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Peptide late-stage C(sp^3)–H arylation by native asparagine assistance without exogenous directing groups†

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There is a strong demand for novel native peptide motifs for post-synthetic modifications of peptides without pre-installation and subsequent removal of directing groups. Herein, we report an efficient method for peptide late-stage C(sp^3)–H arylations assisted by the unmodified side chain of asparagine (Asn) without any exogenous directing group. Thereby, site-selective arylations of C(sp^3)–H bonds at the N-terminus of di-, tri-, and tetrapeptides have been achieved. Likewise, we have constructed a key building block for accessing agouti-related protein (AGRP) active loop analogues in a concise manner.

Introduction

Peptides are increasingly important drug candidates, which are largely employed to treat metabolic disorders, cancer, allergy, and immune and cardiovascular diseases.[1] They also represent key tools that modulate biological events mediated by protein–protein interactions (PPIs).[2] Native peptides usually suffer from poor pharmacological features due to lack of structural diversity or enzymatic degradation,[3] but chemically modified non-natural peptides could feature higher binding affinities to the target, as well as improved pharmacokinetics, stability, and cell permeability.[4]

The late-stage modification represents an effective strategy to obtain structurally diverse peptides and peptidomimetics. Thus, late-stage modification methods of peptides have been achieved in terms of arylations,[5] alkylations,[6] and cycloadditions.[7] Over the past few years, C–H activation has been recognized as an atom- and step-economical pathway towards molecular syntheses,[8] with remarkable applications in materials science,[9] the agrochemical industry,[10] and drug discovery,[11] among others.[12] To the best of our knowledge, studies on late-stage functionalizations of peptides *via* C(sp^3)–H activation have been scarcely reported. In this context, Yu[13] successfully implemented C(sp^3)–H activation of peptides using native *N*,*O*- or *N*,*N*-bidentate coordination without external auxiliary (Fig. 1a). On a different note, Noisier/Albericio[14] reported the synthesis of a novel class of stapled peptides. Likewise, research studies of post-synthetic modification of peptides through C(sp^3)–H activation by installing exogenous auxiliary assistance have been pursued. In 2017, Ackermann[15] developed a strategy of triazole (Tzl)-assisted C(sp^3)–H arylations of peptides. In the same year, Chen[16] described 8-aminoquinoline (AQ)-directed C(sp^3)–H arylation to generate cyclophane-braced peptide macrocycles. Recently, Shi[17] established a palladium-catalyzed site selective γ-C(sp^3)–H silylation and δ-C(sp^3)–H alkylation of amino acids and peptides utilizing picolinamide (PA) auxiliary (Fig. 1b). The installation and subsequent removal of DGs often implies additional and non-trivial steps. Considering the atom- and step-economy of late-stage modification of peptides, we intended to utilize the natural amino acid embedded in the peptide backbone for chelation assistance. To our knowledge, C(sp^3)–H functionalizations of peptides assisted by the unmodified side chain of a natural amino acid has not been accomplished thus far.

Asn is a natural amino acid with a side chain bearing a primary amide and could potentially be exploited as a directing group. This prompts us to survey whether the side chain and backbone of Asn could coordinate with palladium, leading to a bidentate coordinated palladium complex. Therefore, we introduce Asn as an internal bidentate DG to accomplish C(sp^3)–H activation of peptides. Simultaneously, Asn is a common residue contained in many bioactive peptides, which display a range of biological activities, such as antioxidant activity,[18] blocking the neprilysin activity,[19] and inhibiting ACE activity.[20] Remarkably, Phe–Asn is an essential sequence that exists in some bioactive peptides, for example novel ACE inhibitory peptides,[21] anticancer peptides,[22] and AGRP.[23] Inspired by the significant work by Ackermann *et al.*,[15,24] we

