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Site-Selective δ-C(sp³)–H Alkylation of Amino Acids and Peptides with Maleimides via a Six-Membered Palladacycle

Bei-Bei Zhan,[a] Ya Li,[a] Jing-Wen Xu,[a] Xing-Liang Nie,[a] Jun Fan,[a] Liang Jin,[a] and Bing-Feng Shi*[a,b]

Abstract: The site-selective functionalization of unactivated C(sp³)-H bonds remains one of the greatest challenges in organic synthesis. Herein, we report a site-selective δ-C(sp³)−H alkylation of amino acids and peptides with maleimides via a kinetically less favored six-membered palladacycle in the presence of more accessible γ-C(sp³)−H bonds. Experimental studies revealed that C-H bond cleavage occurs reversibly and preferentially at γ-methyl over δ-methyl C-H bonds, while the subsequent alkylation proceed exclusively at six-membered palladacycle that generated via δ-C-H activation. The selectivity can be explained by the Curtin-Hammett principle. The exceptional compatibility of this alkylation with various oligopeptides renders this protocol valuable for late-stage modification of peptides. Notably, this also represents the first Pd(II)-catalyzed Michael-type alkylation reaction via C(sp³)-H activation.

The direct functionalization of unactivated C(sp³)-H bonds offers new strategic approaches for the synthesis of useful molecular entities.[1] However, the realization of this promising strategy requires the ability to achieve the selective activation of a single aliphatic C-H bond among many others on the substrates, since C-H bonds are ubiquitous in organic molecules.[2] The introduction of a directing group that coordinates with palladium catalyst and facilitates the cleavage of a proximal C-H bond has become one of the most successful strategies. Typically, selective functionalization of γ-methyl C-H was favored over those of a C(sp³)-H bond at other positions (eg, γ-methylene and δ-methyl) through the preferencial formation of a kinetically favored five-membered palladacycle **INT-A** (Figure 1A, path a).[1] A fundamental challenge is whether an exclusively site-selective functionalization of δ-methyl C-H bonds in the presence of γ-methyl C-H bonds can be achieved via a kinetically less favored six-membered palladacycle?[3,4] The availability of such a strategy would enrich our toolkit for streamlining synthesis of complex molecules, particularly bioactive natural products and pharmaceutical targets.

Regardless of the detailed elementary reactions of the whole catalytic process, the selectivity for Pd-catalyzed C-H functionalization might arise from each of the following two steps or both: i) C-H activation to generate a palladacycle, and ii) functionalization of the resulting palladacycle (Figure 1A).[2a] Previous γ-selectivity resulted from the fast functionalization of kinetically favored **INT-A** (path a, the C-H activation step is the selectivity-determining step (SDS)), which was well established.[1] We reasoned that if the C-H activation step is reversible and the interconversion of **INT-A** and **INT-B** is significantly fast, the selectivity might originate from a Curtin-Hammett situation.[5] Thereafter, we assumed that under certain conditions, δ-selectivity could be achieved via the functionalization of **INT-B** if the functionalization of **INT-A** could not occur due to high energy barrier (Figure 1A, path b, the functionalization step is the SDS). Guided by this hypothesis, we have realized the first site-selective alkenylation of δ-methyl C−H bonds in the presence of more accessible γ-methyl C−H bonds by using picolinamide (PA) as the directing group.[4] Unfortunately, this proof-of-concept study was far from practical, due to the narrow substrate scope and low yields. Thus, it would be highly desirable to make this complementary site-selective protocol to be general for a broad range of densely functionalized substrates, such as peptides.

