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Pd-Catalyzed δ-C(sp^3)–H Thiolation of Amino Acid Derivatives

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Abstract: Herein, we report a protocol for the selective δ-thiolation of aliphatic α-amino acids catalyzed by a Pd(II)/Ag(I) system. This reaction employs disulfides as thiolating agents and *N*-COPy as directing group, providing valuable non-proteinogenic amino acid derivatives in moderate to good diastereoselectivities and yields. Remarkably, the method is also suitable for the late-stage functionalization of a dipeptide. Experimental and DFT studies have provided significant insights into the mechanism and underlying factors controlling the selectivity of the process and determining the key role of the silver salt.

Keywords: δ-thiolation; C–H functionalization; amino acids; palladium catalysis

Introduction

Amino acids (AAs) are bio-renewable, chiral *C*- and *N*-containing raw materials with many different applications.[1] Besides their biological function as building blocks of proteins, AAs with bulky side chains are important structural motifs in a broad range of organocatalysts,[2] ligands[3] and optimal structural backbones in pharmaceuticals[4] and agrochemicals.[5] Therefore, incorporating new functionalities into their structure is extremely useful to fine-tune their physicochemical properties[6] and physiological activity.[7]

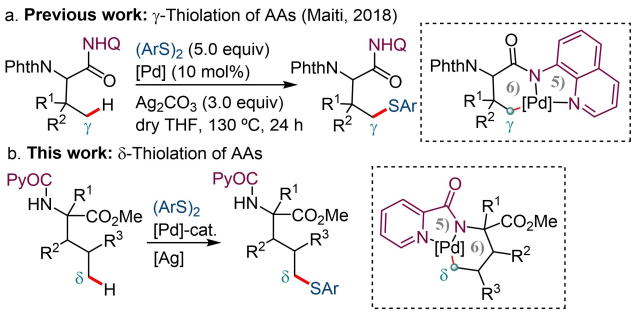
In pursuit of this objective, Pd-catalyzed direct C(sp^3)–H functionalization of AAs′ side chain has become a remarkably attractive synthetic tool.[8] Most often, despite the inert and ubiquitous nature of C(sp^3)–H bonds in the AAs′ structure, directing group (DG)-assisted metallacycle formation reduces the energy barrier of C–H bond activation, enabling site-selective functionalization processes.[9] Notably, most reported reactions involve accessible proximal C–H bonds through the formation of a kinetically favored five-membered palladacycle intermediate;[10] typically, at β-position if the DG is installed at the *C*-terminus of the α-AA, or at γ-position when it is attached at the *N*-terminus. In contrast, only a few reports describe C–H functionalization in the AAs′ structure involving a larger-membered palladacycle intermediate.[11] Among them, elegant contributions by B.-F. Shi and Maiti, as well as by our group, have detailed diverse strategies for the selective construction of C–C bonds at the δ-position of the AAs′ side chain.[12] However, only scattered examples involving δ-C–heteroatom bond forming reactions have been described. In pioneering contributions, Chen, Daugulis, Yao and Zhao, Liu and Wu explored the intramolecular amination reaction, using either the picolinamide (*N*-COPy) as DG or an oxalyl amide auxiliary.[13] Very recently, our group has achieved the *N*-(2-pyridyl)sulfonyl (*N*-SO_2Py)-assisted δ-acetoxylation of α-AAs.[14] Therefore, new approaches capable of expanding the scope to other C-heteroatom bond forming reactions are highly appeal-

ing for accessing new non-proteinogenic AAs. For this reason, continuing with our research on DG-assisted remote C–H bond functionalization of AAs and peptides, we decided to investigate the underdeveloped Pd-catalyzed direct δ-C(sp^3)–H thiolation of α-AAs′ side chain.

