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Site-Selective C(sp^3)−H Functionalization of Di-, Tri-, and Tetrapeptides at the N-Terminus

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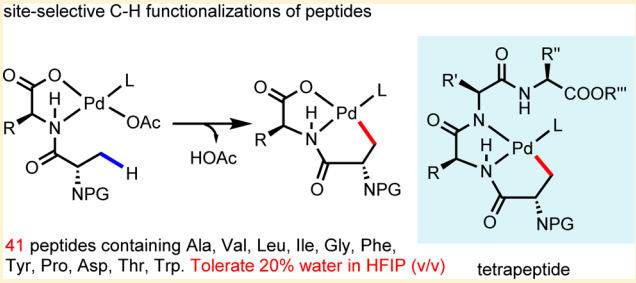
Supporting Information

ABSTRACT: Although the syntheses of novel and diverse peptides rely mainly on traditional coupling using unnatural amino acids, postsynthetic modification of peptides could provide a complementary method for the preparation of nonproteinogenic peptides. Site selectivity of postsynthetic modification of peptides is usually achieved by targeting reactive moieties, such as the thiol group of cysteine or the C-2 position of tryptophan. Herein, we report the development of site-selective functionalizations of inert C(sp^3)−H bonds of N-terminal amino acids in di-, tri-, and tetrapeptides without installing a directing group. The native amino acid moiety within the peptide is used as a ligand to accelerate the C−H activation reaction. In the long run, this newly uncovered reactivity could provide guidance for developing site-selective C(sp^3)−H activation toward postsynthetic modification of a broader range of peptides.



1. INTRODUCTION

Peptide therapeutics have recently attracted broad attention from the pharmaceutical industry because of their superior specificity for their targets over small molecules.[1−3] The number of approved peptide drugs has also steadily increased in the past decade.[1] Therefore, postsynthetic modification of peptides has emerged as a significant task of current interests.[4−9] For example, the "tag-and-modify" approach has been developed by Davis to covalently modify peptides and proteins through a diverse range of transition metal-catalyzed C−C bond-forming reactions.[6,10] Direct C(sp^2)−H functionalization of inherent phenylalanine and tryptophan moieties has also been elegantly exploited to modify the structures of bioactive small peptides.[11−13] It has long been recognized that site-selective functionalization of various inert C(sp^3)−H bonds in a peptide side chain will greatly enrich the toolbox for postsynthetic modification of peptides. Despite the significant progress in developing C(sp^3)−H activation reactions of amino acids using directed C−H activation (Figure 1a),[14−24] site-selective functionalizations of alkyl side chains in peptides without installing an external auxiliary remains to be developed, an attribute that is essential for postsynthetic modification of a broad range of peptides.

We recently discovered that monoprotected amino acid ligands coordinated to Pd(II) complexes in a bisdentate manner can drastically accelerate both C(sp^2)−H and C(sp^3)−H activation reactions (Figure 1b).[25−31] This finding prompted us to investigate whether native amino acids embedded in the peptide backbone could bind to Pd(II), leading to analogous complexes that activate proximate C−H bonds in the adjacent amino acid unit (Figure 1c). Herein, we report the successful implementation of this approach, through which site-selective arylation and acetoxylation of C(sp^3)−H bonds at the N-terminus of various peptides are accomplished without installing a directing group. Postsynthetic modification

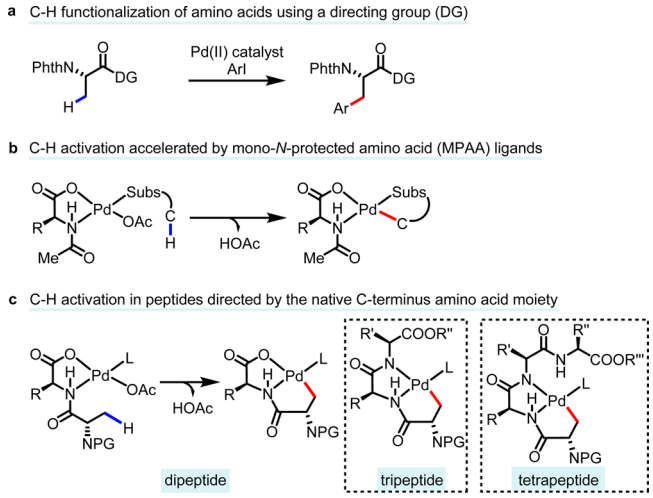


Figure 1. Site-selective C−H functionalization. (a) C(sp^3)−H functionalization of amino acids using specifically designed directing groups. (b) C−H activation by Pd(II)/amino acid complexes. (c) C(sp^3)−H activation of peptides at the N-terminus. Phth = phthaloyl, DG = directing group, Subs = substrate, NPG = protected amino group.

