Letter

Highly Efficient and Divergent Construction of Chiral #-Phosphono-#-Amino Acids via Palladium-Catalyzed Alkylation of Unactivated C(sp3)-H Bonds

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Highly Efficient and Divergent Construction of Chiral γ-Phosphono-α-Amino Acids *via* Palladium-Catalyzed Alkylation of Unactivated C(sp^3)-H Bonds

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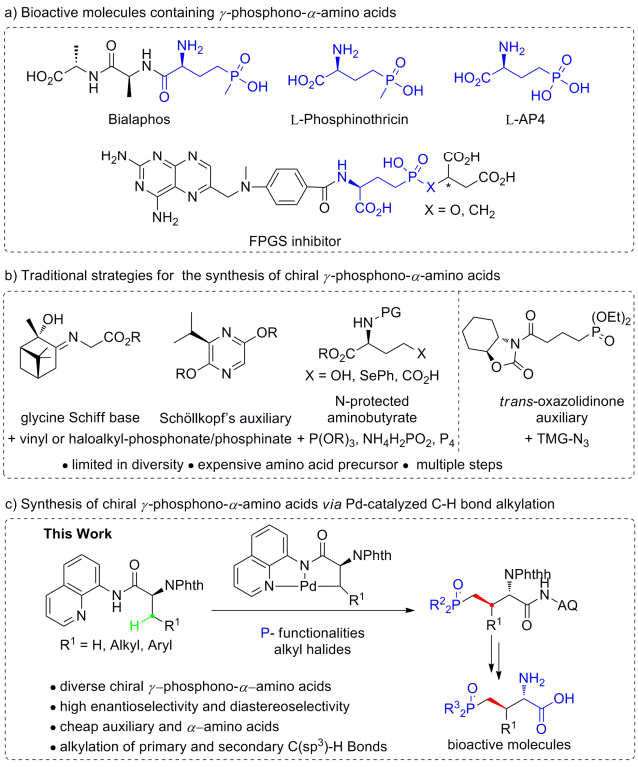
ABSTRACT: Chiral γ-phosphono-α-amino acids play a crucial role in inhibitors of natural enzymes, as well as agonists and antagonists of metabotropic glutamate receptors. In this paper, an efficient and general protocol for the construction of chiral γ-phosphono-α-amino acids *via* Pd-catalyzed AQ-directed C(sp^3)–H alkylation of α-amino acid derivatives is developed. The reaction shows reactivity between methylene C(sp^3)-H bonds with phosphonated alkyl iodides with high yields, enantioselectivity and diastereomeric ratios, which enables access to a wide range of challenging and important γ-phosphono-α-amino acids in large-scale. Meanwhile, δ-phosphono-α-amino acid and δ-phosphono-propionic acid derivatives can also be successfully obtained. The derivatization reaction in the synthesis of L-AP4 and L-phosphinothricin highlight the applicability of this method.

KEYWORDS: *C-H activation, γ-phosphono-α-amino acids, alkylation, palladium, synthetic methods*

Amino acids are specifically important constituents of peptides, proteins and biologically active compounds.[1] The introduction of tetrahedral phosphonic acid functional groups in α-amino acids can simulate the tetrahedral transition state in peptide hydrolysis, which enable these derivatives act as inhibitors of peptidase or esterase (Scheme 1a),[2] such as L-phosphinothricin[3] and (L)-2-amino-4-phosphonobutanoic acid (L-AP4).[4] In addition, chiral γ-phosphono-α-amino acid is a crucial component of a potent inhibitor of human folylpolyglutamatesynthetase (FPGS).[5] Over the past years, numerous asymmetric methodologies have been developed for the synthesis of chiral γ-phosphono-α-amino acids by chiral auxiliary and α-amino acids (Scheme 1b),[6] including glycine Schiff base,[6c-6d] Schöllkopf's auxilliary,[6e-6g] *trace*-oxazolidinone auxilliary[6h] and *N*-protected aminobutyrate.[5b, 6i-6l] Although remarkable progresses have been achieved, these approaches suffer from several limitations, such as poor diversity, expensive amino acids and multiple steps, especially, some of preparative methods are only suitable for the synthesis of γ-phosphonated glycine derivative, whereas other classes of amino acids, such as leucine, cyclohexylalanine and lysine are rarely involved. Therefore, the development of efficient and universal methods for the synthesis of chiral γ-phosphono-α-amino acid derivatives is still highly desirable and challenges.

