lacks the ester group, gave a modest, yet useful, 41 % yield. Additional branching at γ-position was very well tolerated, preserving high levels of reactivity and selectivity (**35**–**42**, 52–98 % yield). Even a quaternary center at γ-position was compatible (**40**, 52 %), which also illustrated the preference for δ-CH_3 activation over electronically activated benzylic δ-CH_2 bonds. The monoselective acetoxylation of amines bearing equivalent δ-methyl groups could not be achieved because overacetoxylation tends to predominate even under decreased loadings of PIDA. However, this method proved to be well suited for multiple acetoxylation (**38-di**, **39-di**, **41-di** and **42-tri**).

α-AAs lacking any further branching displayed diminished reactivity due to competitive intramolecular δ-amination (**43**, 15 %; **43′**, 19 %). Additional γ-substitution also resulted in formation of acetoxylaton (**44**, 28 %) and amination (**44′**, 25 %) products in almost equal amounts. In sharp contrast, β-branched α-AAs, which is an important subclass of αAAs in drug discovery because of the structural rigidity imposed by the two adjacent stereogenic centers,[17] enabled full recovery of δ-acetoxylation selectivity regardless of the relative stereochemistry at the two sterocenters (**45**–**47**, 60–89 % yield).

To achieve mono-acyloxylation in substrates having two equally reactive δ-positions, we explored the use of a bulkier carboxylate source such as $PhI(OPiv)_2$. The reaction of **19** with 3 equiv of $PhI(OPiv)_2$ in the absence of AcOH enabled monoselective pivaloxylation in 63 % yield (**48-mono**, Scheme 3). This provides the access to products with two orthogonally protected oxygens by subsequent δ-acetoxylation with PIDA (**49**, 80 %).

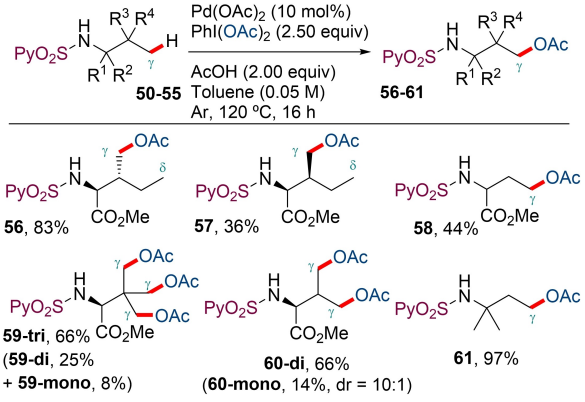
The reaction of *allo*-isoleucine derivative **50**, having two competing γ- and δ-methyl groups revealed a strong preference for γ-acetoxylation, providing **56** in good yield



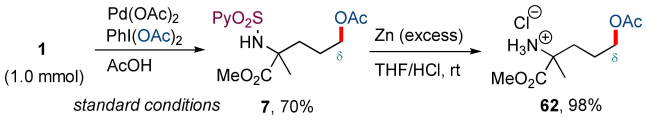
Scheme 3. Sequential double δ-acyloxylation of **19** towards orthogonally protected products.

even under slightly milder reaction conditions. Indeed, this method is broadly applicable to γ-Me acetoxylation of amino acid and amine derivatives (**56**–**61**) (Scheme 4).

To evaluate the synthetic utility of this protocol, a 1 mmol scale acetoxylation of **1** was performed under the standard conditions, affording **7** in 70 % yield (Scheme 5).



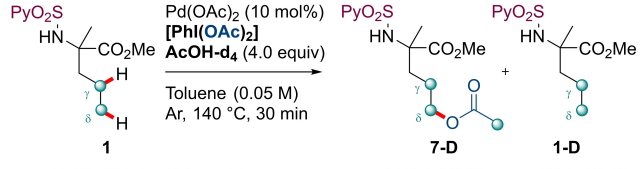
Scheme 4. γ-Me acetoxylation of amino acid and amine derivatives.



Scheme 5. 1 Mmol-scale δ-acetoxylation and removal of the DG.

Facile and high yielding removal of the DG from **7** was also achieved using Zn/HCl in THF at room temperature (**62**, 98 %).