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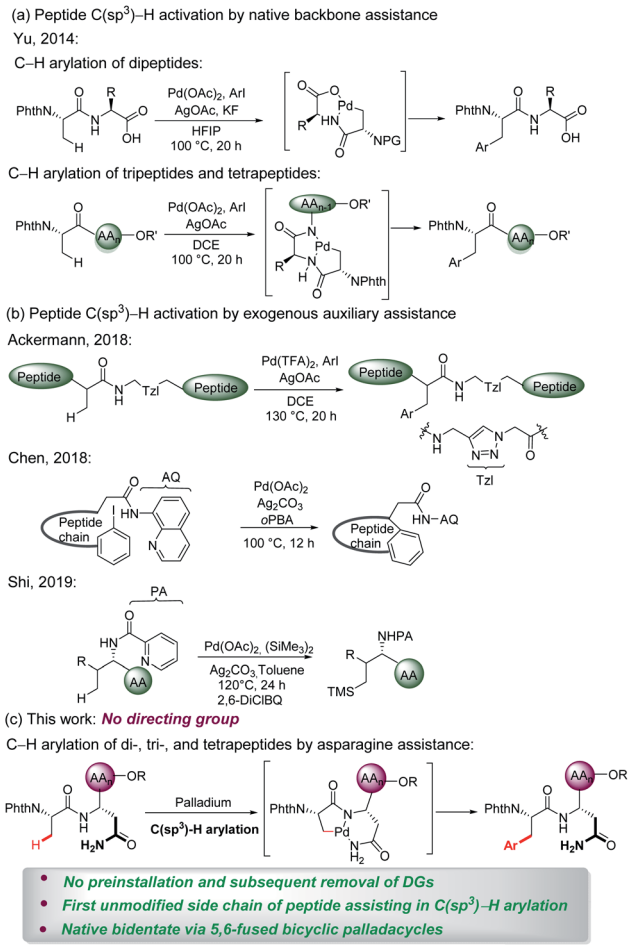


Fig. 1 Palladium-catalyzed C(sp^3)–H functionalization of peptides.

provide a useful strategy employing Asn as an internal directing group for C(sp^3)–H functionalization of peptides. The unmodified side chain of Asn combined with the backbone was utilized as the *N*,*N*- bidentate coordination *via* 5,6-fused bicyclic palladacycles (Fig. 1c) to perform the late-stage peptide C(sp^3)–H arylation.

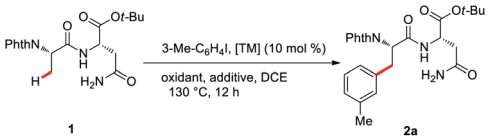
The complex has facilitated the inert C(sp^3)–H bond arylation in peptides. Thereby, arylated di-, tri-, and tetrapeptides containing Asn have been assembled. The salient features of our approach comprise (a) C(sp^3)–H activation of peptides assisted by a natural amino acid which circumvent the preinstallation and removal of DGs; (b) the first unmodified side chain of the natural amino acid as the endogenous auxiliary assistance applied in C(sp^3)–H activation; and (c) discovery of native bidentate assistance through less-strained 5,6-fused bicyclic palladacycles.[25]

Results and discussion

Optimization of reaction conditions

To validate our hypothesis, we initiated our studies by exploring reaction conditions for the palladium(II)-catalyzed primary C(sp^3)–H arylation of *N*-phthaloyl protected dipeptide **1** with 3-iodotoluene (Tables 1 and S1 in the ESI†). Initial optimization revealed DCE to be the best solvent of choice (Table S1,† entries 1–5), with KF being identified as the optimal additive (entries 1–3). By replacing $Pd(OAc)_2$ by $PdCl_2$ as the catalyst the yield of product **2a** was excitingly increased to 67% when the amount of AgOAc and KF was increased to 2.5 equivalent (entry 4). Notably, the reaction failed to proceed using AgOTf as the additive (entry 5), while $Cu(OAc)_2$ gave a dramatically decreased yield (entry 6). Encouraged by the good efficiency of $PdCl_2$, other palladium catalysts were further investigated. Gratifyingly, $Pd(MeCN)_2Cl_2$ was found to slightly improve the yield of peptide **2a** to 72% (entries 7–9). It is noteworthy that other metal catalysts, based on ruthenium, rhodium or cobalt, were ineffective (entries 10–12). The control experiment verified the essential role of the palladium catalyst (Table S1,† entry 20).