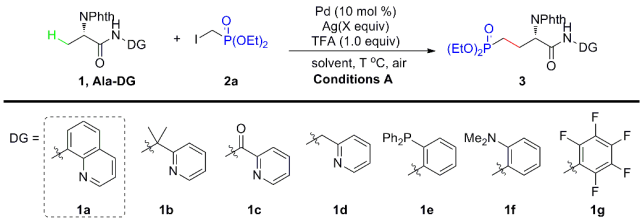
Scheme 1. Design for Chiral γ-Phosphono-α-Amino Acids



Recently, transition-metal-catalyzed,[7] specifically auxiliary-assisted C(sp^3)–H functionalization[8] has been proved great potential in organic synthesis. Among the reported auxiliaries, the 8-aminoquinoline (AQ) directing group gets high attention for its unique coordination model and easier to remove. In the past more than 10 years, AQ-directed C(sp^3)–H functionalization has made important progress, representative contributions come from the groups of Daugulis,[9] Chatani,[10] Chen,[11] Shi,[12] Ge[13], Baran,[14] and Nakamura[15] as well as others.[16] However, examples of transition-metal-catalyzed AQ directed alkylation of unactivated C(sp^3)–H to build C(sp^3)–C(sp^3) bond is still very rare, mostly due to the low reactivity of aliphatic C(sp^3)–H bonds and the influence of the sterics and electronics of alkyl coupling partners. In 2010, Daugulis first reported that the primary C(sp^3)–H of AQ-coupled propanamide could be alkylated under palladium catalysis,[17] as well as alkylated with nickel catalysis reported by Ge.[18] Recently, Daugulis, Chen and Shi groups independently reported a few examples of Pd-catalyzed AQ-directed alkylation of aliphatic C(sp^3)–H for the synthesis of α-amino acid derivatives.[19] Due to the specifically biological activity, the modification of these chiraly-phosphono-α-amino acids will provide direct resource for searching potential inhibitors of natural enzymes, as well as new agonists and antagonists of metabotropic glutamate receptors. As an efficient alternative strategy, we envisioned these molecules could be expeditiously accessed through the selective alkylation of C(sp^3)–H bonds on the side chains of simple amino acid precursors. As part of our efforts to synthesize new-style organophosphorus compounds,[20] herein, we report a Pd-catalyzed α-amino acid alkylation of primary and secondary C(sp^3)–H bonds with P-functionalities-contained alkyl halides to synthesize chiral γ-phosphono-α-amino acids (Scheme 1c). This strategy enables the divergent and gram-synthesis of various chiral γ-phosphono-α-amino acids.

Inspired by Daugulis and Chen's work,[19, 21] we initiated this alkylation reaction by using the *N*-Phth-protected Alanine (Ala) **1a** with (iodomethyl)phosphonate (**2a**) as the model substrates. In the presence of $Pd(OAc)_2$ and AgOAc, we could only get moderate yield of **3a** (see Table 1 (entry 1)). After extensive screening of the reaction conditions (see Table S1 in the Supporting Information for details), we were delighted to find that γ-phosphono-α-amino acids **3a** could be obtained in 97% yield under the following reaction conditions (**Conditions A**): **2a** (2 equiv), $Pd(TFA)_2$ (10 mol %), Ag_2CO_3 (1.5 equiv) and TFA (1 equiv) in DCE under air atmosphere at 60 °C for 20h. It is noteworthy that **3a** was obtained without racemization (99% ee), while traditional methods were difficult to obtain such a high yield and enantioselectivity.[6a,6b] After obtaining the best conditions, various alternative directing groups were tested under the optimized conditions (Table 1). When using 2-(pyridin-2-yl)isopropyl (PIP) (**1b**) as directing group, it a satisfactory yield (77%) was achieved. However, no reaction occurred when the *N*-linked picolinamide (PA) (**1c**) and pyridyl methylamine (PM) (**1d**) were served as the directing groups, and the same result was obtained for 2-(diphenylphosphino)aniline (**1e**) applied under reaction system. In addition, neither the *N,N'*-bidentate 2-dimethylaniline (**1f**) or weak coordinating fluorinated aniline (ArF) (**1g**) provided any desired product.