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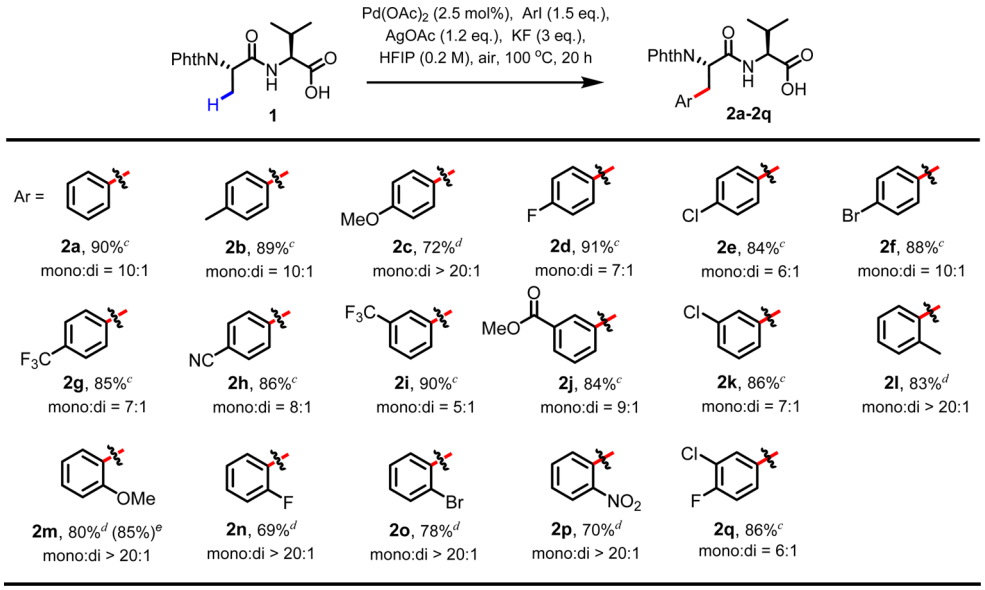
Table 1. Scope of Aryl Iodides for the C−H Arylation of Dipeptide 1[a,b]



[a]Reaction conditions: substrate (0.2 mmol), $Pd(OAc)_2$ (2.5 mol %), ArI (1.5 equiv), AgOAc (1.2 equiv), KF (3 equiv), HFIP (0.2 M), air, 100 °C, 20 h. [b]Ratio of mono- to diarylated product based on analysis of crude ^{1}H NMR spectra. [c]Combined yield of mono- and diarylated products. [d]Isolated yield of monoarylated products. [e]Isolated yield of a 5 mmol scale reaction with 5 mol % $Pd(OAc)_2$. HFIP, hexafluoroisopropanol.

of a wide range of di-, tri-, and tetrapeptides using these C−H activation reactions are thus made possible, demonstrating potential applications of Pd-catalyzed C(sp^3)−H activation reactions in peptide synthesis.

2. RESULTS AND DISCUSSION

We have previously discovered that mono-N-protected amino acids (MPAAs) can enable or accelerate a diverse range of C−H bond activation/carbon−carbon and carbon-heteroatom bond-forming reactions.[25−31] Kinetic and computational studies[32−34] suggest that the monomeric Pd(II) complex coordinated by a monoprotected amino acid in a bisdentate manner is highly reactive for cleaving inert C−H bonds. We reasoned that the C-terminus of a dipeptide is a native monoprotected amino acid that can coordinate to Pd(II) species, thus forming a reactive complex that could potentially activate the proximate C−H bonds in the N-terminus. If successful, this strategy could be potentially expanded to longer peptides (for example, tripeptides and tetrapeptides), which may form analogous N,N-biscoordinated complexes with Pd(II) catalyst and promote the C−H activation process.

To test these hypotheses, we initially focused on the direct β-C(sp^3)−H functionalization of N- phthaloyl protected dipeptide **1**, which is readily synthesized from optically pure Phth−Ala−OH (99% ee)[35] via a two-step sequence at 20-g scale (see Supporting Information (SI) for details). We chose the arylation reaction because it can provide rapid access to peptides containing modified phenylalanine moiety. After extensive experimentation, we found that with $Pd(OAc)_2$ (2.5 mol %) as the catalyst, KF (3 equiv) as the base and AgOAc (1.2 equiv) as the additive, the arylation of the dipeptide **1** with phenyl iodide in *tert*-amyl alcohol at 100 °C could afford the monoarylation product **2a** in 56% NMR yield. Further optimization revealed that the reaction could reach full conversion when hexafluoroisopropyl alcohol (HFIP) is used as the solvent. Thus, **2a** was obtained as a single diastereomer in 88% NMR yield, along with the formation of 8% diarylated product (see SI for detailed screening of reaction conditions).