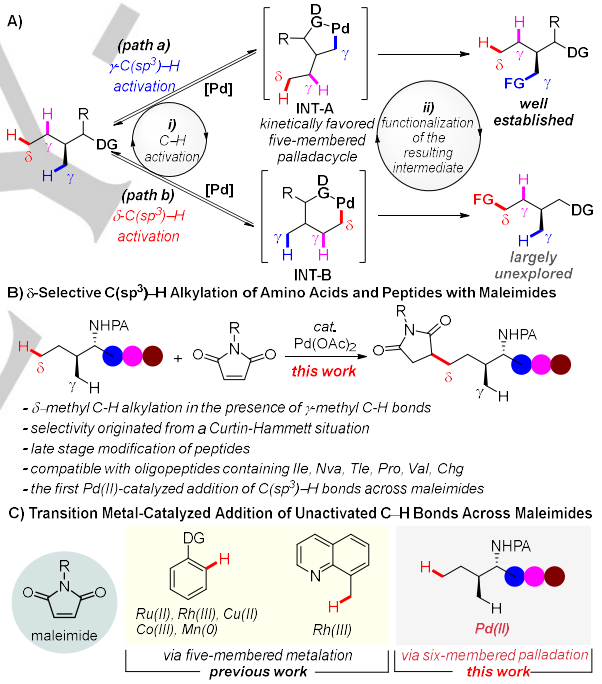

Figure 1. Pd-catalyzed site-selective C(sp³)−H functionalization

Peptides, being the building blocks of proteins and drug candidates, have attracted broad attention in biochemistry and pharmaceuticals.[6] On several occasions, unnatural peptides are found to shown enhanced biological activities and improved pharmacokinetic properties when compared to their natural counterparts.[7] Motivated by the need for postassembly peptide modification, it is highly desirable to develop new strategies which are capable of site-specific funcationalization of amino acids and peptides. Thus far, only scattered examples of site-selective C(sp³)−H functionalization of peptides have been achieved. [8,9] Yu reported the late-stage β-C(sp³)−H arylation[9a] and alkynylation[9b] at the N-terminal amino acid of short peptides by choosing peptide backbones as directing groups. Noisier and Albericio achieved the Pd-catalyzed C(sp³)-H

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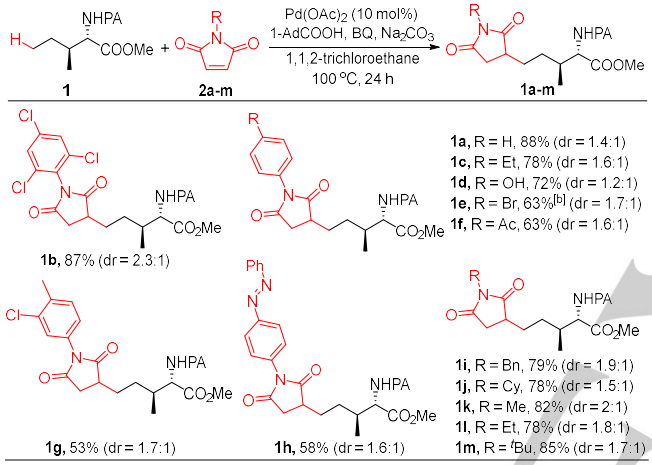
peptide macrocyclization based on Yu's backbone-enabled C(sp^3)-H activation.[10] Carretero and coworkers demonstrated the Pd-catalyzed γ-C(sp^3)-H carbonylation of amino acids and peptides.[11a] More recently, Ackermman developed a site-selective C(sp^3)−H arylation of amino acids and peptides by using internal 1,2,3-triazole moieties as directing group.[12] However, site-selective δ-C(sp^3)−H functionalization of peptides via a kinetically less favored six-membered palladacycle has not been realized. In continuation of our ongoing research on modification of amino acids via C(sp^3)−H functionalization,[4,13] herein, we report the first example of Pd-catalyzed site-selective δ-methyl C−H alkylation of amino acids and peptides with maleimides in the presence of more accessible γ-methyl C−H bonds (Figure 1B). It is worth noting that maleimides were frequently used in C-H alkylation catalyzed by Ru(II), Rh(III), Cu(II), Co(III), and Mn(0) complexes.[14] This reaction represents the first Pd(II)-catalyzed C(sp^3)-H alkylation with maleimides (Figure 1C).[15,16]

Table 1. The Scope of the Maleimides.[a]



[a] Reaction conditions: **1** (0.1 mmol, 1.0 equiv), maleimide **2** (2.5 equiv), $Pd(OAc)_2$ (10 mol %), 1-AdCOOH (0.2 equiv), BQ (0.3 equiv), Na_2CO_3 (2.0 equiv) in 1,1,2-trichloroethane (1 mL) at 100 °C for 24 h, isolated yields. Diastereomeric ratio was determinated by HPLC. [b] $Pd(OAc)_2$ (15 mol %).