The C(sp^3)–S bond possesses a prime position among valuable chemical entities due to its prevalence in a myriad of biological systems and pharmaceuticals,[15] and its presence in the structure of AAs facilitates the metabolism process of related proteins.[16] However, transition-metal-catalyzed directed C(sp^3)–H thiolation remains a synthetic challenge.[17] This is largely on account of the inherent low reactivity of C(sp^3)–H bonds and the competitive coordination of the sulfur species to interfere with the C–H functionalization reaction.[18]

In this regard, in 2015, B.-F. Shi,[19] X. Shi,[20] Zhang[21] and Yin[22] independently reported the 8-aminoquinoline (8-AQ)-assisted nickel-catalyzed thiolation of primary β-C(sp^3)–H bonds of a broad range of aliphatic carboxamides with disulfides. Additionally, in the same year, Besset[23] published the 8-AQ-assisted palladium-catalyzed direct trifluoromethylsulfanylation of primary and secondary C(sp^3)–H bonds on carboxylic acid derivatives using an electrophilic SCF_3 source. More recently, in 2020, Xie[24] described an appropriate methodology for the palladium-catalyzed directed sulfenylation of benzylic C(sp^3)–H bonds with disulfides and with the assistance of the *N*-COPy as DG. All these protocols have in common that they are mainly governed by the thermodynamics of the 5-membered metallacycle intermediates involved. Nonetheless, Maiti[25] has demonstrated the feasibility of the 8-AQ-assisted palladium-catalyzed γ-thiolation of aliphatic carboxylic acids and aliphatic α-AAs via a six-membered palladacycle intermediate (Scheme 1a). However, to our knowledge, no example has shown the viability of thiolating the more challenging remote δ-position in α-AAs.

Overcoming this challenge, we herein unveil a methodology for the direct regioselective Pd(II)-catalyzed δ-thiolation of aliphatic α-AAs employing *N*-COPy as DG, providing access to valuable non-proteinogenic sulfur-containing amino acids as potential metalloprotease inhibitors and neuroprotective analogues (Scheme 1b).[26] The versatility of this protocol has been demonstrated by extending the scope of our strategy to sequential δ-C(sp^3)–H activation, as well as to the functionalization of a dipeptide. Experimental and DFT mechanistic studies have provided insights into the crucial role of the *N*-COPy in controlling the selectivity and reactivity, and how the Ag-salt may assist the regeneration of the active Pd species.



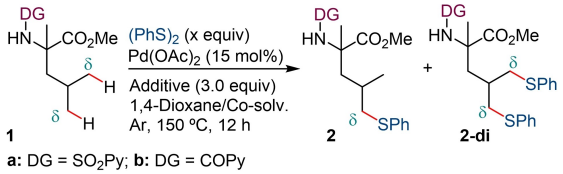
Scheme 1. Remote C–H thiolation of aliphatic AAs.

Results and Discussion

Based on our previous work on the use of *N*-SO_2Py as DG in successfully assisted δ-C(sp^3)–H functionalization of AAs and peptides,[12d,14] we first explored the reactivity of the *N*-SO_2Py-protected α-methyl-leucine derivative **1 a** with diphenyl disulfide, using $Pd(OAc)_2$ as catalyst (15 mol%), AgOAc as additive, and 1,4-dioxane as solvent (Table 1, entry 1). Under these conditions, the δ-thiolated product **2 a** was obtained in 34% yield with a *dr* = 3:1. This scarce reactivity,[27] along with preliminary computational studies on the influence of the DG (see SI for details and full optimization studies), led us to evaluate *N*-COPy as DG (**1 b**).[28] Indeed, the reaction of *N*-COPy-protected **1 b** offered enhanced reactivity, providing the mono-functionalized product **2 b** in 41% yield and *dr* = 5:1, along with 25% of the di-thiolated derivative **2 b-di** (entry 2). Blank experiments showed that both Pd-$(OAc)_2$ and AgOAc are essential for the C–H functionalization (entries 3–7). Interestingly, replacing AgOAc with AgTFA led to suppression of the catalytic activity, likely due to the lower basicity of trifluoroacetate (entry 5). Consequently, adding 3.0 equiv. of NaOAc to the Pd/AgTFA system restored the catalytic activity (entry 6). Likewise, the need for Ag was demonstrated since no reaction occurred when using NaOAc as the sole acetate source (entry 7).