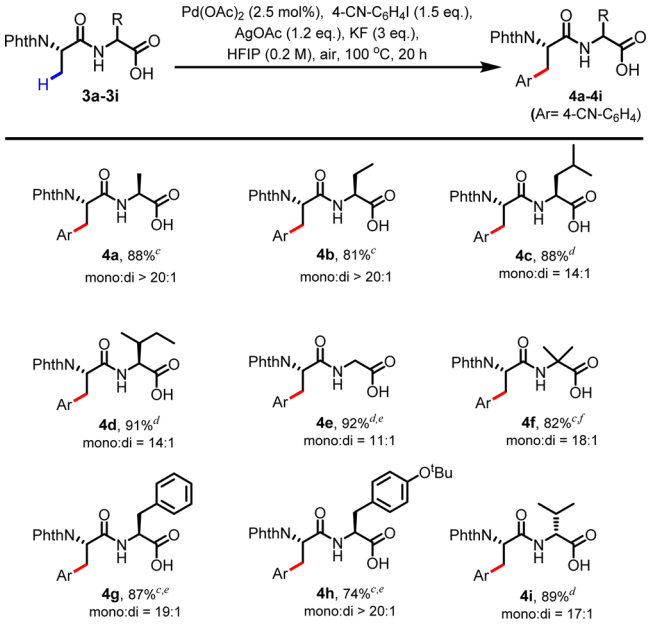
We also discovered that selective monoarylation of **1** could be achieved in the absence of KF, although with lower yields (54−73% with various aryl iodides, mono-/diarylation product > 20:1). The Pd catalyst loading can be reduced to 1 mol % in a gram-scale reaction, albeit lowering the combined yield to 77% (mono/di = 10:1, see SI). The relatively low catalyst loading demonstrates the high efficiency of this C−H activation reaction directed by the C-terminal amino acid moiety. The protection of C-terminal carboxylic acid as a benzyl ester led to a complete loss of reactivity supporting the involvement of the free carboxylate in the active complex, as is proposed in Figure 1c. The conservation of the two chiral centers without epimerization is verified by ^{1}H NMR and HPLC analysis of the arylation product in comparison with a standard sample prepared using known procedure (see SI). It is noteworthy that this reaction could tolerate up to 20% water in HFIP (v/v) to give the desired arylation product in 55% NMR yield with 10% $Pd(OAc)_2$, potentially a useful feature when solubility of peptide in pure organic solvent is poor.

With the optimized conditions in hand, dipeptide **1** was arylated at the N-terminus with a wide range of aryl iodides in good yields (Table 1). Both electron-donating (Me− and MeO−) and electron-withdrawing (F−, Cl−, Br−, CF_3−, CN−, NO_2−, and CO_2Me−) groups at either the para or meta position of the aryl iodide are well tolerated (72−90% yield). The bromo group in **2f** and **2o** can be used for further coupling using Davis' conditions developed for peptide chemistry.[6] Aryl iodides with various ortho substituents were also compatible with the reaction condition (69−83% yield). The dipeptide **1** could be smoothly arylated with disubstitued iodide to give **2q** in 86% yield. A gram-scale synthesis of the dipeptide **2m** with an ortho substituent (MeO) on the phenyl ring was conducted to afford the desired product in 85% isolated yield when 5 mol % $Pd(OAc)_2$ was employed. A few heteroaryl iodides, such as 4-iodopyridine, 3-iodopyridine, 3-iodothiophene, 2-iodo-5-meth-

yl-thiophene, 5-iodo-1*H*-indole, and 5-iodo-1-tosyl-1*H*-indole, were tested as the coupling partner in the arylation of dipeptide **1**; however, only the reaction with 5-iodo-1-tosyl-1*H*-indole gave ∼30% NMR yield of the desired product using 20 mol % $Pd(OAc)_2$ at 120 °C. Reactions with other heteroaryl iodides did not give any product.

To examine the scope of peptides, dipeptides **3** containing various amino acids at the C-terminus were prepared in high purity from Phth−Ala−OH and the corresponding natural or unnatural amino acid derivatives (Table 2). Dipeptides **3a**−**3d**

Table 2. Scope of Amino Acids at the C-Terminus of Dipeptides[a,b]