Table 1. Optimization of Reaction Conditions[a]



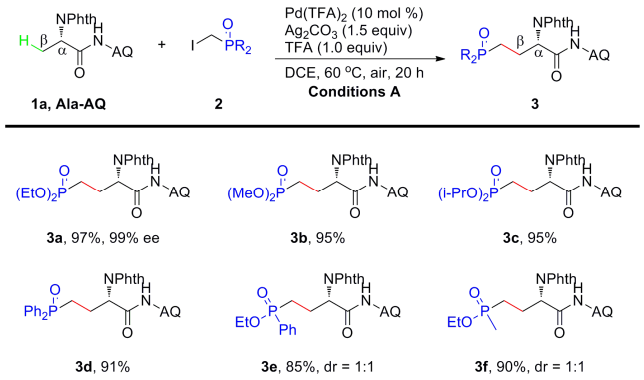
entry	DG	Pd (10 mol %)	Ag (equiv)	Solvent	Yield[b] (%)
1	1a	$Pd(OAc)_2$	AgOAc (2.0)	Dioxane	63
2	1a	$Pd(OAc)_2$	AgOAc (2.0)	DCE	72
3	1a	$Pd(TFA)_2$	AgOAc (2.0)	DCE	80
4	1a	$Pd(TFA)_2$	Ag_2CO_3 (2.0)	DCE	86
5[c]	1a	$Pd(TFA)_2$	Ag_2CO_3 (1.5)	DCE	97
6[c]	1b	$Pd(TFA)_2$	Ag_2CO_3 (1.5)	DCE	77
7[c]	1c	$Pd(TFA)_2$	Ag_2CO_3 (1.5)	DCE	n.r.
8[c]	1d	$Pd(TFA)_2$	Ag_2CO_3 (1.5)	DCE	n.r.
9[c]	1e	$Pd(TFA)_2$	Ag_2CO_3 (1.5)	DCE	n.d.
10[c]	1f	$Pd(TFA)_2$	Ag_2CO_3 (1.5)	DCE	trace
11[c]	1g	$Pd(TFA)_2$	Ag_2CO_3 (1.5)	DCE	n.r.

[a]**1** (0.2 mmol), **2a** (0.3 mmol), Pd (10 mol %), Ag (0.4 mmol), TFA (0.2 mmol), solvent (2 mL), 80 °C, air, 20 h. [b]Isolated yields of **3**. [c]**Conditions A: 1** (0.2 mmol), **2a** (0.4 mmol), $Pd(TFA)_2$ (10 mol %), Ag_2CO_3 (0.3 mmol), TFA (0.2 mmol), DCE (2 mL), 60 °C, air, 20 h.

Having the optimized reaction conditions and the perfect auxiliary in hand, the scope of α-iodomethylphosphonates and α-iodomethyl phosphine oxides were then tested (Scheme 2). To our delight, the procedure tolerated a variety of phosphonates, for example, dimethyl and diisopropyl phosphonates produced the desired products (**3b**, **3c**) in excellent yields. α-Iodomethyldiphenylphosphine oxide (**2d**) afforded the product (**3d**) in 91% yield. In addition, other phosphinates, such as ethyl (iodomethyl)(phenyl)phosphinate (**2e**) and ethyl(iodomethyl)(methyl)phosphinate (**2f**) were compatible with the reaction and could obtained the desired products **3e** and **3f** in excellent yields, but with low diastereoselectivity of phosphinate groups. It is worth

noting that product **3f** is the precursor of L-phosphinothricin, which is used as a powerful antibacterial, antifungal and nonselective herbicidal.[3]