Table 1 Optimization of reaction conditions[a]



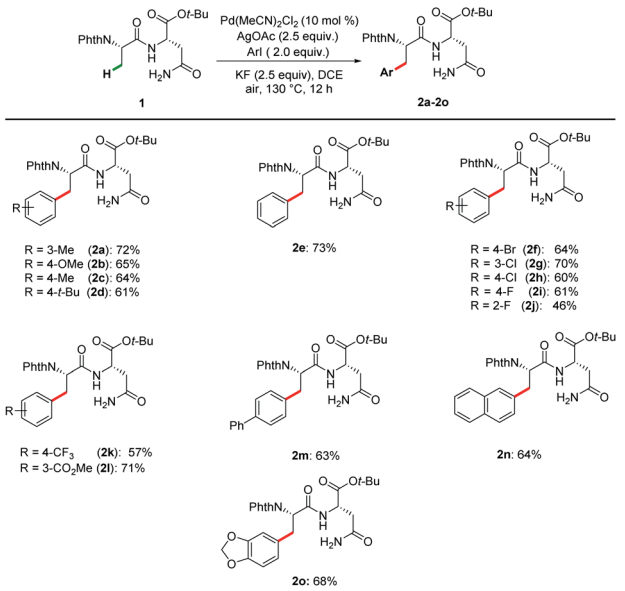
Entry	[TM]	Oxidant	Additives	Yield/%
1	$Pd(OAc)_2$	AgOAc	NaOAc	26
2	$Pd(OAc)_2$	AgOAc	Cs_2CO_3	Trace
3	$Pd(OAc)_2$	AgOAc	KF	41
4	$PdCl_2$	AgOAc	KF	67[b]
5	$PdCl_2$	AgOTf	KF	—[b]
6	$PdCl_2$	$Cu(OAc)_2$	KF	10[b]
7	$Pd(MeCN)_2Cl_2$	AgOAc	KF	72[b]
8	$Pd_2(dba)_3$	AgOAc	KF	36[b]
9	$Pd(PPh_3)_2Cl_2$	AgOAc	KF	35[b]
10	$[RuCl_2(p\text{-cymene})]_2$	AgOAc	KF	—[b]
11	$[Cp^*RhCl_2]_2$	AgOAc	KF	—[b]
12	$Co(OAc)_2 \cdot 4H_2O$	AgOAc	KF	—[b]

[a] Reaction conditions: **1** (0.20 mmol), 3-Me–C_6H_4I (0.40 mmol), oxidant (0.40 mmol), [TM] (10 mol%), additive (0.40 mmol), DCE (2.0 mL), 130 °C, 12 h, yields of isolated products. [b] Oxidant (0.50 mmol), additive (0.50 mmol).

Substrate scope

With the optimal reaction conditions in hand, the substrate scope of a range of aryl iodides was investigated, and the results are summarized in Scheme 1. Both substrates with electron-donating (Me–, MeO–, and *t*-Bu–) and electron-withdrawing (F–, Cl–, Br–, CF_3–, and CO_2Me–) groups reacted smoothly and afforded the desired products in good yields. Pleasingly, biphenyl and naphthyl moieties were also tolerated, leading to the corresponding products (**2m** and **2n**) in 63% and 64% yields. The reaction performed with good chemo-selectivity.