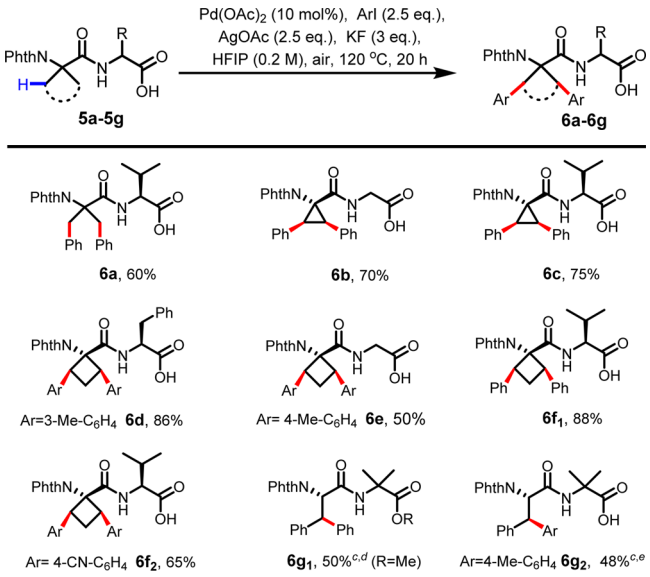


[a]Reaction conditions: substrate (0.2 mmol), $Pd(OAc)_2$ (2.5 mol %), 4-CN-C_6H_4I (1.5 equiv), AgOAc (1.2 equiv), KF (3 equiv), HFIP (0.2 M), air, 100 °C, 20 h. [b]Ratio of mono- to diarylated product. [c]Isolated yield of monoarylated products. [d]Combined yield of mono- and diarylated products. [e]5 mol % $Pd(OAc)_2$ was used. [f]Racemic substrate was used.

with alkyl substituents at the C-terminus reacted smoothly with 4-CN-phenyl iodide to provide the desired products in high yields under standard conditions (81−91%). Arylation of dipeptides derived from glycine and 2-aminoisobutyric acid (**3e**, **3f**) also proceeded in good to high yields using 5 and 2.5 mol % $Pd(OAc)_2$, respectively. Phenylalanine and tyrosine in the dipeptides **3g** and **3h** were also tolerated. Interestingly, the dipeptide **3i** containing D-valine also proved to be a good substrate for this arylation reaction, affording the mono- and diarylation products in 89% combined yield.

The scope of the amino acids at the N-terminus was also surveyed. Dipeptide **5a** was prepared from 2-aminoisobutyric acid and valine. Arylation of **5a** under the standard conditions gave a mixture of mono- and diarylated products. Diarylation product **6a** was obtained as a major product in 60% yield by using 10 mol % $Pd(OAc)_2$), along with small amount of monoarylation product. Similarly, peptides **5b**−**5f** derived from 1-aminocyclopropanecarboxylic acid or 1-aminocyclobutane-carboxylic acid were also arylated to give the diarylation products **6b**−**6f** in reasonable to good yields (50−88%, Table 3).[36] Benzylic $C(sp^3)$−H bonds in phenylalanine of dipeptide

Table 3. Scope of Amino Acids at the N-Terminus of Dipeptides[a,b]

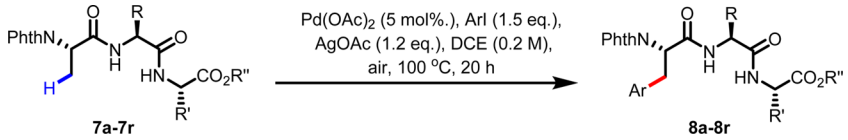


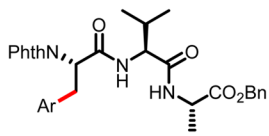
[a]Reaction conditions: substrate (0.2 mmol), $Pd(OAc)_2$ (10 mol %), ArI (2.5 equiv), AgOAc (2.5 equiv), KF (3 equiv), HFIP (0.2 M), air, 120 °C, 20 h. [b]Isolated yield. [c]Racemic substrate was used. [d]Methyl ester was synthesized directly from crude acid product with $SOCl_2$ in MeOH. [e]Diastereomeric ratio = 9:1 determined by crude ^1H NMR.

5g were also arylated with phenyl iodide and tolyl iodide to give $\mathbf{6g_1}$ and $\mathbf{6g_2}$, respectively, albeit providing the products in lower yields. For the ease of purification, the arylation product with phenyl iodide was converted to the corresponding methyl ester $\mathbf{6g_1}$ in one pot (see SI). The arylation of dipeptide **5g** with tolyl iodide afforded two diasteremoers (d.r. = 9:1), with $\mathbf{6g_2}$ as the major product.