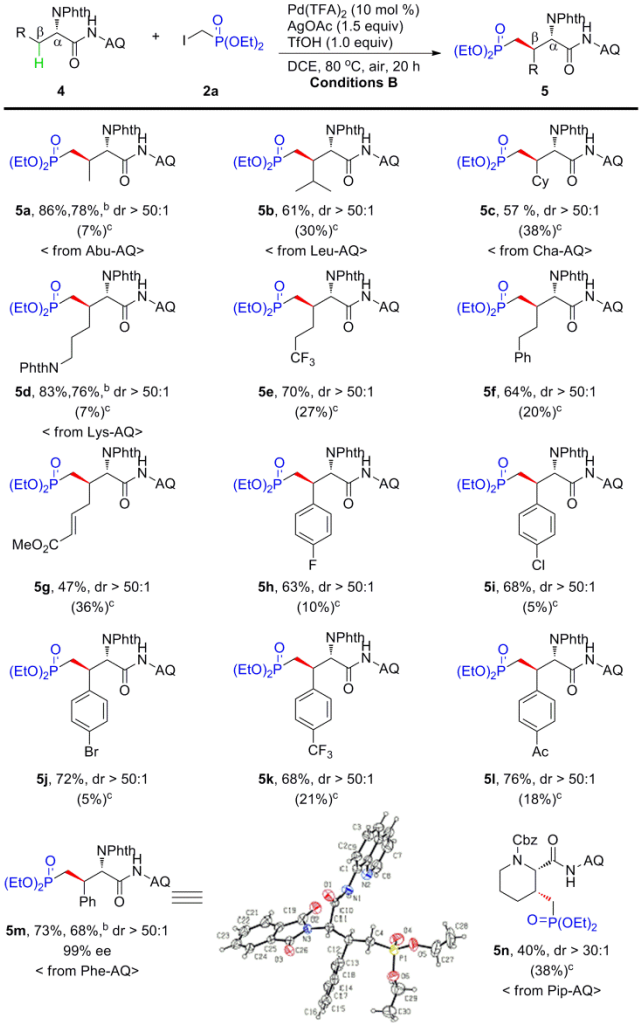
Scheme 2. AQ-directed Pd-catalyzed β-C(sp³)-H Bonds Alkylation of Primary C-H Bond[a]



[a]**Conditions A**: **1a** (0.2 mmol), **2** (0.4 mmol), $Pd(TFA)_2$ (10 mol %), Ag_2CO_3 (0.3 mmol), TFA (0.2 mmol), DCE (2 mL), 60 °C, air, 20 h. Isolated yields of **3**. Enantioselectivity determined by chiral-stationary-phase HPLC. Diastereoselectivity determined by ^{31}P NMR analysis of reaction crude mixture.

Encouraged by these results, we further examined the substrates scope regarding methylene C(sp³)-H bonds alkylation to prepare an array of more complicated chiral γ-phosphono-α-amino acids. To our disappointment, we only got a 12% yield of desired product under **Conditions A** with *N*-Phth-protected phenylalanine (Phe) **4m** (see Table S2 (entry 1) in the Supporting Information). As the low reactivity and the significant steric hindrance of methylene C(sp³)-H bonds, the reactions were facing a huge challenge to afford the product in good yield. Then after we further screened the catalyst, silver, acid and temperature based on **Conditions A**, we obtained a good yield for **5m** by using $Pd(TFA)_2$ (10 mol %), AgOAc (1.5 equiv) and trifluoromethanesulfonic acid (TfOH) (1 equiv) in DCE under air atmosphere at 80°C for 20h (**Conditions B** (see Table S2 in the Supporting Information for details)). A series of α-amino acid derivatives (Scheme 3) were then tested under this new reaction conditions. Gratifyingly, 2-amino-butyric acid (**Abu**, **4a**), and lysine (**Lys**, **4d**) derivatives were all compatible with the new alkylation protocol, and generated the chiral γ-phosphono-α-amino acids **5a** and **5d** in good yields. On the other hand, the C(sp³)-H bonds alkylation of steric bulky substrates, such as leucine (**Leu**, **4b**) and cyclohexylalanine (**Cha**, **4c**) proceed smoothly and generated desired products **5b** and **5c** in moderate yields. α-Amino acid derivatives bearing other functional groups, for example CF_3, Ph and crotonic acid ester groups (**4e**-**4g**) were tolerated and afforded the desired products **5e**-**5g** in moderate to good yields. Meanwhile, alkylation of phenylalanine derivatives (**4h**-**4m**) also took place and produced the desired products **5h**-**5j** in good yields. Furthermore, pipecolinic acid derivative (**4n**) could also afford the secondary C(sp³)-H bonds alkylation product **5n** in a moderate yield. Importantly, the chiral γ-phosphono-α-amino acids **5m** was obtained with excellent enantioselectivity (99% ee) and all these products were afforded with excellent diastereoselectivity. It has been proven that stereoinduction by the α,β-*trans*-configured five-membered palladacycle intermediate provided us a simple and reliable model to get the excellent diastereoselectivity of the β-alkylations with steric bulky phosphinate groups.[19] In addition, the structure of **5m** was confirmed by single-crystal X-ray

Scheme 3. AQ-directed Pd-catalyzed β-C(sp3)-H Bonds Alkylation of Secondary C-H Bonds[a]