We initiated our investigation by choosing picolinamide (PA) - protected isoleucine methyl ester **1** as the model substrate and N-phenylmaleimide **2a** as the alkylation reagent (Table S1).[17] Preliminary screenings led to the formation of δ-selective alkylation product **1a** in 44% yield (entry 2). The yield was slightly improved to 52% when 1,1,2-trichloroethane was used as solvent, probably due to its better solubility of catalyst and additives (entry 5). The subsequent investigation of additive led to an exciting finding that, benzoquinone (BQ) could promote the reaction, which may act both as a ligand and a co-oxidant (entry 7). **1a** was obtained in 75% yield when the amount of BQ was increased to 0.3 equivalent (entry 9). After further optimization, we finalized the conditions for the δ-selective alkylation of **1** with **2a** as follows: 10 mol% $Pd(OAc)_2$, 30 mol% BQ, 20 mol% 1-AdCOOH, 2.0 equiv Na_2CO_3, with 1,1,2-trichloroethane as solvent at 100 °C for 24 h (entry 10, 88%, dr = 1.4:1). Various directing groups were evaluated under the optimized conditions, the unmodified PA was found to be the optimal (Table S8). Other types of olefins were also tested, however, no alkylation products at either positions were detected (Table S9, see Supporting Information).

Having optimized the reaction conditions, we next turned to the evaluation of the scope of the maleimides (Table 1). In general, δ-selectivities were obtained exclusively in good to excellent yields under the optimized conditions. The phenyl, *N*-2,4,6-trichlorophenyl, *N*-4-ethylphenyl and *N*-4-hydroxyphenyl maleimides reacted smoothly with **1** to give the desired products in good to excellent yields (**1a**−**1d**, 72%−88%). Maleimides bearing *N*-4-bromophenyl, *N*-4-acetylphenyl and *N*-(3-chloro-4-methyl)phenyl groups were also compatible with this protocol, albeit in slightly lower yields (**1e**−**1f**, 53%−63%). We were pleased to find that *N*-4-phenyldiazenylphenyl maleimides **2h**, whose derivates can be used as bioprobes to control the enzyme activity of a bacterial histone[18] also react with **1** to afford the product **1h** in good yields. Eventually, the *N*-alkyl maleimides, including benzyl, cyclohexyl, methyl, ethyl, and *tert*-butyl, also displayed high reactivity to give the corresponding products in high yields (**1i**−**1m**, 78%−85%).

We further examined the scope of other amines (Table 2). Gratifyingly, other isoleucine derivatived esters, such as ethyl (**3**), benzyl (**4**), and allyl (**5**), were also viable, giving the desired products in good yields. Isoleucinols that masked by synthetically useful protecting group, such as acetyl (**6**), benzoyl (**7**), and benzyl (**8**) were also applicable with this reaction. γ-Arylated isoleucine derivative **9** reacted with **2a** to provide the desired site-specific alkylation product **9a** in 59% isolated yield.[17a] Moreover, γ-alkoxylated[17b] (**10** and **11**) and γ-alkylated[3c] (**12** and **13**) isoleucine derivatives also reacted smoothly with **2a** to furnish the δ-alkylation products in acceptable yields. *Notably, γ-arylated, γ-alkoxylated and γ-alkylated isoleucine derivatives (**9-13**) were all synthesized through γ-C(sp^3)-H functionalization of **1**,[3c,17] showcasing this protocol might be valuble for derivatization of α-amino acid via sequencial C(sp^3)-H functionalization.* In addition, the L-norvaline derivative **14** was also reactive (**14a**, 31%). The presence of another amide bond in isoleucine derivative didn't affect the reaction, affording the target product in moderate yield (**15a**, 40%; **16a**, 52%). These results were extremely attractive, since these kind of substrates were known to be incompatible with our previous δ-alkenylation reaction[4] due to the competing *N*,*N*-coordination.[9,10]

Encouraged by these results, we rationalized that the reaction conditions could also be amenable to peptides. To our delight, various dipeptides with an isoleucine at the *N*-terminus were well tolerated. As shown in Table 2, dipeptide with *L*-*tert*-leucine methyl ester at the *C*-terminus proceed smoothly to give **17a** in 62% yield in a mixture of 1,1,2,2-tetrachloroethane (TCE) and trifluoroethanol without adding any base. Moreover, dipeptides containing valine (**18**), proline (**19**) and isoleucine (**20**) reacted with **2a** to give the alkylated products **18a**-**20a** in slightly lower yields (36-45%). Dipeptide with norvaline at the *N*-terminus was also tolerated, albeit in low yield (**21a**, 28%).