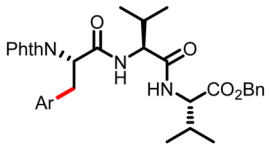
In these dipeptide substrates, the C-terminus essentially provides a native coordinating ligand that is structurally analogous to our monoprotected amino acid ligand (MPAA). It would be synthetically useful and mechanistically interesting to test how tripeptides or even tetrapeptides behave under these conditions. The key question is whether the amino acid moiety embedded in longer peptides could form a N,N-biscoordinated complex with Pd(II) in a manner similar to the N,O-bisdentate coordination in the dipeptides and still be reactive toward $C(sp^3)$−H activation (Figure 1c). To investigate this fundamental question, tripeptide **7a** was prepared in high purity via direct coupling of dipeptide **1** with the corresponding alanine derivative. Although the free carboxylic acid at the C-terminus inhibited the arylation of tripeptides and resulted in a low yield (20%), we found that the benzyl ester substrate **7a** was arylated in 1,2-dichloroethane (DCE) to give the desired product $\mathbf{8a_1}$ in 86% isolated yield. Importantly, a wide range of amino acids, including alanine, valine, leucine, isoleucine, proline, phenylalanine, glycine, aspartic acid, threonine, tryptophan, or 2-aminoisobutyric acid, embedded in the tripeptides are compatible with these conditions (**8a**−**r**, Table 4). A variety of aryl iodides possessing electron-donating or electron-withdrawing groups in para, meta, or ortho position are used as the coupling partners to provide the desired products in moderate to high yields (51% to 89%). To demonstrate that the site selectivity at the N-terminus of the tripeptide is not specific to alanine, but rather

Table 4. C−H Arylation of Tripeptides[a,b]

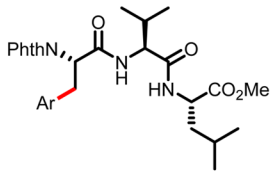




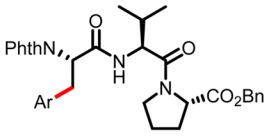
Ar=4-Me-C_6H_4 **8a$_1$**, 86%
Ar=4-Br-C_6H_4 **8a$_2$**, 80%
Ar=4-Ac-C_6H_4 **8a$_3$**, 75%



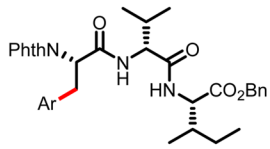
Ar=4-CF_3-C_6H_4 **8b**, 78%



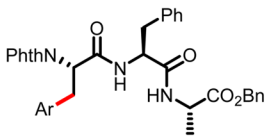
Ar=4-F-C_6H_4 **8c$_1$**, 81%
Ar=3-NO_2-C_6H_4 **8c$_2$**, 80%



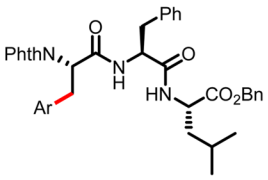
Ar=4-Me-C_6H_4 **8d**, 86%



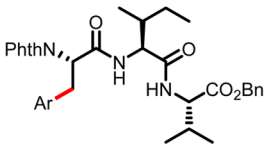
Ar=4-Me-C_6H_4 **8e$_1$**, 73%
Ar=4-Cl-C_6H_4 **8e$_2$**, 66%



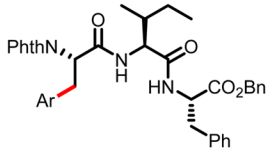
Ar=4-Me-C_6H_4 **8f$_1$**, 86%
Ar=4-CO_2Me-C_6H_4 **8f$_2$**, 72%



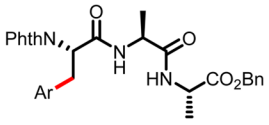
Ar=4-MeO-C_6H_4 **8g$_1$**, 62%
Ar=3-F-C_6H_4 **8g$_2$**, 75%



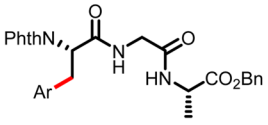
Ar=3-F-C_6H_4 **8h$_1$**, 80%
Ar=2-F-C_6H_4 **8h$_2$**, 73%[c]



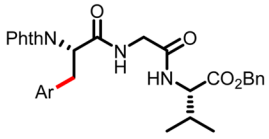
Ar=3-Cl-4-F-C_6H_3 **8i**, 67%



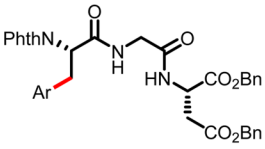
Ar=4-Cl-C_6H_4 **8j**, 79%



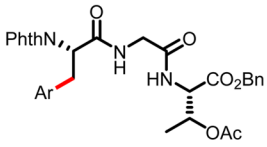
Ar=4-MeO-C_6H_4 **8k**, 89%



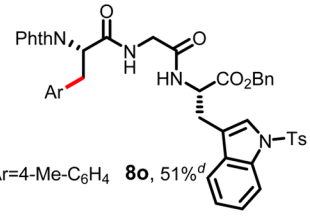
Ar=3-Me-C_6H_4 **8l$_1$**, 87%
Ar=4-MeO-C_6H_4 **8l$_2$**, 78%