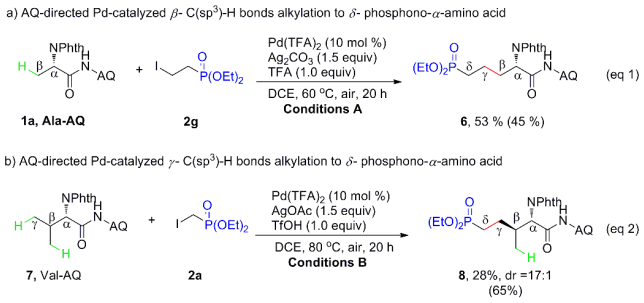


[a]**Conditions B:** **4** (0.2 mmol), **2a** (0.4 mmol), $Pd(TFA)_2$ (10 mol %), AgOAc (0.3 mmol), TfOH (0.2 mmol), DCE (2 mL), 80 °C, air, 20 h. Isolated yields of **5**; Diastereoselectivity determined by ^1H NMR analysis of reaction crude mixture. Enantioselectivity determined by chiral-stationary-phase HPLC. [b]Isolated yields of 3 mmol scale reactions. [c]Yields in parentheses are for recovered starting materials.

diffraction.[22] Notably, when the reactions were carried out on a gram-scale, the corresponding products could also be obtained in a good yield, such as **5a**, **5d**, **5m**.

In order to highlight the applicability of this method, we then use our system to synthesize δ-phosphono-α-amino acid. Several studies have shown that 2-amino-5-phosphonopentanoic acid (AP5), which belongs to δ-phosphono-α-amino acids is the most potent of the series as an antagonist of *N*-methyl-D-aspartate (NMDA)-mediated neurotransmission.[23] We thus used *N*-Phth-protected Alanine (**Ala, 1a**) reacted with diethyl (2-iodoethyl)phosphonate (**2g**), and the reaction generated the δ-phosphono-α-amino acid **7** in 53% yield (eq 1). Furthermore, besides alkylation of the β-C-H bonds, alkylation of γ-C(sp^3)-H bonds could also be achieved. As shown in Scheme 4 eq 2, *N*-Phth-protected Valine (**Val**, **7**) afforded the desired products **8** in 28% yield via a six-membered palladacycle intermediate.

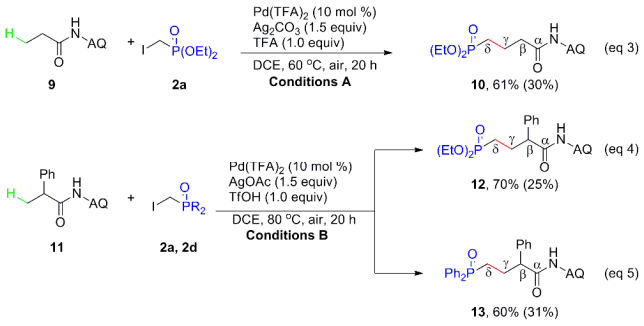
Scheme 4. Synthesis of δ-Phosphono-α-Amino Acids[a]



[a]Isolated yields of **6** and **8;** yields in parentheses are for recovered starting materials. Diastereoselectivity determined by ^{1}H NMR analysis of reaction crude mixture.

As propionic acid and 2-aryl propionic acid are common structure motifs in drug molecules, including metalaxyl, propanil, naproxen and ibuprofen. We then applied this Pd-catalyzed C(sp^3)-H bonds alkylation method in the introduction of phosphono into propionic acids. As shown in Scheme 5, δ-phosphono-propionic acid derivatives (**10**, **12-13**) could be easily obtained in moderate to good yields under our reaction system.

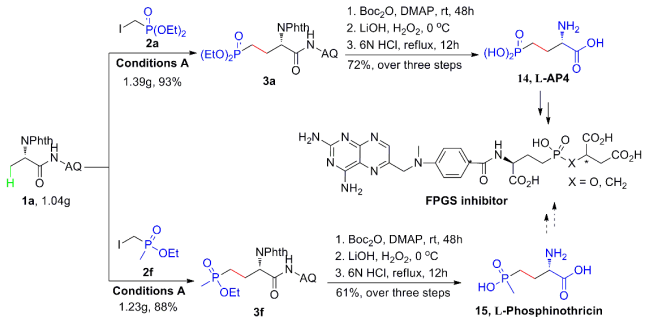
Scheme 5. Synthesis of δ-Phosphono-Propionic Acids[a]



[a]Isolated yields of **10, 12** and **13;** yields in parentheses are for recovered starting materials.