The direct C(sp^3)-H functionalization of longer peptides would be more challenging because additional amide bonds in longer peptides could deactivate the palladium catalyst by the formation of a *N*,*N*-biscoordinating complex.[9] The robustness of this protocol was shown by the site-selective δ-alkylation of tri- and tetrapeptides (Table 2). Four representative tripeptides bearing *tert*-leucine, isoleucine, cyclohexylglycine, or proline residues reacted smoothly with **2a** under slightly modified conditions (**22a**−**25a**, 42%−47%). Remarkably, δ-alkylation of isoleucine at the *N*-terminus of tetrapeptides, as exemplified by **26** (Ile-Pro-Tle-Ala-OMe) and **27** (Ile-Pro-Tle-Val-OMe), also proceeded in reasonable yields (**26a**, 55%; **27a**, 48%). It was worth mentioning that the alkylation occurred exclusively at the δ-methyl C-H bond among all substrates listed above.

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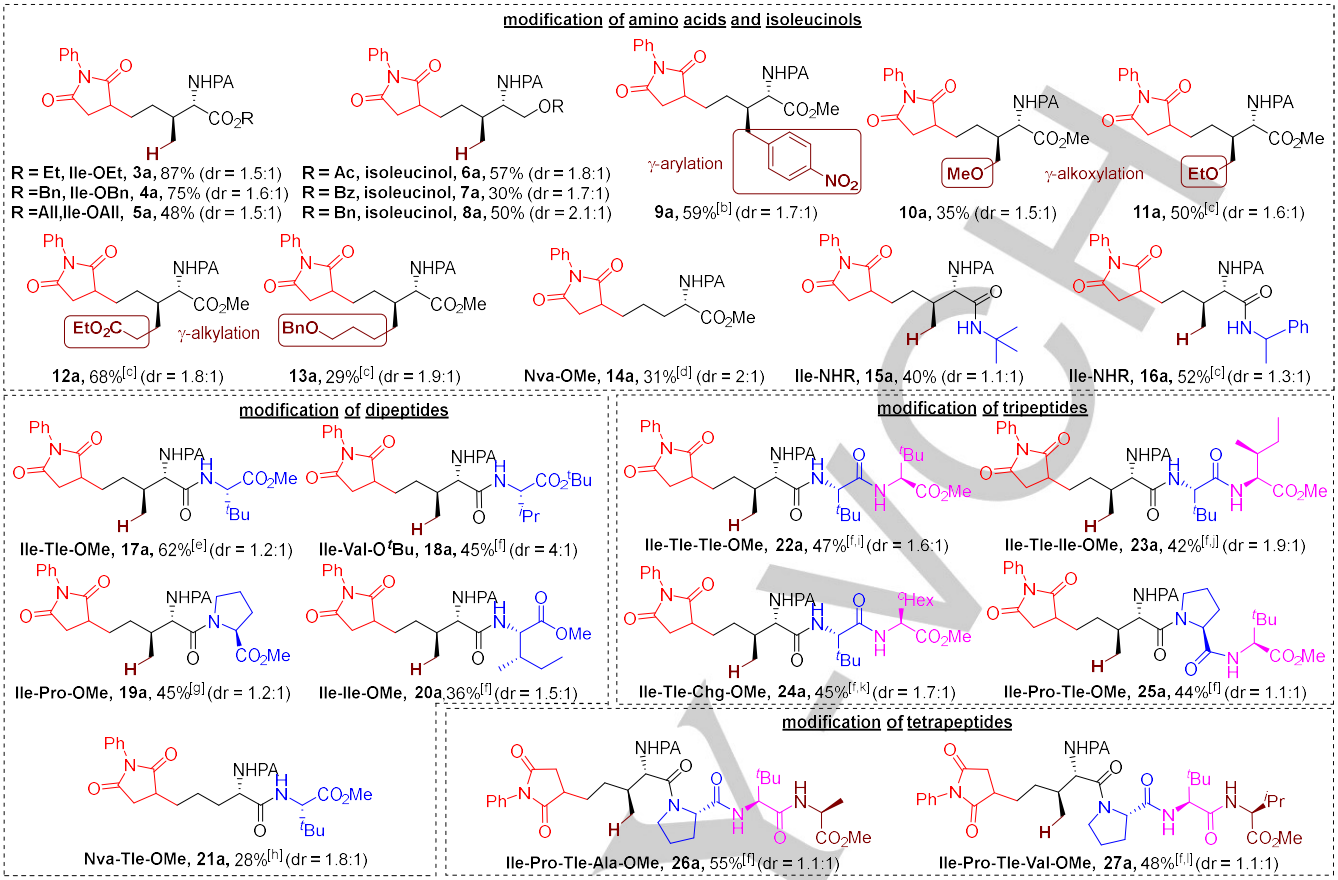
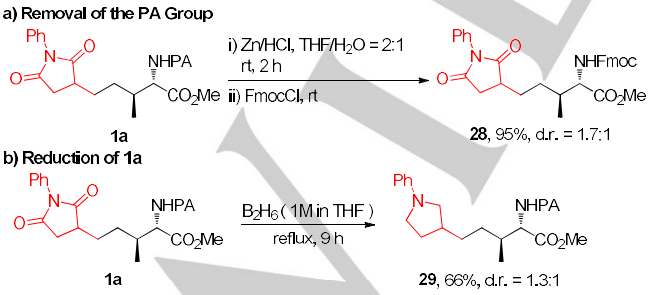
Table 2. The Scope of α-Amino Acids and Peptides. [a]