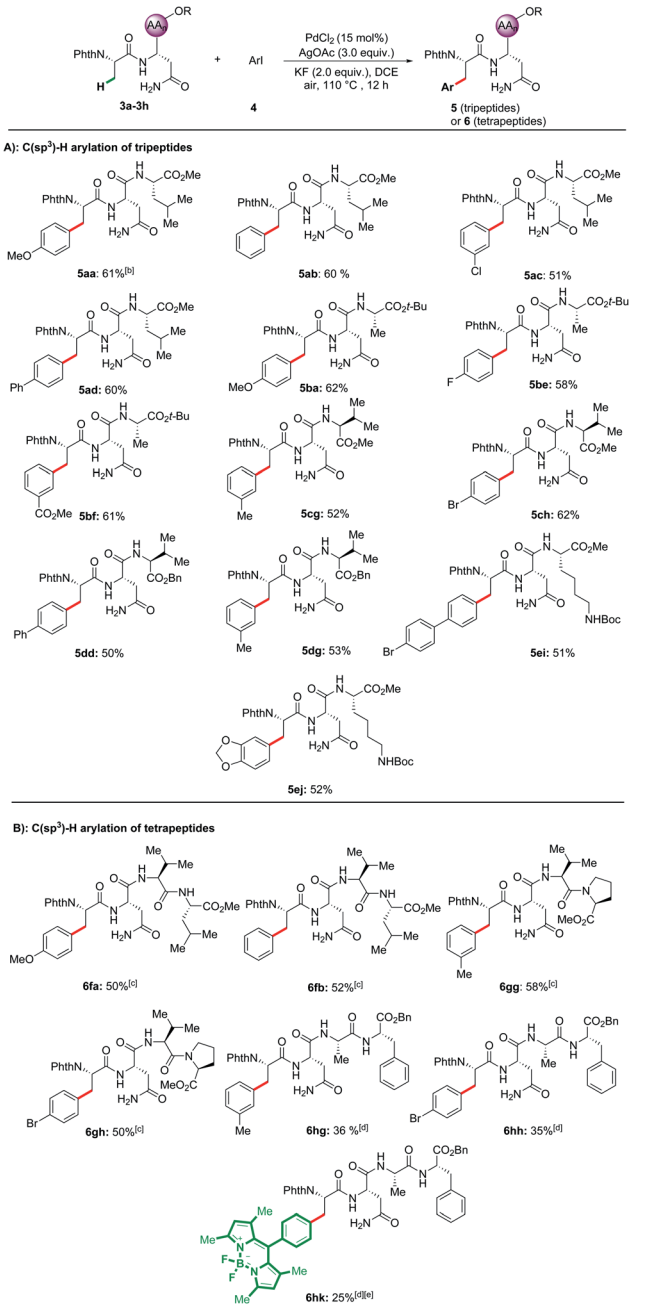
Encouraged by the success of the arylation of dipeptides, we next investigated the feasibility of applying this approach to the arylation of tripeptides and tetrapeptides (Scheme 2). Using tripeptide **3a** as the substrate, through minor adjustment of the reaction conditions (Table S2 in the ESI†), we were pleased to



Scheme 1 Scope of ArI C(sp^3)–H arylation of dipeptides. Reaction conditions: **1** (0.2 mmol), ArI (2.0 equiv.), $Pd(MeCN)_2Cl_2$ (10 mol%), AgOAc (2.5 equiv.), KF (2.5 equiv.), DCE (2.0 mL), 130 °C in air, 12 h, yields of isolated products.

find that the arylation of **3a** with 1-iodo-4-methoxybenzene **4a** could deliver the expected product **5aa** in 61% isolated yield. Then, the scope of substrates was evaluated under the optimized reaction conditions. Satisfyingly, a wide range of aliphatic amino acids, including Leu, Ala, Val, and Lys, at the C-terminus of the tripeptides are compatible with these conditions. In addition, aryl iodides bearing electron-donating as well as electron-withdrawing substituents were tolerated, affording products **5aa–5ej**. Given the feasibility of the tripeptide arylation, we expanded the peptide substrates to structurally complex tetrapeptides. The arylation products of tetrapeptides **6fa–6gh** could be obtained in moderate yields (50–58%). Phe-containing tetrapeptide **3h** could also be arylated albeit with lower yields (**6hg–6hk**, 25–36%). While considerable progress has been made in C(sp^3)–H activation,[26] our strategy enabled position-selective arylation of Ala assisted by *N*,*N*-bidentate coordination of the Asn in tri- and tetra-peptides.

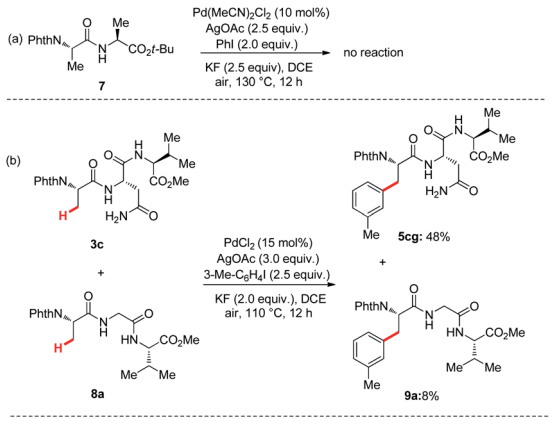
To further demonstrate that the reaction coordination site is the primary amide of Asn, the control reaction and competition reaction were investigated under the standard conditions (Scheme 3). First, we removed the Asn side chain of dipeptide **1** and replaced it with a methyl group, while retaining the *tert*-butyl ester of the dipeptide. Therefore, *N*-phthaloyl protected dipeptide **7** was independently prepared, and subjected to the optimized reaction conditions. It failed to afford arylated products of arylation of C(sp^3)–H bonds at the N-terminus (Scheme 3a). Since tripeptides or tetrapeptides both contain Asn bidentate and backbone amide bidentate, it is important to analyze the key role of Asn bidentate in promoting C(sp^3)–H functionalization. For the competition experiment between tripeptides **3c** and **8a**, product ratio of approximately (**5cg : 9a** = 6 : 1) (Scheme 3b) was obtained.