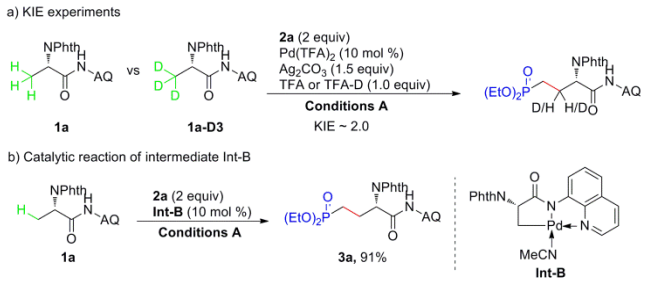
We then scaled up the reaction to 3 mmol (gram-scale) and the alkylated products **3a** and **3f** were obtained in 93% and 88% yields, separately (Scheme 6). At the same time, the auxiliary group AQ could be removed by treatment the product with Boc_2O, DMAP and LiOH, H_2O_2 *via* a two-step sequence.[11b, 21] After removal of the phthaloyl and ester groups in the presence of 6N HCl, L-AP4 (**14**) and L-phosphinothricin (**15**), which are a significant class of bioactive molecules and useful synthetic intermediates, then could be easily obtained according to literature report.[6j-6l, 24]

Scheme 6. Gram-scale Synthesis and Further Transformations of γ-Phosphono-α-Amino Acids



To gain further insight into the mechanism for this reaction, a primary kinetic isotope effect was observed with **1a** in the process (Scheme 7a), indicating that C-H activation was the rate-determining step. In addition, the possible Pd-containing intermediate **Int-B** was isolated. Subsequently, we found that **Int-B** reacted with **2a** smoothly to give the alkylation products **3a** in 91% yield (Scheme 7b). Catalytic reaction also suggested that this palladacycles is viable intermediate for the C-H alkylation.

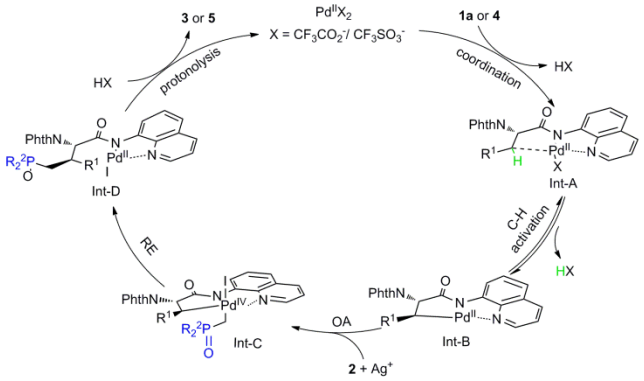
Scheme 7. Investigation of the Reaction Mechanism



Based on these results and previous reports on C(sp^3)-H bonds alkylation,[19] a proposed reaction mechanism was shown in Scheme 8. First, coordination of the amide **1a** or **4** reacted with the Pd^{II} generated intermediate **Int-A** ligated by *N, N'*-bidentate directing group. Subsequently **Int-A** underwent an intramolecular C-H concerted metalationdeprotonation (CMD) to give the key five-

membered intermediate **Int-B**. Then the **Int-B** reacted with **2** to give intermediate **Int-C** *via* oxidative addition (OA). Afterwards, through reductive elimination (RE) of

Scheme 8. Proposed Mechanism



Int-C to build the desired C-C bond and afforded Pd^{II} coordinating with assistance species intermediate **Int-D**. Finally, the desired products **3** or **5** were obtained by protonolysis of intermediate **Int-D** and given Pd^{II} to recycle into the reaction.

In conclusion, an efficient synthesis method towards *γ*/*δ*-phosphono-*α*-amino acids via AQ directed palladium-catalyzed C(sp^3)–H alkylation of amino acids has been developed. Compared with previous methods, AgOAc with TfOH-promoted conditions provide excellent reactivity to alkylation of methylene C(sp^3)-H bonds. A range of *γ*-phosphono-*α*-amino acids are quickly prepared *via* this simple method. Meanwhile, *δ*-phosphono-*α*-amino acid and *δ*-phosphono-propionic acid derivatives can also be successfully obtained. This research opens a new door to the synthesis of new *γ*/*δ*-phosphono-*α*-amino acids. Further transformations of the *γ*-phosphono-*α*-amino acids highlight the potential synthetic utility of this method in medicinal and biological applications.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, spectra data for all compounds, copies of ^1H, ^{13}C, ^{31}P and ^{19}F NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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