To gain mechanistic insights, substrate **1** was subjected to standard acetoxylation using AcOH-d_4 (4 equiv) and the reaction was stopped at low conversion (30 min, 26 % yield) to reveal no deuterium incorporation at either γ or the δ position of the unreacted **1** or the product **7** (Scheme 6). These results suggest that the C–H activation step is irreversible. The absence of deuteration at the newly incorporated OAc evidenced that it originates from PhI-$(OAc)_2$, and that acetate exchange between the Pd-complex



Scheme 6. H/D scrambling experiments in substrate **1**.

and the solvent does not take place or is much slower than the C–H activation. The same experiment carried out in the absence of $PhI(OAc)_2$ resulted in the exclusive recovery of the starting material with no D-scrambling, supporting the notion that the cleavage of the C–H bond is either irreversible or it occurs at a Pd^{IV} center.[18,19]

Based on previous contributions[5] and our own experience in SO_2Py-directed δ-functionalization,[13] DFT calculations were performed using **IM1** as starting Pd^{II} complex model (Figure 1). Directed OAc-assisted CMD C–H activation revealed an almost identical barrier for functionalization at both δ and γ position (**TS1′-δ**/**TS1′-γ**), which does not account for the observed regioselectivity (path in blue, see Supporting Information for details). In contrast, when oxidation to Pd^{IV} complex **IM2** by $PhI(OAc)_2$ was considered to take place prior to the C–H activation step (path in black), the difference in stability of the transition states for δ- and γ-activation (**TS2-δ**/**TS2-γ**) was in complete agreement with the observed selectivity (**TS2-γ** is highlighted in green). Additionally, **TS2-δ** would evolve into a very stable intermediate (**IM3-δ**) making this step irreversible, which is also in accordance with the lack of D-scrambling (see Scheme 6). Then, **IM3-δ** could evolve through three different pathways: i) Reductive elimination to give the acetoxylation product via **TS3-δ-1** (−5.9 kcal mol^{-1}, path in green). ii) Reductive elimination to give the amination product through **TS3-δ-2** (−6.8 kcal mol^{-1}, path in green). iii) Once protonated after CMD, the acetic acid ligand on Pd serves as a proton shuttle facilitating a barrierless protonation of the N intramolecularly through **TS3-δ-3**, to afford **IM4-δ**. From this intermediate, the regenerated OAc would promote acetoxylation through **TS4-δ** (−10.8 kcal mol^{-1}, path in