Further optimization experiments increased the conversion of **1 b** up to 76% by adding HFIP to the reaction mixture [1,4-dioxane:HFIP (2:1), 0.07 M]. However, the chemoselectivity towards the mono-functionalized product remained low [50% of **2 b** (*dr* = 5:1) along with 26% of the **2 b–di** product, entry 8]. To improve the mono-selectivity was necessary to use diphenyl disulfide as the limiting reactant, observing a marked improvement when AgOAc was replaced by AgOBz (entries 9–12) [67% of **2 b** (*dr* = 5:1) along with 9% of the **2 b-di** product, entry 12]. Under these conditions, reaction time could be reduced from 12 to 3 h without a significant change in the reaction yield (entry 13). It should be noted that no potential competitive δ–C–N bond formation was observed in

Table 1. δ-C(sp^3)–H functionalization of α-methyl-leucine derivative **1**.[a]



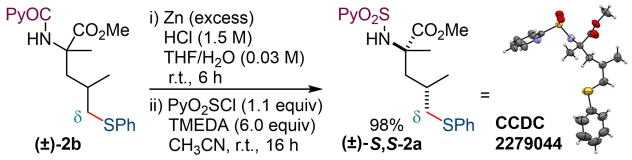
Entry	DG (equiv.)	$(PhS)_2$ (equiv.)	Additive	Co-solv.	**2** (%)[b]	**2-di** (%)[b]
1	SO_2Py (1.0)	3.0	AgOAc	–	34[c]	n.d.
2	COPy (1.0)	3.0	AgOAc	–	41[d]	25
3[e]	COPy (1.0)	3.0	AgOAc	–	n.d.	n.d.
4	COPy (1.0)	3.0	–	–	n.d.	n.d.
5	COPy (1.0)	3.0	AgTFA	–	n.d.	n.d.
6[f]	COPy (1.0)	3.0	AgTFA	–	46[d]	14
7	COPy (1.0)	3.0	NaOAc	–	n.d.	n.d.
8	COPy (1.0)	3.0	AgOAc	HFIP	50[d]	26
9	COPy (1.0)	2.0	AgOAc	HFIP	53[d]	16
10	COPy (1.0)	2.0	AgOBz	HFIP	59[d]	28
11	COPy (1.0)	1.0	AgOBz	HFIP	47[d]	10
12	**COPy (1.5)**	**1.0**	**AgOBz**	**HFIP**	**67**[d] **(67)**[g]	**9 (7)**[g]
13[h]	COPy (1.5)	1.0	AgOBz	HFIP	59[d]	8
14[i]	COPy (1.5)	1.0	AgOBz	HFIP	58[d]	10

[a] *Reaction conditions:* **1** (equiv.), PhSSPh (equiv.), $Pd(OAc)_2$ (15 mol%), Ag^I-salt (0.3 mmol, 3.0 equiv.), 1,4-dioxane/Co-solvent (2:1) (1.50 mL), 150 °C, 12 h.
[b] Determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.
[c] *dr* = 3:1.
[d] *dr* = 5:1.
[e] Without $Pd(OAc)_2$.
[f] NaOAc was also added (0.3 mmol, 3.0 equiv.).
[g] Isolated yield.
[h] 3 h.
[i] Gram-scale [4.6 mmol of $(PhS)_2$].

any experiment, which allowed to recover the starting material unaltered.