[a] Standard conditions, isolated yields. [b] PivOH (0.3 equiv) instead of 1-AdCOOH. [c] $Pd(OAc)_2$ (15 mol %),110 °C. [d] MesCOOH (0.2 equiv) instead of 1-AdCOOH, NaOAc (2.0 equiv) instead of Na_2CO_3, 110 °C. [e] $Pd(OAc)_2$ (15 mol %), TCE:TFE = 2:1 (1 mL) at 120 °C for 24 h. [f] $Pd(OAc)_2$ (15 mol %), 1-AdCOOH (0.3 equiv). [g] TCE as solvent. [h] TCE as solvent without Na_2CO_3. [i] 2, 5-DiPhBQ instead of BQ, *L*-Boc-Ser-OH (0.2 equiv) as additive, Na_2CO_3 (3.0 equiv). [j] Na_2HPO_4 (2.0 equiv) instead of Na_2CO_3, PivOH (0.3 equiv) instead of 1-AdCOOH. [k] Li_3PO_4 (2.0 equiv) instead of Na_2CO_3. [l] $NaHCO_3$ (2.0 equiv) instead of Na_2CO_3.

The easy removal of the PA group under mild conditions and further transformation of product were conducted to demonstrate the versatility of this reaction. The PA group was readily replaced with synthetically more useful protecting group Fmoc (fluorenylmethyloxycarbonyl) by treating **1a** with excess zinc in a mixture of THF and aqueous hydrochloric acid at room temperature and subsequent protecting with FmocCl (95% yield, Scheme 1a).[19] Reduction of **1a** using B_2H_6 gave tetrahydropyrrole **29** in 66% yield (Scheme 1b).

