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Palladium-Catalyzed sp^3 C–H Acetoxylation of α,α-Disubstituted α-Amino Acids

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Abstract: The sp^3 C–H acetoxylation at the β-position of α,α-disubstituted α-amino acids proceeds smoothly under palladium catalysis in the presence of $PhI(OAc)_2$. This reaction provides a straightforward synthetic route to non-natural β-acetoxy-α-amino acids. The reaction of α-aminocyclopropanecarboxylic acid takes place via ring-opening to selectively afford an acyclic γ-acetoxy-α,β-unsaturated amino acid.

Keywords: C–H functionalization; palladium; acetoxylation; α-amino acid

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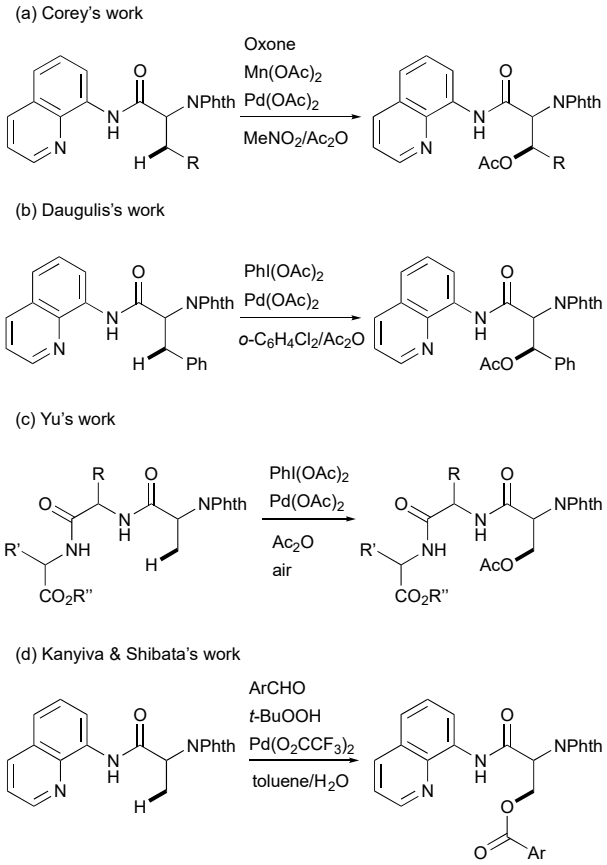
1. Introduction

α-Amino acid scaffolds can be seen in a wide range of natural products. Recently, the class of non-proteinogenic α,α-disubstituted α-amino acids has been focused on in biochemical research and drug discovery [1,2]. The biological and chemical properties of these molecules have inspired various new synthetic methodologies [3–6]. Especially β-hydroxy-α,α-disubstituted amino acids, a key component in the structure of many biologically active natural products, such as sphingofungin F [7] and kaitocephalin [8,9], are highly challenging target molecules due to the motif's densely functionalized structure [10].

One of the most powerful methods for their synthesis is the modification of readily available, natural α-amino acids such as α-aminoisobutyric acid (Aib). Specifically, Aib and its analogues have been recognized as important building blocks for functional peptides because their introduction induces drastic macrostructural changes due to their bulky α,α-disubstituted structure [11,12].

Meanwhile, transition-metal-catalyzed C–H functionalization has been developed and has provided step- and atom-economical routes in the organic synthesis field [13–26]. A number of sp^3 C–H arylations and alkylations at the β-position of α-amino acids have been developed to enable the direct production of non-natural α-amino acids [27–32]. Compared to such C–C coupling, C–heteroatom coupling including the acetoxylation of α-amino acids has been relatively less explored. Corey first reported palladium-catalyzed β-acetoxylation of α-*N*-phthaloylamino acid 8-aminoquinoline amides (Scheme 1a) [33]. Daugulis reported a single example for the β sp^3 C–H acetoxylation of a phenylalanine derivative utilizing the same bidentate directing group (Scheme 1b) [34]. Yu achieved acetoxylation on the methyl carbon of alanine moiety of tripeptides (Scheme 1c) [35]. Recently, Kanyiva and Shibata reported the benzoxylation of alanine derivatives using benzaldehydes as benzoxyl reagents (Scheme 1d) [36]. Since bidentate directing groups were employed in these precedents, substrate scope was limited mostly to sterically less-hindered ones. At least to the best of our knowledge, there is no precedent for effective sp^3 C–H acetoxylation of bulky α,α-disubstituted α-amino acids. During our studies on transition-metal-catalyzed C–H functionalization utilizing the monodentate directing group [37–41], we succeeded in finding that β sp^3 C–H acetoxylation of α,α-disubstituted α-amino acid derivatives proceeds efficiently under palladium catalysis directed by their monodentate amide functional group to provide a straightforward synthetic route to non-natural β-acetoxylated amino acids. It

has also been shown that the acetoxylated products can be readily transformed to β-hydroxy amino acids. These new findings are described herein.