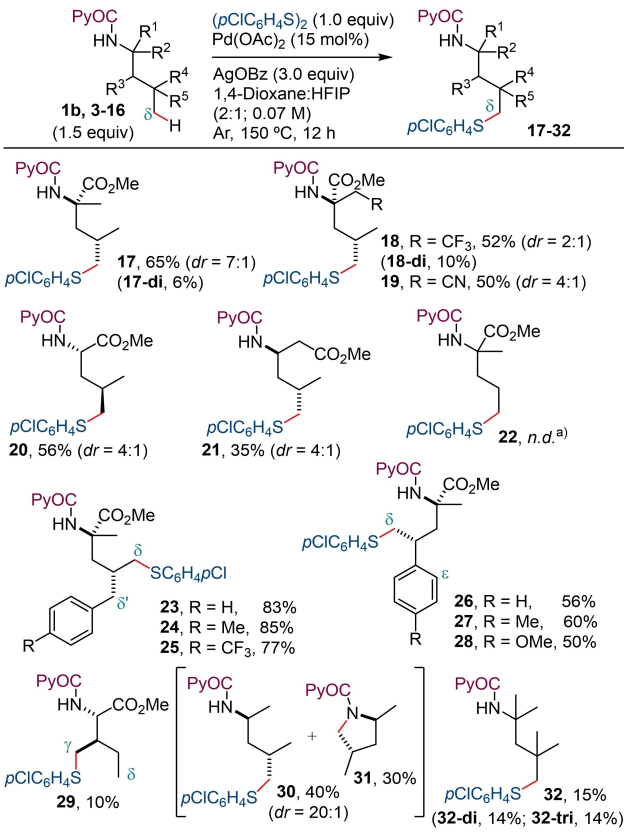
Finally, it is worth mentioning that the practicality of this transformation was established by carrying out a gram-scale reaction (4.6 mmol scale of $(PhS)_2$), which afforded the desired δ-thiolated product **2 b**, as a colorless oil, in 58% yield (entry 14). To harness the applicative potential of this methodology, the major diastereomer of the δ-thiolated product **2 b** was treated with Zn/HCl in a mixture of THF/H_2O at room temperature to remove the DG effectively. Subsequent *N*-protection with 2-pyridyl sulfonyl chloride led to the derivative **2 a** as a white solid, from which the *S,S* relative configuration at both stereocenters was determined by X-ray diffraction (Scheme 2).[29]

Upon completion of our optimization studies, structurally diverse AAs were surveyed in the reaction with bis(4-chlorophenyl) disulfide under the optimized conditions (**1 b**, **3**–**16**; Scheme 3). Whereas the reaction of α-methyl-leucine derivative **1 b** led to the mono δ-thiolated derivative **17** in 65% yield (*dr* = 7:1), along with 6% of the di-functionalized product **17-di**,



Scheme 2. Identification of the major diastereomer.

substrates possessing α-alkyl chains containing strong electron-withdrawing groups resulted in modest, though practical, 50–52% yields (**18** and **19**).[30] This effect can be ascribed to the more acidic character of the NH group, thus strengthening the coordination of the δ-thiolated derivatives to the metal, inhibiting the regeneration of the active Pd(II) species. On the other hand, a slight decrease in yield was observed for α- and β-leucine derivatives with an α-tertiary carbon (**20** and **21**,[31] 56% and 35%, respectively), suggesting a Thorpe-Ingold effect in the reactivity. Unfortunately, no reactivity was detected with the *N*-COPy-protected α-methyl norvaline derivative (compound **22** was not



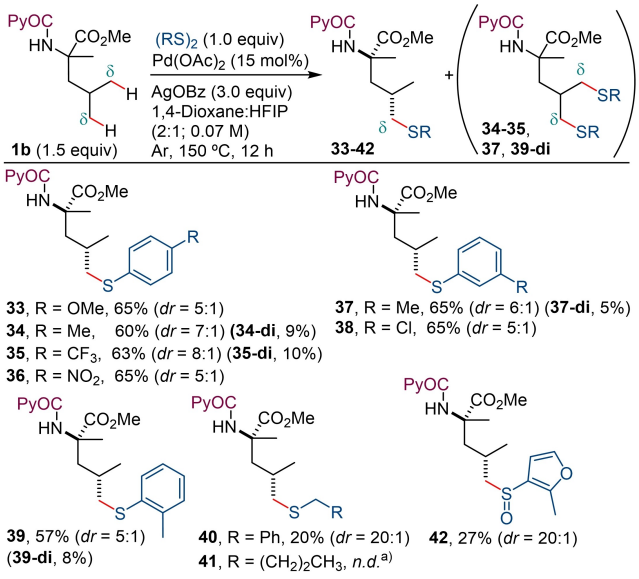
Scheme 3. Scope regarding AAs derivatives. [a] Starting material recovered unaltered.