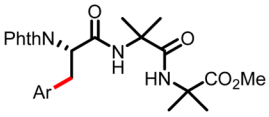
Ar=4-Me-C_6H_4 **8m**, 84%



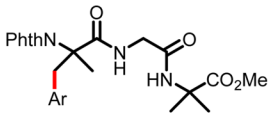
Ar=4-Me-C_6H_4 **8n**, 84%



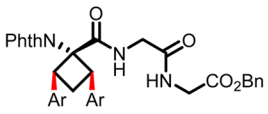
Ar=4-Me-C_6H_4 **8o**, 51%[d]



Ar=4-Me-C_6H_4 **8p**, 85%[e]



Ar=4-Me-C_6H_4 71%[f]
8q$_{mono}$ (38%) + **8q$_{di}$** (33%)



Ar=4-Me-C_6H_4 60%[f]
8r$_{mono}$ (21%) + **8r$_{di}$** (39%)

[a]Reaction conditions: $Pd(OAc)_2$ (5 mol %), ArI (1.5 equiv), AgOAc (1.2 equiv), DCE (0.2 M), air, 100 °C, 20 h. [b]Isolated yield. [c]10 mol % Pd(OAc) was used. [d]A mixture of inseperable rotamers (ratio = 1.5:1). [e]Racemic substrate was used. [f]Reaction conditions: $Pd(OAc)_2$ (10 mol %), ArI (2.5 equiv), AgOAc (2.5 equiv), DCE (0.2 M), air, 120 °C, 20 h. DCE, dichloroethane.

controlled by the N,N-biscoorindation of the peptide backbone (Figure 1c), tripeptide **7j** consisting of three alanine moieties was selectively arylated at the N-terminus. Tripeptides containing $C^{\alpha,\alpha}$-disubstituted amino acids at the N-terminus (**7q** and **7r**) could also undergo arylation using slightly modified conditions to give mono- and diarylation products. We were pleased to find that the current protocol for arylation of tripeptide is also suitable for gram-scale synthesis of novel tripeptides (arylation of **7a** in 5 mmol scale proceeded in 77% isolated yield to give 2.20 g of tripeptide **8a$_1$**; see the SI for details).

The selective arylation of tripeptides demonstrates that N,N-biscoordinated Pd (II) complexes can activate proximate $C(sp^3)$−H bonds; however, we were concerned that the additional coordinative amide bonds in longer peptides could inhibit the reaction in a manner similar to that of the C-terminus carboxylic acid. Remarkably, minor modification of the reaction conditions (10% $Pd(OAc)_2$, 2 equiv. of ArI and 2

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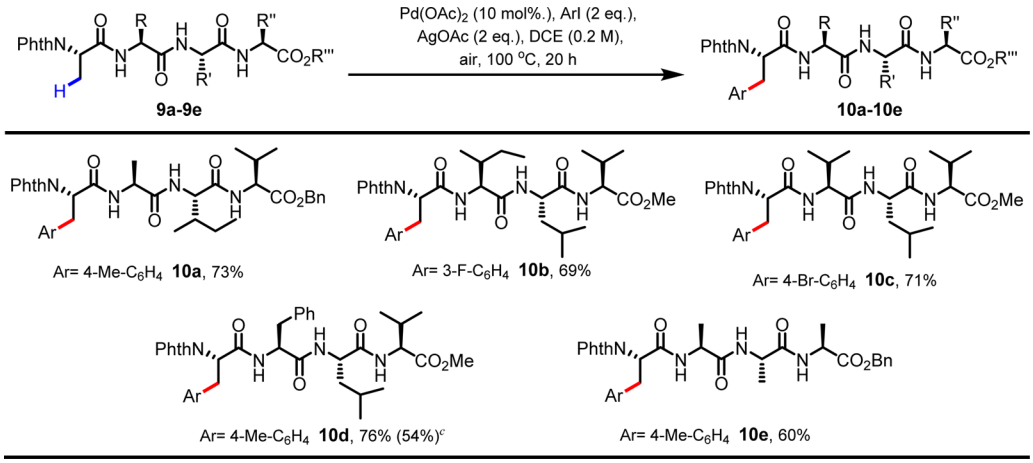
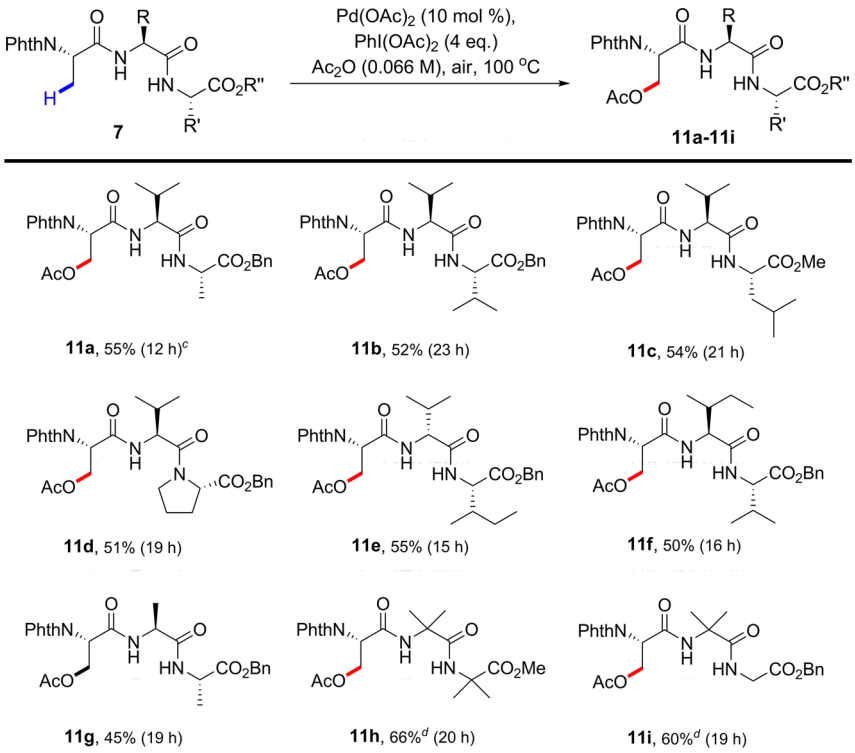
Table 5. C−H Arylation of Tetrapeptides[a,b]