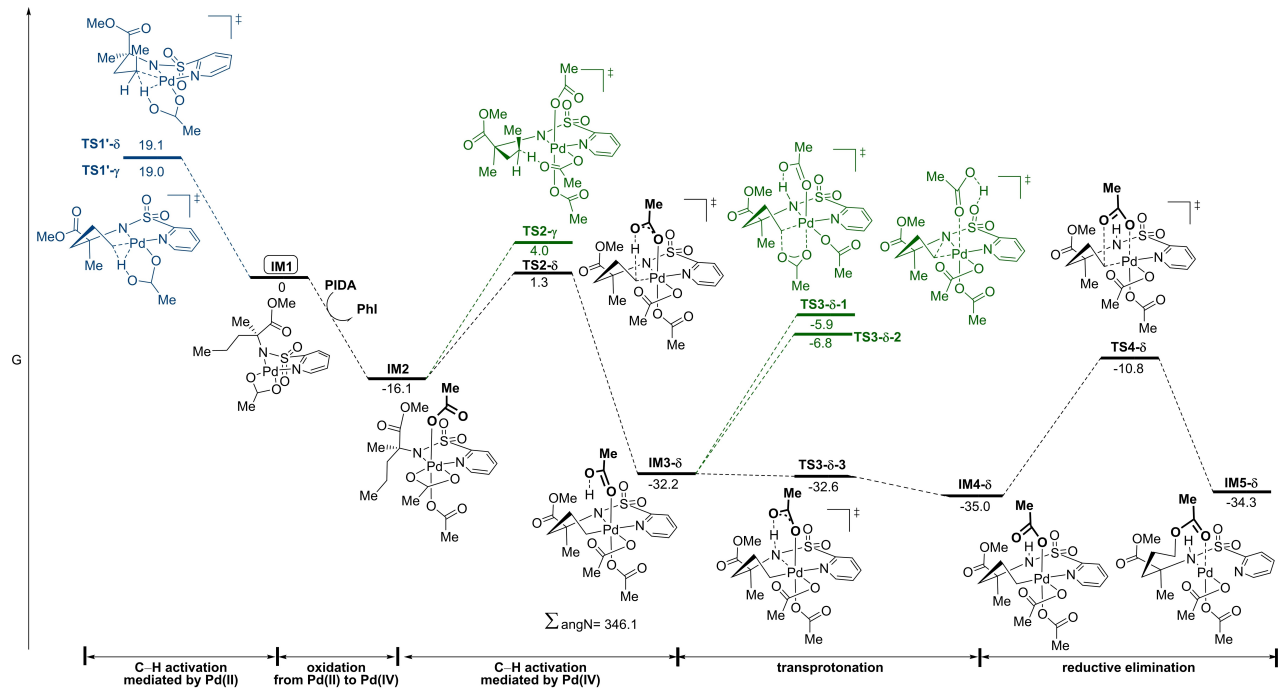


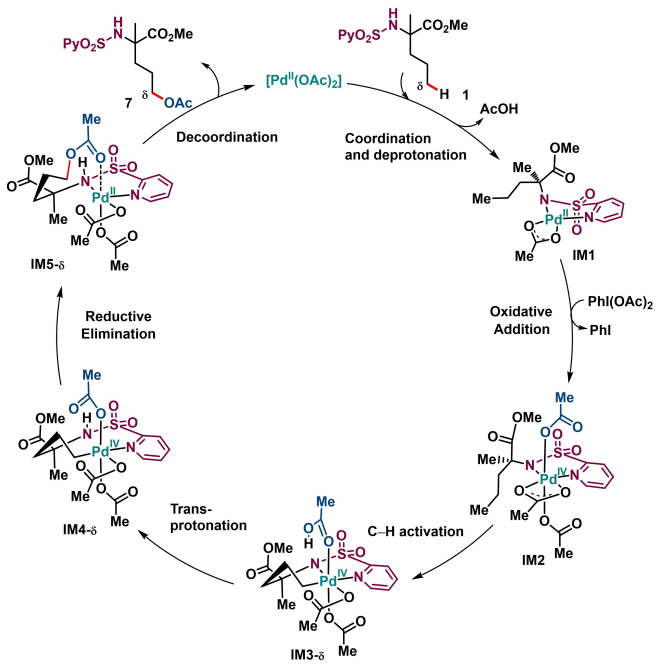
Figure 1. Energy profile for the acetoxylation reaction of **1** in toluene ($B97D3_{SMD}$/6-311++G(d,p) (C,H,N,O,S), SDD (Pd,I)//$B97D3_{SMD}$/6-31G(d) (C,H,N,O,S), LANL2DZ(f)(Pd), LANL2DZ(d)(I). Relative G values at 298 K (kcal mol^{-1}).

black). Considering the easy interconversion between **IM3-δ** and **IM4-δ**, the process would fit a Curtin-Hammet scenario evolving through the most stable **TS4-δ** to afford exclusively intermediate **IM5-δ**.[20] Subsequently, to close the catalytic cycle, **IM5-δ** would easily undergo product dissociation from Pd^{II}, followed by substrate coordination with concomitant loss of AcOH to regenerate **IM1**. This process is expected to occur with low activation barriers and has not been calculated. It should be emphasized the multiple important roles played by the OAc ligand at Pd: (i) by switching its denticity, it acts as an inner-sphere base to assist CMD, (ii) it serves as an intramolecular acid to facilitate N protonation, which is key in deactivating the competitive amination pathway, and (iii) it promotes C–O bond formation by reductive elimination.

The strong preference of palladacycle **IM3-δ** to evolve through intramolecular NH protonation lies in its unusual twisted-boat conformation imposed by the presence of the fully substituted α-carbon atom and the sp^3 hybridized sulfur atom that prevents conjugation with the sulfonamide nitrogen. Consistent with this proposal, when the SO_2 connector of the DG was replaced by a CO group,[20] in which N gets more planar (compare ΣangN in both cases), DFT calculations supported the exclusive formation of the amination product, as corroborated experimentally (see Supporting Information).[21] The absence of a fully substituted α-carbon induces conformational changes that lead to similarly stable transition states for amination and acetoxylation, which is in accordance with experimental observations (compounds **43** and **43′**, see Supporting Information for computational details).