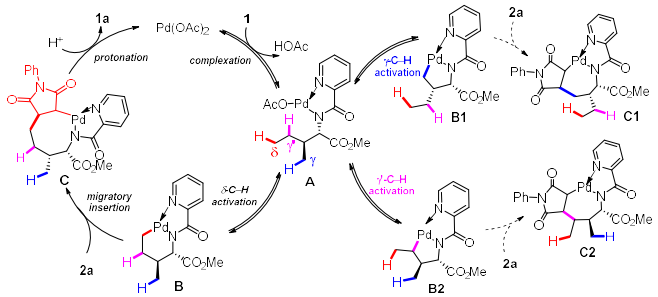


Scheme 1. Application of the Alkylation Reaction

To gain information on the origin of the selectivity, several H/D exchange experiments were conducted. Previous experimental studies indicated that both γ- and δ-methyl C-H activation steps are reversible.[3a,b,4] Consistent with these precedents, we also observed appreciable amounts of deuterium incorporation into γ-, and δ-C-H bonds of **1** under the standard conditions in the absence of **2a**, with a significant lower incorporation into the δ-position (Scheme S1a, γ, 57% D; δ, 29% D). In sharp contrast, only trace of deuterium incorporation into δ-C-H bonds was observed in the presence of **2a** (Scheme S1b, δ, <5% D; γ, 50% D). Furthermore, the reaction of PA-protected valine derivative **23** with **2a** resulted in significant deuteration of γ-C-H bonds (Scheme S1c, 62% D). However, no γ-alkylation product was detected. Similar results were observed form the isotope exchange study of L-2-aminobutyric acid derivative **24** (Scheme S1d). These results indicated that: 1) both γ- and δ-C-H activation is reversible with the cleavage of γ-C-H bonds favored under the reaction conditions; 2) the subsequent functionalization of δ-palladacycle **B** is significantly faster than the back reaction of the δ-C-H activation; 3) although γ-C-H activation is kinetically favored, the subsequent alkylation of γ-palladacycle **B1** couldn't occur. Overall, the selectivity can be explained by Curtin-Hammett principle.[5] Notably, only γ-arylated product **46** was observed when methyl 4-iodobenzoate was used as reactant instead of maleimide **2a** (Scheme S1f), suggesting that the δ-selectivity is resulted from the selectivity-determining migratory insertion of maleimides.[20]

On the basis of deuteration experiments and earlier precedents, a putative mechanistic pathway was proposed (Scheme 2).[4] Complexation of amide **1** with $Pd(OAc)_2$ affords a Pd(II) complex **A**, which could undergo reversible C-H cleavage to form the kinetically favored five-membered palladacycles (**B1** and **B2**, via γ-C−H activation) and the kinetically less favored six-membered palladacycles (**B**, via δ-C−H activation), which were proved by deuteration experiments. However, subsequent migratory insertion of palladacycles **B1** and **B2** with maleimide

2a to form **C1** and **C2** is less favored, while palladacycle **B** undergoes a fast migratory insertion with maleimide **2a** to form a eight-membered intermediate **C**, which undergoes protodemetalation to form the δ-alkylation product **1a** and regenerate $Pd(OAc)_2$.



Scheme 2. Proposed Mechanism for δ-Selective C–H Alkylation

In conclusion, the first site-selective δ-C(sp^3)−H alkylation of amino acids and peptides with maleimides via a kinetically less favored six-membered palladacycle in the presence of more accessible γ-C(sp^3)−H bonds was reported. The exceptional compatibility with various oligopeptides and the facile removal of the PA group renders this protocol valuable for late-stage modification of peptides. Notably, this also represents the first Pd(II)-catalyzed Michael-type alkylation reaction via C(sp^3)-H activation. Experimental studies indicated that the selectivity originated from a Curtin-Hammett situation. We anticipate that this new mode of selectivity might offer a unique opportunity for reaction development.

Acknowledgements

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Keywords: Site-selective • alkylation • six-membered palladacycle • peptides • palladium

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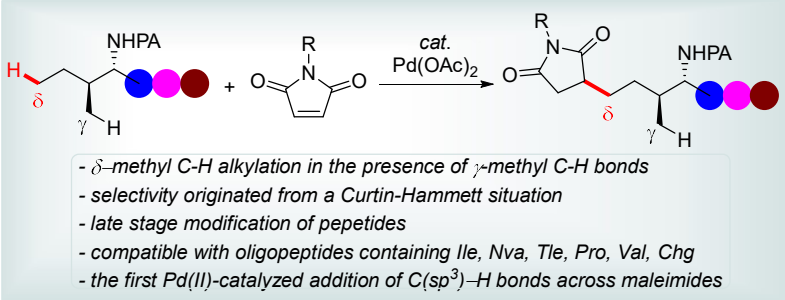

Site-selective δ-C(sp^3)−H alkylation of amino acids and peptides with maleimides via a kinetically less favored six-membered palladacycle in the presence of more accessible γ-C(sp^3)−H bonds was reported. Experimental studies revealed that C-H bond cleavage occurs reversibly and preferentially at γ-methyl over δ-methyl C-H bonds, while the subsequent alkylation procced exclusively at six-membered palladacycle that generated via δ-C-H activation. The selectivity can be explained by the Curtin-Hammett principle. The exceptional compatibility of this alkylation with various oligopeptides renders this protocol valuable for late-stage modification of peptides. Notably, this also represents the first Pd(II)-catalyzed Michael-type alkylation reaction via C(sp^3)-H activation.

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Site-Selective δ-C(sp^3)−H Alkylation of α-Amino Acids and Peptides with Maleimides via a Six-Membered Palladacycle