Scheme 2 Scope of C(sp^3)–H arylation of tripeptides and tetrapeptides. [a]Reaction conditions: **3** (0.2 mmol), ArI (2.5 equiv.), $PdCl_2$ (15 mol%), AgOAc (3.0 equiv.), KF (2.0 equiv.), DCE (3.0 mL), 110 °C in air, 12 h, yields of isolated products. [b]AgOAc (2.5 equiv.). [c]KF (1.0 equiv.) [d]120 °C, no base. [e]130 °C.

Mechanistic investigation

Additionally, we probed the catalyst mode of action by means of computational studies at the PW6B95-D4/def2-TZVP+SMD (DCE)//PBE0-D3BJ/def2-SVP level of theory (Fig. 2).[27] A detailed analysis between the C–H activation and reductive elimination elementary steps provided support for the C–H activation to be the rate-determining step with an activation energy of 19.6 kcal mol^{-1}, with oxidative addition being energetically more favorable by only 1 kcal mol^{-1}. An alternative pathway



Scheme 3 (a) Control experiment under the standard conditions. (b) Competition experiments under optimized conditions.

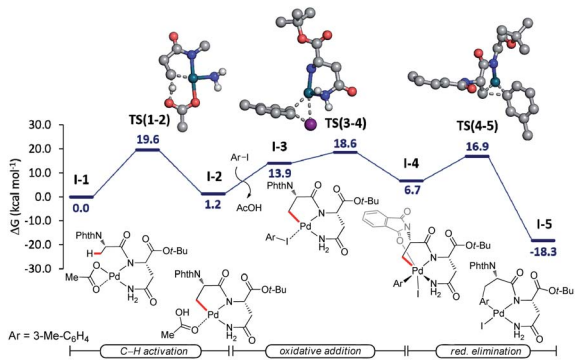
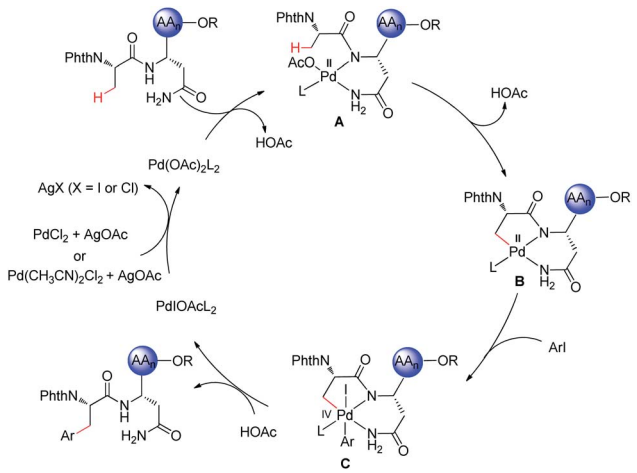


Fig. 2 Computed relative Gibbs free energies ($\Delta G_{403.15}$) in kcal mol^{-1} for palladium(II)-catalyzed C(sp^3)–H arylation at the PW6B95-D4/def-TZVP+SMD(DCE)//PBE0-D3BJ/def2-SVP level of theory. Non-relevant hydrogen atoms on the transition state structures were omitted for clarity.

where the NH_2 of the terminal amide is deprotonated was also taken into consideration (Fig. S1, see the ESI†). The latter was shown to be overall energetically disfavored, with reductive elimination as the rate-determining step with a high energy barrier of 30.9 kcal mol^{-1}. These studies provide strong support for the palladium-catalyzed C(sp^3)–H arylation to occur through a Pd(II/IV) pathway where the NH of the internal, instead of the terminal amide is deprotonated.