Scheme 1. Acyloxylation utilizing bidentate directing group. (**a**) Corey's work; (**b**) Daugulis's work; (**c**) Yu's work; (**d**) Kanyiva & Shibata's work.

2. Materials and Methods

2.1. General

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, for $CDCl_3$ and DMSO-d_6 solutions. NMR measurements were performed at 80 °C, if necessary. HRMS data were obtained by DART using a TOF mass spectrometer. The structures of all products listed below were unambiguously determined by ^{1}H and ^{13}C NMR, and X-ray crystal structure analysis.

Amino acid derivatives **1** and **3** [35,42–45] and mono-*N*-protected amino acid ligand **L6** [46] were prepared according to published procedures. Other reagents were purchased from commercial sources and used without further purification.

The following experimental procedures may be regarded as typical in methodology and scale.

2.2. General Procedure for Pd-Catalyzed Acetoxylation of **1** *and* **3**

To a flame-dried 5 mL vial or 15 mL pressure-resistant tube, **1** or **3** (0.3 mmol), $PhI(OAc)_2$ (0.9 mmol, 290 mg), $Pd(CH_3CN)_4(BF_4)_2$ (0.015 mmol, 7 mg), *N*-acetyl-L-valine (**L1**, 0.03 mmol, 5 mg), and HFIP/DME/Ac_2O (5/4/1, 0.7 mL) were added. The mixture was stirred under argon (1 atm) at 80 °C (hot plate temperature or oil bath) for 20 h. The mixture was diluted with EtOAc (1 mL) and then passed through a short column with activated alumina to remove insoluble solids. After removal of the solvents under vacuum, the crude residue was purified by column chromatography on silica gel using hexane−EtOAc as eluent to afford acetoxylated products **2** or **4**. Further purification by GPC (gel permeation chromatography) was performed, if needed.

2.3. Procedure for Methanolysis of **2a** *[47]*

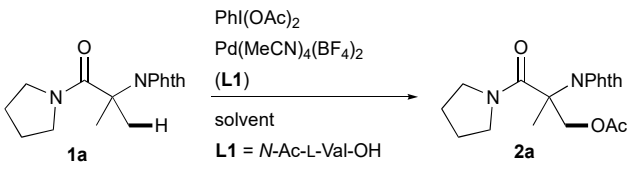
To a 50 mL flask, **2a** (0.26 mmol, 89 mg), HCl-MeOH (5–10%, 10 mL), and MeOH (5 mL) were added. The mixture was stirred under air (1 atm) at 60 °C for 0.5 h. After removal of the solvents under vacuum, the product was purified by column chromatography on silica gel using hexane−EtOAc as eluent. Further purification by GPC (gel permeation chromatography) was performed to afford **5** (63 mg, 80%).