detected, recovering the starting material unaltered). It is worth noting that δ-CH_3 thiolation was observed despite the presence of even more acidic benzylic δ-CH_2 bonds, which remained intact after the transformation (**23**–**25**, 77–85%).[32] In addition, α-methyl-γ-aryl-norvaline derivatives were compatible (**26**–**28**, 50–60%), which also illustrates the preference for δ-CH_3 thiolation over electronically activated ε-C(sp^2)–H bonds.[31] Interestingly, the reactivity of the *N*-COPy-protected *allo*-isoleucine **14**, having two competing γ- and δ-methyl groups, was low and led exclusively to the γ-thiolated product **29** in 10% yield. On the other hand, the amine derivative **15**, which lacks the ester group, gave **30** in a modest, yet useful, yield of 40%.[30] In this case, the product resulting from the δ–C–N bond formation (**31**) was also obtained in a 30% yield. Finally, it is worth mentioning that *tert*-octyl amine derivative **16** led to the mono-thiolated product **32** in 15% yield along with the multi-functionalized products: **32-di** (14%) and **32-tri** (14%). This high reactivity is compromised by the loss of selectivity towards the monothiolation product. This is probably due to the importance of the influence of Thorpe-Ingold effect.

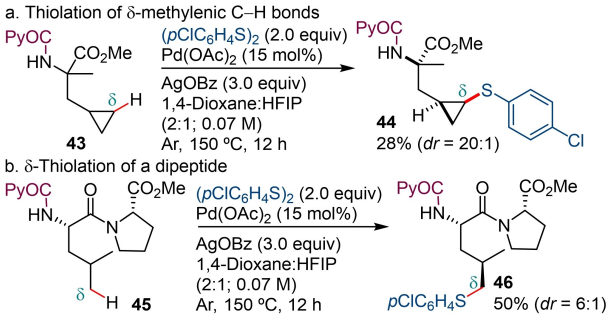
Next, we evaluated the variability of the diaryl disulfide coupling partner on the α-methyl-leucine derivative **1b** (Scheme 4).[30] Regardless of the electronic nature and position of the arene ring substituents, a wide range of disulfides were well suited for the present transformation, affording satisfactory yields of the corresponding δ-thiolated products. Electron-donating groups (**33** and **34**) and electron-withdrawing groups (**35** and **36**) at the *para*-position gave good yields of their respective products (60–65%). Likewise, substituents at the *meta*- (**37** and **38**) and *ortho*-positions (**39**) were tolerated (57–65%). Furthermore, benzylic (**40**) and *O*-heteroaromatic systems (**42**) were also suitable for this transformation, albeit with low yields (20 and 27%, respectively). The latter was isolated as a sulfoxide derivative. In all cases, high mono-δ-selective thiolation was observed, isolating only traces of the corresponding difunctionalized derivatives (less than 10%). Unfortunately, the method was not compatible with the use of aliphatic disulfide derivatives since when preforming the reaction of *N*-COPy-protected α-methyl-leucine derivative **1b** with dibutyl disulfide, **1b** was recovered unaltered, without detecting the corresponding δ-thiolated derivative **41**.

To our knowledge, only a handful of examples have been reported on the activation of δ-CH_2 bonds to functionalize α-AAs.[12d,28c] Therefore, we wondered whether this method could enable the activation of challenging methylenic C–H bonds. As shown in Scheme 5a, the cyclopropyl derivative **43** reacted smoothly under these conditions, affording the mono-thiolated product in modest yield with excellent diastereoselectivity (**44**, 28%, *dr* = 20:1).[31]

Likewise, the robustness of this method was further demonstrated by the post-synthetic modification of a dipeptide (**45**) (Scheme 5b). The reaction occurred



Scheme 4. Scope regarding disulfides. [a] Starting material recovered unaltered.