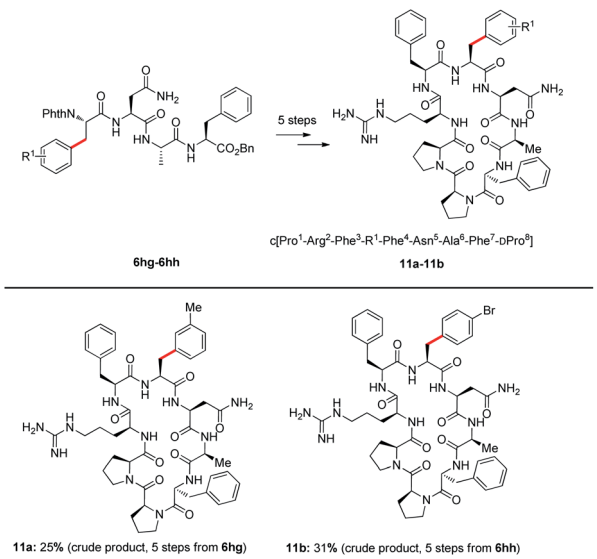
Based on previous reports on palladium-catalyzed amide-directed C–H bond activation and computational studies, we propose a plausible catalytic cycle to be initiated by a facile organometallic C–H activation (Scheme 4). Initially, the palladium catalyst coordinates covalently with the deprotonated NH of the internal amide generating a bidentate coordinated palladium(II) complex **A**. Subsequently, complex **A** undergoes slow C(sp^3)–H bond cleavage to form the 5,6-fused bicyclic palladium complex **B**. The oxidative addition of the aryl iodide to **B** affords palladium(IV) intermediate **C**, which then undergoes reductive elimination followed by protonation leading to the formation of the corresponding arylated product. The silver salt is proposed



Scheme 4 Proposed mechanism.

to accelerate the rate of the oxidative addition or the reductive elimination, while likewise acting as a halide scavenger.[8i,24a,28]

Agouti-related protein (AGRP) is a potent orexigenic peptide that antagonizes the melanocortin-3 and melanocortin-4 receptors (MC3R and MC4R).[29] This protein has been physiologically implicated in regulating food uptake, body weight control, and energy homeostasis.[30] In attempts to improve the antagonist activity and selectivity of AGRP active loop, previous studies have applied a substitution strategy to prepare AGRP active loop analogues.[31] The results have indicated that some substitutions of amino acid could increase potency of AGRP. However, the synthesis of AGRP loop analogues requires the introduction of modified unnatural amino acids. Some unnatural amino acids are expensive and difficult to synthesize, such as L-4,4′-biphenylalanine (Bip) and 3-(2-naphthyl)-L-alanine (Nal(2′)). Through C–H activation, the functional group could be installed directly into native peptides, such an approach is



Scheme 5 Synthesis of AGRP loop analogues, details see the ESI.†

highly efficient, step- and atom-economical. Thus, we attempted to apply our strategy to synthesize new AGRP loop analogues. The arylation products **6** through deprotection of phthaloyl (Phth) gave NH_2-free tetrapeptides **10** (details see the ESI†). Tetrapeptides **10a** and **10b** subsequently were coupled with Cbz–D-Pro–Pro–Arg(Pbf)–Phe–OH to obtain linear octapeptides, which were cyclized to access AGRP loop analogues. AGRP loop analogues **11a** and **11b** were obtained through this strategy (see the ESI† synthesis of AGRP loop analogues); the introduction of a bromide atom in **11b** potentially enables further late-stage derivatization of this peptide (Scheme 5).

Conclusion

In conclusion, we have developed an efficient strategy for palladium(II/IV)-catalyzed late-stage C(sp^3)–H arylations of peptides using unprecedented internal Asn. The protocol avoids the additional requirement for installation and removal of exogenous directing groups. Importantly, our approach has provided a novel synthetic route to access the key building block for the synthesis of AGRP loop analogues.

Conflicts of interest

There are no conflicts to declare.

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