3. Results and Discussion

3.1. Optimization of Reaction Conditions

In an initial attempt, 2-(2-methyl-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)isoindoline-1,3-dione (**1a**) (0.3 mmol) was treated with $PhI(OAc)_2$ (0.9 mmol) in the presence of $Pd(OAc)_2$ (0.015 mmol) in HFIP/Ac_2O (9/1, 0.7 mL) [48] (HFIP = hexafluoro-2-propanol) under argon at 80 °C for 20 h. As a result, a trace amount of 2-(1,3-dioxoisoindolin-2-yl)-2-methyl-3-oxo-3-(pyrrolidin-1-yl)propyl acetate (**2a**) was formed (Table 1, entry 1). The use of cationic palladium precursor $Pd(MeCN)_4(BF_4)_2$ in place of $Pd(OAc)_2$ improved the acetoxylation efficiency to give **2a** a 19% yield (entry 2). The addition of an ethereal co-solvent was found to influence the reaction efficiency. Thus, the addition of THF or 1,4-dioxane enhanced the yield to 24 and 44% yield (entries 3 and 4, respectively). The use of solvent system HFIP/DME/Ac_2O brought about further improvements of up to 45% (entry 5), while HFIP/diglyme/Ac_2O was less suitable (entry 6). It has been reported that mono-*N*-protected amino acid (MPAA) ligands effectively enhanced the activity of palladium catalysts toward C–H functionalization [49–51]. Therefore, *N*-acetyl-L-valine (*N*-Ac-L-Val-OH (**L1**), 0.03 mmol) was added to the present reaction system. To our delight, the reaction efficiency was significantly improved to afford **2a** with a 65% isolated yield (entry 7). In this case, a small amount of diacetoxylated product was also detected by crude NMR analysis. Moreover, it was confirmed that this reaction could easily be scaled up to a 1 mmol scale. Thus, the reaction of **1a** (1 mmol) with $PhI(OAc)_2$ (3 mmol) gave **2a** in a reasonable yield (214 mg, 62%) (entry 8). Both decreasing and increasing the amount of DME slightly reduced the product yield (entries 9 and 10). Even under conditions with **L1**, $Pd(OAc)_2$ was not effective (entry 11). At 100 °C, the **2a** yield decreased to 59% (entry 12).

Table 1. Optimization of the acetoxylation reaction conditions [1].

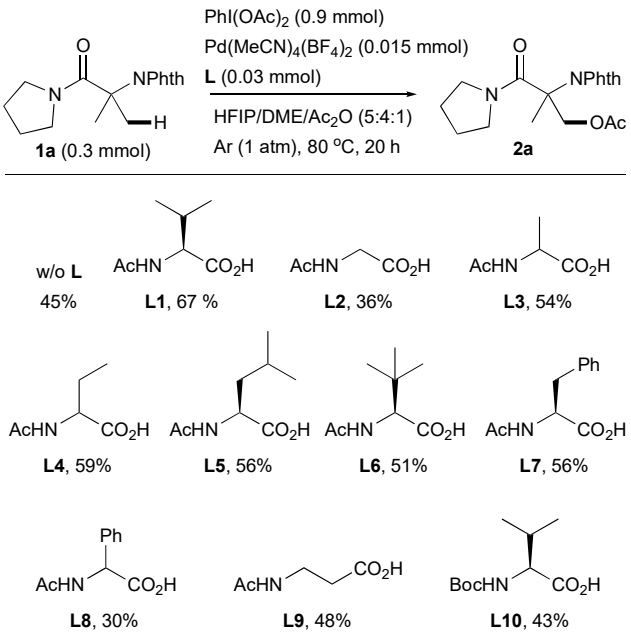


Entry	L1 (mol%)	Solvent	Yield of 2a (%) [2]
1 [3]	0	HFIP/Ac_2O (9:1)	tr.
2	0	HFIP/Ac_2O (9:1)	19
3	0	HFIP/THF/Ac_2O (5:4:1)	24
4	0	HFIP/dioxane/Ac_2O (5:4:1)	44
5	0	HFIP/DME/Ac_2O (5:4:1)	45
6	0	HFIP/diglyme/Ac_2O (5:4:1)	36
7	10	HFIP/DME/Ac_2O (5:4:1)	67 (65)
8 [3]	10	HFIP/DME/Ac_2O (5:4:1)	(62)
9	10	HFIP/DME/Ac_2O (6:3:1)	59
10	10	HFIP/DME/Ac_2O (4:5:1)	58
11 [4]	10	HFIP/DME/Ac_2O (5:4:1)	tr.
12 [5]	10	HFIP/DME/Ac_2O (5:4:1)	59

[1] Reaction conditions: **1a** (0.3 mmol), $PhI(OAc)_2$ (0.9 mmol), $Pd(MeCN)_4(BF_4)_2$ (0.015 mmol), (**L1** (0.03 mmol)) in solvent (0.7 mL) under argon (1 atm) at 80 °C for 20 h, unless otherwise noted. [2] Determined by ^1H NMR using 1,4-dimethoxybenzene as internal standard. Value in parentheses indicates yield after purification. [3] Together, **1a** (1 mmol), $PhI(OAc)_2$ (3 mmol), $Pd(MeCN)_4(BF_4)_2$ (0.05 mmol), and **L1** (0.1 mmol) were used in solvent (2.1 mL). [4] $Pd(OAc)_2$ was used in place of $Pd(MeCN)_4(BF_4)_2$. [5] At 100 °C.