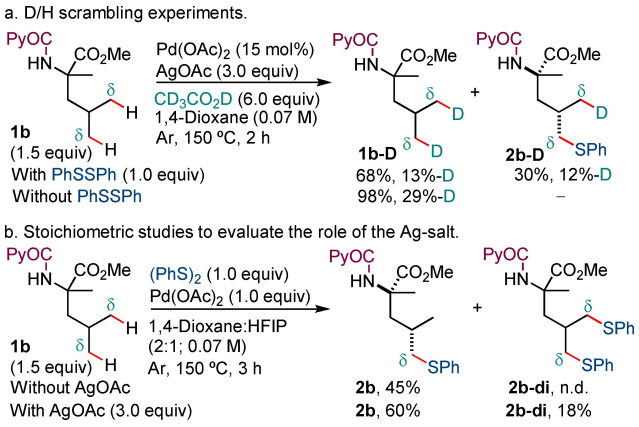


Scheme 5. Thiolation of challenging substrates.

with complete mono-selectivity control to provide the δ-thiolated dipeptide **46** in moderate yield (50%, *dr* = 6:1).[33]

To gain mechanistic insight, substrate **1 b** was subjected to standard reaction conditions, both in the presence and absence of diphenyl disulfide, and using acetic acid-d_4 (6.00 equiv.) as deuterium source (Scheme 6a). When stopped at early stages (2 h), the thiolation provided the corresponding product **2 b-D** in 30% yield. Interestingly, **2 b-D** and **1 b-D** showed a small percentage of deuterium incorporation (12% and 13%, respectively), lower than that observed in the substrate when the test was carried out in the absence of diphenyl disulfide (**1 b-D**, 29% D). Therefore, these results suggest that the C–H activation step is reversible and occurs through Pd^{II} species, while the oxidative addition of the diphenyl disulfide and subsequent functionalization seems more favored.

Furthermore, to figure out the role of silver in the thiolation process, we evaluated the reactivity of **1 b** using stoichiometric amounts of $Pd(OAc)_2$, both in the presence and absence of a Ag^I-salt. As shown in Scheme 6b, the thiolation readily proceeds without a silver salt, obtaining **2 b** in 45% yield. Nonetheless, the addition of a silver salt increases the reactivity of the system (conversion of **1 b** up to 78%). Therefore,



Scheme 6. Control experiments.

considering that a catalytic loading of $Pd(OAc)_2$ requires the presence of a Ag^I-source, we hypothesized that it might be involved in regenerating the catalytically active Pd species.