[a]Reaction conditions: substrate (0.2 mmol), $Pd(OAc)_2$ (10 mol %), ArI (2 equiv), AgOAc (2 equiv), DCE (0.2 M), air, 100 °C, 20 h. [b]Isolated yield. [c]NMR yield based on internal standard (1,3,5-trimethoxybenzene) when 20% water (v/v) was added as a cosolvent.

Table 6. C−H Acetoxylation of Tripeptides[a,b]



[a]Reaction conditions: substrate (0.2 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (4 equiv), Ac_2O (0.066 M), air, 100 °C. [b]Isolated yield. [c]Reaction time. [d]Racemic substrate was used.

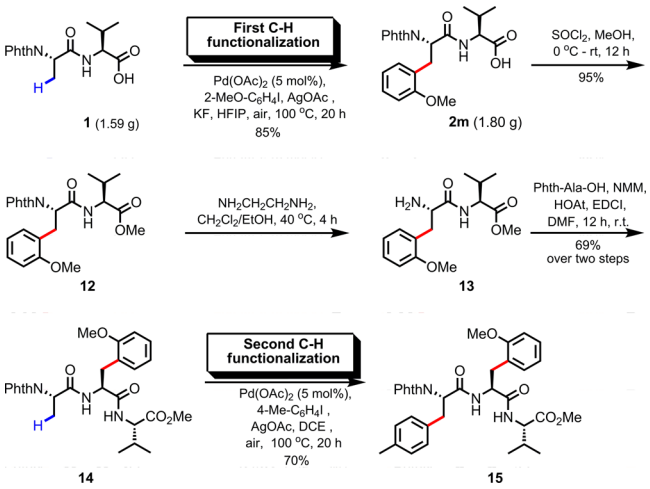
equiv of AgOAc, Table 5) allows the selective arylation of tetrapeptides **9a**−**9e** at the N-terminus end to provide the desired products in good yields (60−76%). To vigorously demonstrate that this method is site-selective at the N-terminus, tetrapeptide **9e** containing four alanine units was also arylated to give **10e** as the major product in 60% yield. Further arylation of another methyl group in Ala(2) of **10e** also occurred to give a diarylated product in 10% yield. Arylation of **9d** could occur in the presence of water (20% v/v) as a cosolvent to give **10d** in 54% NMR yield. The reactivity observed with tetrapeptides demonstrates the feasibility of applying this reaction to even longer peptides. To determine the degree of Pd contamination in the peptide products, ICP analysis of product **10d** was performed, and the residual Pd content was 280 ppm.