3.2. Screening of Ligands

As described above, the addition of *N*-Ac-L-Val-OH ligand (**L1**) had a significant impact in determining the reaction efficiency. We next examined the effect of other MPAA ligands (Scheme 2). Under standard conditions using **1a** (0.3 mmol) and $PhI(OAc)_2$ (0.9 mmol) in the presence of $Pd(OAc)_2$ (0.015 mmol) in HFIP/DME/Ac_2O (5/4/1, 0.7 mL) at 80 °C for 20 h, the addition of *N*-Ac-Gly-OH (**L2**, 0.03 mmol) decreased the **2a** yield to 36%. In contrast, other α-alkylated MPAAs **L3**–**6** enhanced the yield (51–59%), although they were somewhat less effective than **L1**. While *N*-Ac-L-Phe-OH similarly increased the yield, *N*-acetyl-α-phenylglycine (**L8**) decreased the yield. The addition of *N*-Ac-β-Ala-OH (**L9**) and N-Boc-Val-OH (**L10**) did not show any significant positive effect.



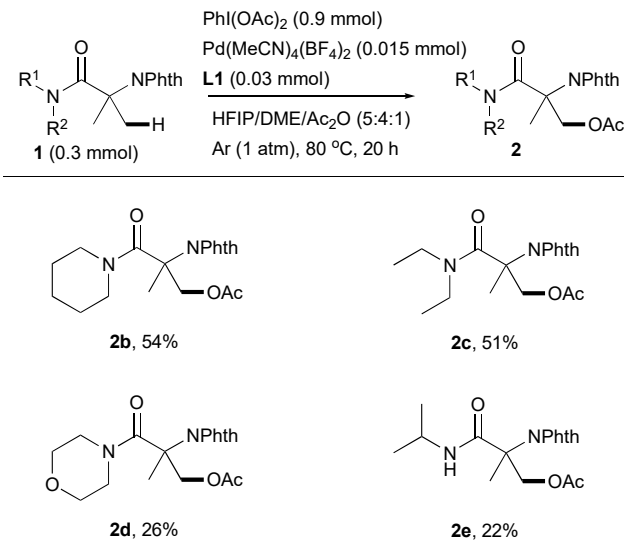
Scheme 2. Screening of ligands. The yield of **2a** was determined by ^1H NMR using 1,4-dimethoxybenzene as internal standard.

3.3. Scope and Limitations

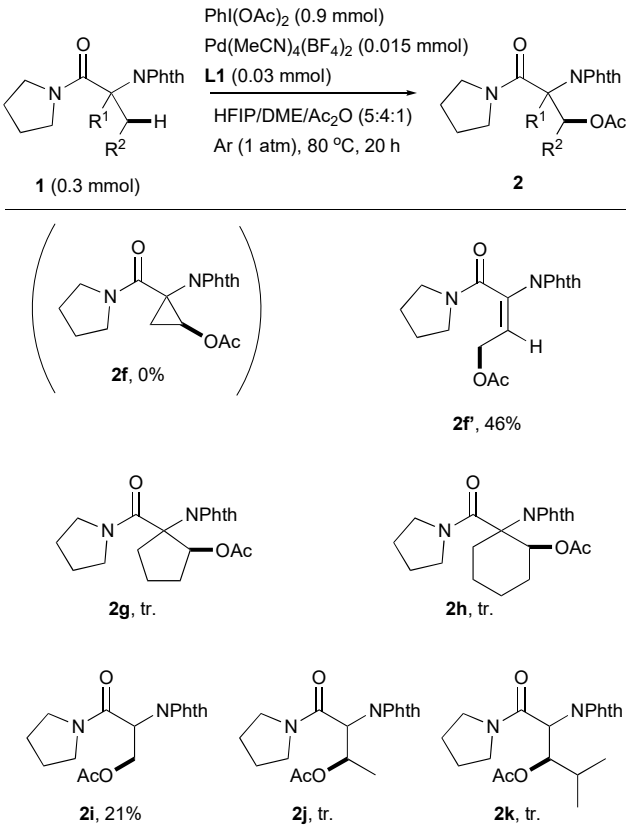
Under conditions using **L1** as a ligand, 2-(2-methyl-1-oxo-1-(piperidin-1-yl)propan-2-yl)isoindoline-1,3-dione (**1b**) underwent the acetoxylation to form **2b** in 54% yield (Scheme 3). Other amide functions also acted as a monodentate directing group. The reaction of **1c** possessing a diethylaminocarbonyl directing group gave **2c** with a 51% yield. The (4-morpholinyl)carbonyl and isopropylaminocarbonyl directing groups of **1d** and **1e**, respectively, were less effective to afford **2d** and **2e** in low yields. These results suggest that a pyrrolidylcarbonyl directing group is suitable for the present acetoxylation.