Next, we undertook DFT calculations of the thiolation process using **1 b** as a model to shed some light on the factors that govern the reactivity and diastereoselectivity (Figure 1). In these studies, based on previous contributions and our own experience in directed δ-functionalization, we chose the Pd(II)-intermediate **IM1** as starting Pd(II)-complex model to evaluate the C–H activation step. As shown in the energy profile, the δ–C–H *proS* cleavage through **TS1** (with a twisted boat-like conformation that allows for greater conjugation of N to the carbonyl group, see SI) would be favored over the δ–C–H *proR* bond activation through **TS1′** by 1.1 kcal·mol^{-1} which predicts a ratio 86:14, in relatively good agreement with the experimental diastereoselectivity observed. Therefore, **IM1** would then preferably undergo the δ–C–H *proS* activation *via* concerted metalation-deprotonation (CMD) pathway, leading to the formation of the six-membered palladacycle **IM2** (1.7 kcal·mol^{-1}) as a plausible reaction intermediate. Next, **IM2**, which holds a boat-like conformation, would smoothly adopt the more stable chair conformation seen in **IM3** (−0.5 kcal·mol^{-1}). Then, BzOH/diphenyl disulfide ligand exchange would occur to afford a relatively stable intermediate **IM4** (−3.7 kcal·mol^{-1}) that shows a stabilizing π-stacking between the pyridine ring and one of the aryl groups of the disulfide unit (centroids distance: 3.94 Å). Subsequent oxidative addition of the Pd(II) center to the disulfide bond would generate the Pd(IV)-complex **IM5** (3.7 kcal·mol^{-1}) that keeps the π-stacking interaction (centroids distance: 3.69 Å). However, a change of conformation through **IM6** (7.8 kcal·mol^{-1}) is required to reach the most stable transition state found for the reductive elimination step (**TS4**) to afford **IM7** (−16.2 kcal·mol^{-1}) in which the δ-thiolated product would be acting as a monoanionic tricoordinate ligand.[27] From this point on, it seems feasible that the Ag species undergo a ligand exchange with the Pd(II) center to sequester the organosulfide byproduct and the concomitant regeneration of the Pd(II)-benzoate catalyst. In fact, the absence of **2 b-di** in the stoichiometric studies without Ag salt (Scheme 6b) reinforces Ag′s role in regenerating a species that undergoes a second C–H activation.[34] Concerning the use of benzoate instead of acetate salt, the influence of this ion in different steps was also evaluated (see SI). Although its influence was negligible in the C–H activation step ($^-$OBz only reduced the barrier in 0.1 kcal·mol^{-1}), the completely different structures found for final complexes **IM9** and **IM10** when using $^-$OBz instead of $^-$OAc as a counterion suggest a higher ability of $^-$OBz to displace $^-$SPh, inactive for the C–H activation step,