Therefore, based on these experimental and theoretical mechanistic studies, the reaction would start by coordination and deprotonation of **1** to the active Pd^{II}-acetate species to form **IM1** as a viable intermediate (Scheme 7). From here, oxidation to Pd^{IV}-complex **IM2** by $PhI(OAc)_2$ woud take place prior to the C–H activation step. The OAc ligand introduced at Pd from the $PhI(OAc)_2$ would act as an inner-sphere base to assist the δ-C–H cleavage through a concerted-metalation-deprotonation (CMD) mechanism. As a result, the Pd^{IV} intermediate **IM3-δ** would be formed, in which the AcOH generated as a ligand on Pd would serve as a proton shuttle, facilitating the intramolecular protonation of the N-sulphonamide to give rise to **IM4-δ**. From this intermediate, the regenerated OAc would promote the δ-acetoxylation by reductive elimination, leading to Pd^{II}-complex **IM5-δ** that would evolve to the active Pd^{II}-acetate species by decoordination of the δ-acetoxylated product **7**.

In conclusion, we have developed a practical method for remote δ-C(sp^3)–H acetoxylation of amine and AAs derivatives. The use of the *N*-SO_2Py as DG proved to be essential for controlling both chemoselectivity (intermolecular C–O over intramolecular C–N bond formation) and regioselectivity (favouring δ-CH_3 over γ-CH_2 activation). This protocol is efficient for the derivatization of α-quaternary and β-branched α-AAs, which are important pharmaceutical targets. Mechanistic analysis revealed distinct features for selectivity control: (i) The C–H cleavage likely occurs at Pd^{IV} via a CMD mechanism. (ii) The sp^3 hybridization of the



Scheme 7. Plausible catalytic cycle for δ-acetoxylation of **1**.

S-atom of the SO_2 linker of the DG and the lack of conjugation with N imposes a twisted-boat conformation of the palladacycle that favors intramolecular protonation of the nitrogen, which deactivates the competitive C–N bond formation.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Acetoxylation · Amino Acids · Directing Groups · Palladium Catalysis · Remote C–H Activation

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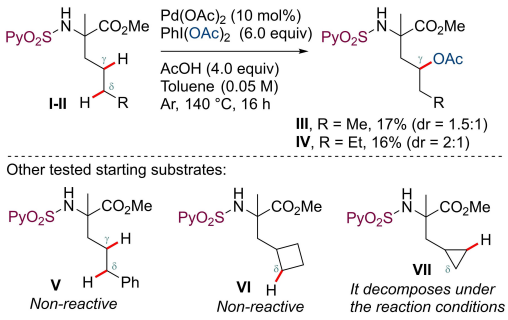
[15] See Supporting Information for complete optimization studies.

[16] The functionalization of non-terminal δ-C(sp^3)–H bonds was also investigated by evaluating substrates with longer alkyl chains, e.g. **I** and **II**. However, in these experiments only a low conversion of the starting substrate to the formation of the corresponding γ-acetoxylated product was observed. On the other hand, substrates **V** and **VI** were also evaluated but no reactivity was observed and the starting material was recovered. It should be noted that compound **VII** decomposes under the reaction conditions used (see the following scheme and the Supporting Information for details).



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[18] It has been reported that no acetate exchange occurs in the Pd complex: F. Tato, A. García-Domínguez, D. J. Cárdenas, *Organometallics* **2013**, *32*, 7487–7494.

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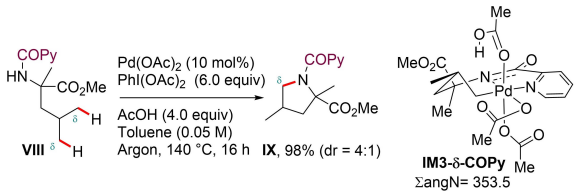
[20] Calculation of thermodynamic parameters at experimetal termperature (413 K) produced only a small decrease in the difference of energy in the key transition states **TS2-γ** and **TS2-δ** (from 2.7 to 2.4 kcal mol^{-1}) and **TS3-δ-2** and **TS4-δ** (from 4.0 to 3.5 kcal mol^{-1}), which still accounts for the complete δ-acetoxylation selectivity.

[21] While the *N*-SO_2Py-protected **19** affords the δ-di-acetoxylation product **38-di** in 98 % yield, the *N*-COPy-analogue **VIII** under identical conditions leads to the exclusive formation of the pyrrolidine derivative **IX** in 98 % yield (see scheme below and Supporting Information for details).



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