Finally, the acetoxylation of variously substituted α-amino acids with the aid of a pyrrolidylcarbonyl directing group was examined (Scheme 4). Treatment of 2-(1-(pyrrolidine-1-carbonyl)cyclopropyl)isoindoline-1,3-dione (**1f**) under the standard conditions did not give the expected acetoxylated product **2f** at all. Instead, acetoxylation took place accompanied by ring-opening [52–55] to produce (*E*)-3-(1,3-dioxoisoindolin-2-yl)-4-oxo-4-(pyrrolidin-1-yl)but-2-en-1-yl acetate (**2f′**) with a 46% yield. The structure of **2f′** was determined by X-ray crystallography (Figure S1 in the Supplementary Materials). Contrastingly, α-amino acids possessing five- and six-membered side chains **1g** and **1h** showed low reactivity and formed only trace amounts of acetoxylation products. An alanine derivative, 2-(1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)isoindoline-1,3-dione (**1i**) underwent acetoxylation to afford **2i** with a 21% yield. However, the present procedure was not applicable to 2-(1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)isoindoline-1,3-dione (**1j**) and 2-(4-methyl-1-oxo-1-

(pyrrolidin-1-yl)pentan-2-yl)isoindoline-1,3-dione (**1k**). In both cases, the acetoxylation was sluggish to form trace amounts of **2j** and **2k**.



Scheme 3. Screening of directing groups.

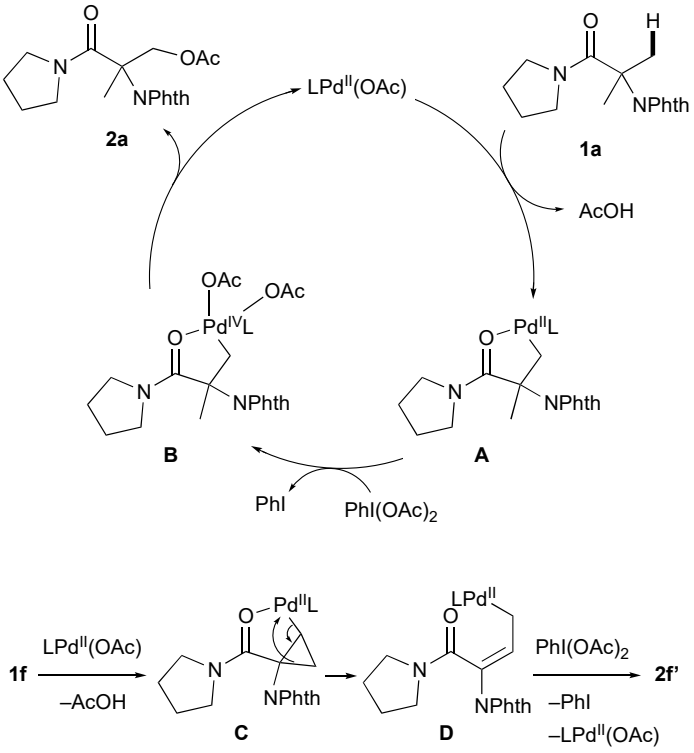


Scheme 4. Substrate scope of α-amino acids **1**.

3.4. Reaction Mechanism

Based on the literature concerning related reactions [48,49], a plausible mechanism for the present acetoxylation of **1a** is illustrated in Scheme 5. Coordination of carbonyl oxygen to Pd^{II} species triggers sp^3 C–H bond cleavage to form a five-membered palladacycle intermediate, **A**. Then, oxidation of **A** to **B** by $PhI(OAc)_2$ and subsequent reductive elimination may occur to form **2a** and active Pd^{II} species. In the case with **1f**, the corresponding