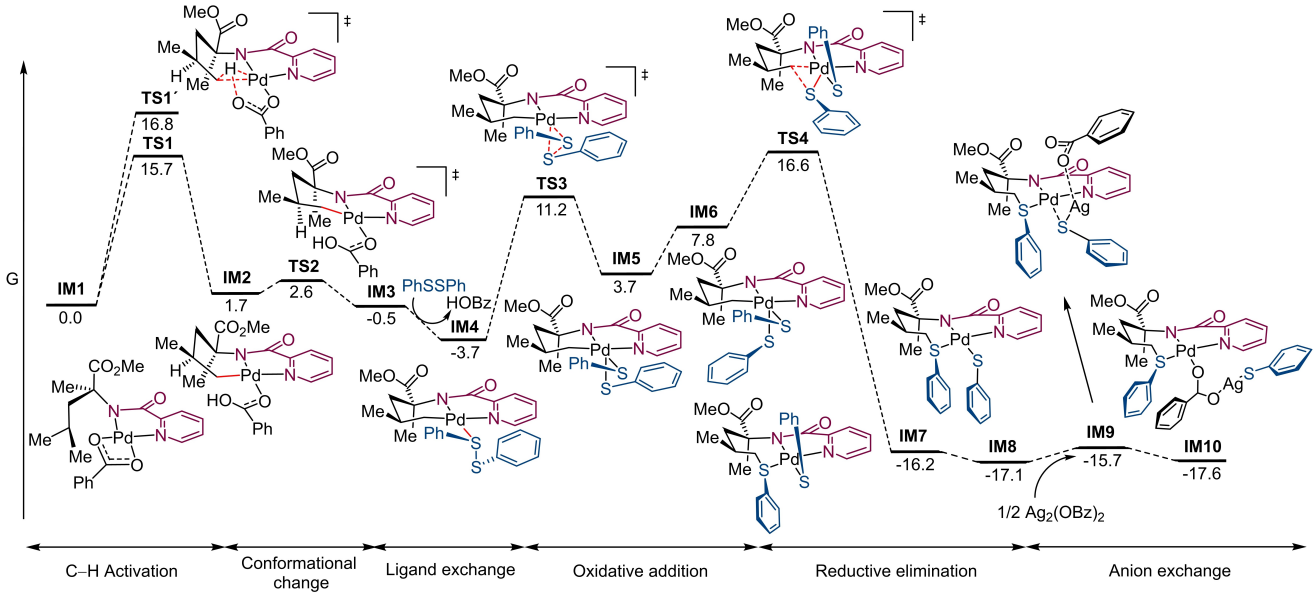


Figure 1. Energy profile for the thiolation reaction of **1b** in 1,4-dioxane (M06/6-311++G(d,p) (C,H,N,O,S), SDD (Pd, Ag)// B3LYP–D3/6-31G(d) (C,H,N,O,S), LANL2DZ(f) (Pd, Ag). Relative G values at 298 K (kcal·mol^{-1}).

favoring the regeneration of the catalytically active species for the reaction to proceed.[35]

Conclusion

In conclusion, we have developed a Pd-catalyzed δ-C(sp^3)–H thiolation of AAs employing *N*-COPy as DG. This transformation provides direct access to structural modifications on the side chains of α-AAs. The versatility of this protocol has been demonstrated by expanding the scope of our strategy to the functionalization of a dipeptide. Experimental and DFT mechanistic studies have provided insight into the mechanism, explaining the diastereoselectivity observed in the C(sp^3)–H thiolation of the α-AAs' side chains. Likewise, the DFT studies justify that AgOBz not only acts as a base but also enables the regeneration of the active Pd-catalytic species.

Experimental Section

General Procedure

An oven-dried, argon flushed 5.0 mL vessel was charged with $Pd(OAc)_2$ (3.38 mg, 0.015 mmol, 0.15 equiv.), the corresponding disulfide (0.10 mmol, 1.00 equiv.), AgOBz (68.7 mg, 0.30 mmol, 3.00 equiv.) and the corresponding amine or amino acid derivative (**1b**, **3**–**16**) (0.15 mmol, 1.50 equiv.). The vessel was sealed with a Teflon lined cap, then evacuated and flushed with argon. Under argon atmosphere, 1,4-dioxane (1.00 mL) and HFIP (0.50 mL) were added *via* syringe. The resulting mixture was placed in an aluminum block and stirred at 150 °C for 12 h. After the reaction was complete, it was diluted with EtOAc, filtered through a short pad of Celite® and concentrated *in vacuo*. The residue was purified by flash column chromatograph on silica gel using a mixture of *n*-heptane : EtOAc (6:1) as eluent.

Acknowledgements

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[30] The indicated configuration was tentatively assigned by analogy to product (±)-*S*,*S*-**2 b**.

[31] The indicated configuration was tentatively supported by DFT studies. See SI for further details.

[32] The indicated configuration was tentatively determined by correlation. See SI for further details.

[33] The indicated configuration was tentatively assigned by analogy to product (+)-*S*,*R*-**20**.

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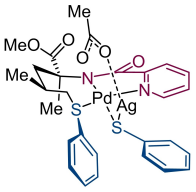
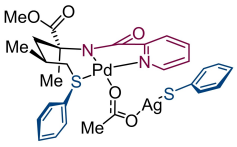
[35] Final complexes **IM9-OAc** and **IM10-OAc** with the OAc instead of the OBz as a counterion. See SI for further details.



IM9-OAc (-19.2 kcal·mol^{-1})



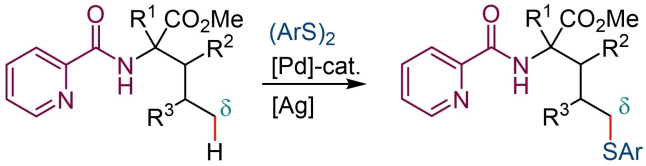
IM10-OAc (-15.4 kcal·mol^{-1})

RESEARCH ARTICLE

Pd-Catalyzed δ-C(sp^3)–H Thiolation of Amino Acid Derivatives

Adv. Synth. Catal. **2023**, *365*, 1–9

A. García-Viada, C. Sánchez-González, M. Martínez-Mingo, I. Alonso*, N. Rodríguez*, J. C. Carretero*



27 examples, up to 85% yield