Next, we examined the feasibility of using this approach to convert C−H bonds in the N-terminus into other functional groups. Considering that site-selective oxidation of peptide-based drug molecules could increase the hydrophilicity of the peptide as well as facilitate the study of the undesired metabolic oxidation pathway,[1−3] we sought to develop C−H oxidation reactions of peptides using previously reported conditions.[37] We found tripeptide **7a** was selectively acetoxylated at the N-terminus with 10 mol % $Pd(OAc)_2$ as the catalyst and

$PhI(OAc)_2$ as the oxidant in acetic anhydride at 100 °C to give the acetate **11a** in 55% isolated yield. A number of tripeptides containing alanine, valine, leucine, isoleucine, glycine, or proline residues are selectively acetoxylated at the N-terminus in moderate yields (45−66%, Table 6). Although the N-terminus is limited to alanine for this acetoxylation at this stage, further optimization could lead to selective oxidation of other amino acids at the N-terminus.

Although C−H functionalization of peptides using this method occurs exclusively at the N-terminus, we envision that multiple structural modifications on other sites can be achieved by performing sequential C−H functionalizations of peptides of different lengths. Thus, gram-scale arylation of **1** was carried out to give 1.8 g of modified dipeptide **2m** (Scheme 1).

Scheme 1. Synthesis of a Novel Tripeptide via Sequential C−H Arylation



Dipeptide **2m** was then converted to **13** and subsequently coupled with Phth−Ala−OH to give the tripeptide **14** in 69% overall yield. The second modification was then performed on **14** to give tripeptide **15** with two unnatural phenylalanine moieties at different sites (Scheme 1). Tripeptide **15** could be potentially incorporated into longer peptide sequences via deprotection-coupling steps.

3. CONCLUSION

In summary, we have developed a method for site-selective functionalization of $C(sp^3)$−H bonds in peptides at the N-terminus. Di-, tri-, and tetrapeptides could be arylated with a broad range of arylating reagents to provide peptides with modified phenylalanine residues. Acetoxylation of $C(sp^3)$−H bonds in tripeptides is also demonstrated. This study illustrates that the amino acid moiety of peptides can coordinate with Pd(II) via N,O- or N,N-bisdentate coordination and promote functionalization of proximate $C(sp^3)$−H bonds. We anticipate that these preliminary results could facilitate further development of C−H bond functionalization of peptide aliphatic side chain in the context of postsynthetic modification of peptides.

4. EXPERIMENTAL SECTION

General Procedure for the Arylation of Dipeptides (Tables 1 and 2). To a microwave tube (5 mL) was added the substrate (0.2 mmol), $Pd(OAc)_2$ (0.005 or 0.01 mmol as indicated in Table 1 or 2), AgOAc (0.24 mmol), ArI (0.3 mmol), KF (0.6 mmol), and HFIP (1 mL) in air. The tube was sealed and heated to 100 °C. The mixture was stirred for 20 h at 100 °C. Upon completion, the reaction mixture was cooled to room temperature. To the mixture was added acetic acid (0.3 mL) and EtOAc (3 mL). The mixture was filtered through a short Celite pad, and the filtrate was concentrated under reduced pressure. The resulting mixture was purified by preparative TLC, typically using hexane/ethyl acetate/HOAc mixtures as the eluent, to give the arylated product as a solid. The arylated product was typically obtained as a single diastereomer (d.r. > 20:1), as evidenced by ^1H NMR and ^{13}C NMR.

General Procedure for the Arylation of Tripeptides (Table 4). To a microwave tube (5 mL) was added the substrate (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), AgOAc (0.24 mmol), ArI (0.3 mmol), and DCE (1 mL) in air. The tube was sealed and heated to 100 °C. The mixture was stirred for 20 h at 100 °C. Upon completion, the reaction mixture was cooled to room temperature. To the mixture was added acetic acid (0.3 mL) and EtOAc (3 mL). The mixture was filtered through a short Celite pad, and the filtrate was concentrated under reduced pressure. The resulting mixture was purified by preparative TLC, typically using hexane/ethyl acetate/CH_2Cl_2 mixtures as the eluent, to give the arylated product as a solid. The arylated product was typically obtained as a single diastereomer (d.r. > 20:1), as evidenced by ^1H NMR and ^{13}C NMR.

General Procedure for the Acetoxylation of Tripeptides (Table 6). To a microwave tube (5 mL) was added the substrate (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), $PhI(OAc)_2$ (0.8 mmol), and acetic anhydride (3 mL) in air. The tube was sealed and heated to 100 °C. The mixture was stirred at 100 °C until the color of the solution turned black, typically after 12−23 h. The reaction mixture was cooled to room temperature. The mixture was filtered through a short Celite pad, and the filtrate was concentrated under reduced pressure. The resulting mixture was purified by preparative TLC, typically using hexane/ethyl acetate/CH_2Cl_2 mixtures as the eluent, to give the acetate as a solid. The acetate was typically obtained as a single diastereomer (d.r. > 20:1), as evidenced by ^1H NMR and ^{13}C NMR.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization of new compounds. 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 interest.

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