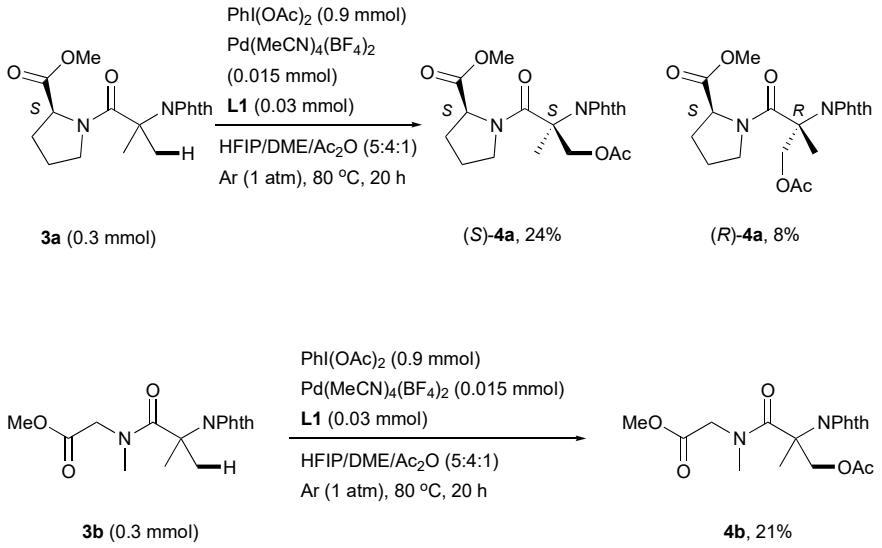
palladacycle intermediate **C** may undergo ring-opening through β-carbon elimination to form **D**, which seems to be transformed to the final acetoxylation product **2f'**.



Scheme 5. A plausible mechanism.

3.5. Acetoxylation of Dipeptide Derivatives **3**

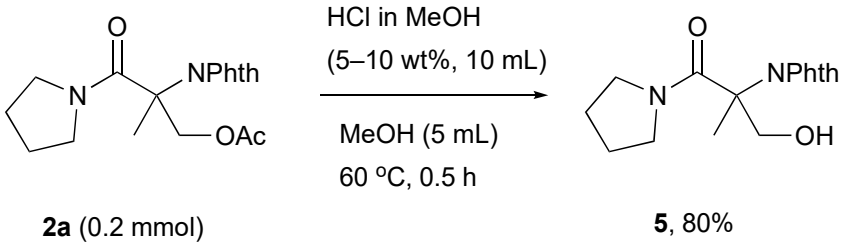
The present acetoxylation procedure was found to be applicable to dipeptide substrates **3** (Scheme 6). Thus, the reaction of methyl (2-(1,3-dioxoisoindolin-2-yl)-2-methylpropanoyl)-*L*-prolinate (**3a**) gave a mixture of separable diastereomers, (*S*)-**4a** and (*R*)-**4a**, with 24 and 8% yields, respectively. The stereochemistry of the major diastereomer (*S*)-**4a** was verified by X-ray crystallography (Figure S2 in the Supplementary Materials). Another dipeptide, methyl *N*-(2-(1,3-dioxoisoindolin-2-yl)-2-methylpropanoyl)-*N*-methylglycinate (**3b**), also underwent the acetoxylation to form **4b** with a 21% yield.



Scheme 6. Acetoxylation of dipeptide derivative **3**.

3.6. Methanolysis of **2a**

It was confirmed that an acetoxylation product can be converted to the corresponding alcohol via methanolysis (Scheme 7). Thus, treatment of **2a** (0.2 mmol) with HCl in MeOH (5–10 wt%, 10 mL) in MeOH (5 mL) at 60 °C for 0.5 h gave **5** with an 80% yield. The hydroxy group is well-known to be usable in further transformations.



Scheme 7. Methanolysis of **2a**.

4. Conclusions

We have demonstrated that α,α-disubstituted α-amino acids undergo sp^3 C–H acetoxylation at their β-position upon treatment with $PhI(OAc)_2$ in the presence of a palladium catalyst in HFIP/DME/Ac_2O to give β-acetoxylated α-amino acids. It was also shown that the procedure is applicable to the acetoxylation of dipeptides. Work is now underway for synthesizing a wide range of non-natural α-amino acids.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/chemistry5020093/s1. The Supplementary Materials contain detailed procedures for synthesizing compounds and analytical data including ^1H and ^{13}C NMR spectra [56–59].

Author Contributions: Conceptualization, T.S. and Y.U.; methodology, T.S.; validation, A.M., Y.U., and T.S.; formal analysis, A.M.; structures, T.S. and Y.U.; experiments, A.M.; writing—original draft preparation, T.S. and Y.U.; writing—review and editing, T.S. and Y.U.; project administration, T.S. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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