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Site-Selective Alkenylation of δ-C(sp^3)−H Bonds with Alkynes via a Six-Membered Palladacycle

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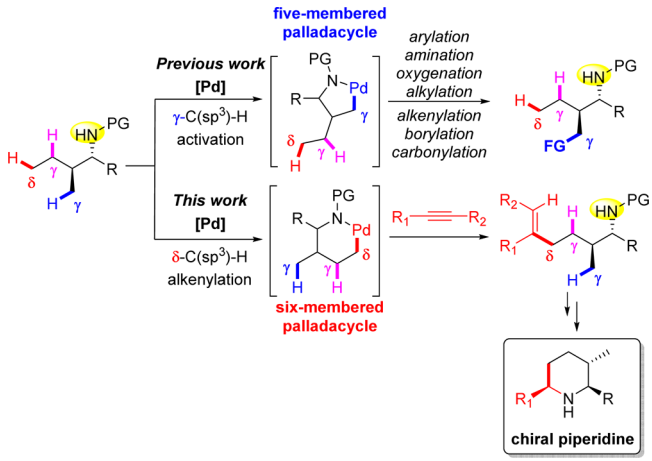
Supporting Information

ABSTRACT: Most chelation-assisted aliphatic C−H activation proceeds through a kinetically favored five-membered cyclometalated intermediate. Here, we report the first site-selective alkenylation of δ-C(sp^3)−H in the presence of more accessible γ-C(sp^3)−H bonds via a kinetically less favored six-membered palladacycle. A wide range of functional groups are tolerated, and the unique protocol can be applied to the synthesis of chiral piperidines. Moreover, mechanistic insights have been conducted to elucidate the origin of the unusual site-selectivity.

Site-selective functionalization of unactivated aliphatic C−H bonds remains a fundamental and ongoing challenge in organic chemistry.[1] One of the most successful strategies to achieve the site-selectivity is the use of directing groups. In particular, various amine-derived directing groups, such as amides, sulfonamides, and carbamates, have been developed to enable the site-selective functionalization of aliphatic amines because amines are ubiquitous in biologically important compounds and building blocks in organic synthesis.[2] Most of these reactions proceed through a kinetically favored five-membered palladacycle over other cyclopalladation ways, leading to the selective cleavage of γ-C(sp^3)−H bonds.[2] To this end, palladium-catalyzed directed arylation,[2] amination,[3] oxygenation,[2i,3a,4] alkylation,[5] alkenylation,[2c,6] borylation,[7] and carbonylation[2i,8] of γ-C(sp^3)−H bonds have been extensively investigated and reported (Scheme 1). In contrast, only scattered examples of δ-C(sp^3)−H functionalizations through a six-membered palladacycle have been achieved when the γ-C(sp^3)−H bonds were sterically or conformationally less accessible.[3b,5,9] Directed functionalization of δ-methyl C−H bonds in the presence of γ-methyl C−H bonds has never been realized. As part of our ongoing program dedicated to site-selective functionalization of unactivated C(sp^3)−H bonds,[10] we were interested in addressing this challenge.

In recent years, transition-metal-catalyzed (hetero)aryl C-(sp^2)−H alkenylation with alkynes has been well-developed.[11] However, alkenylation of C(sp^3)−H bonds with alkynes is still rare.[12,13] In 2014, Wang et al. reported the first Rh-catalyzed C(sp^3)−H alkenylation of 8-methylquinolines with alkynes.[12a] In 2015, the You group[13a] and the Maiti group[13b] independently developed the nickel-catalyzed C(sp^3)−H alkenylation with alkynes. Nevertheless, both reactions required high temperature (140 or 170 °C) and excess amide substrates. The addition products of alkynes have moderate ratios of *Z*/*E*. Herein, we report the first palladium-catalyzed site-selective alkenylation of δ-C(sp^3)−H in the presence of more accessible γ-C(sp^3)−H. The protocol has been successfully applied to the synthesis of chiral piperidines, which are widely found in bioactive natural products such as indolizidine and quinolizidine alkaloids.

Scheme 1. Pd-Catalyzed Site-Selective C(sp^3)−H Functionalization of Aliphatic Amines



At the outset of our studies, we chose picolinamide (PA)-protected isoleucine methyl ester **1** as the model substrate and diphenylacetylene **2a** as the alkenylation reagent. The δ-selective alkenylation product **1a** was obtained in 66% isolated yield with 15 mol % of Pd(OAc)$_2$, 20 mol % of 2,6-dimethylbenzoquinone (2,6-DMBQ), 1.2 equiv of diphenylacetylene **2a**, 1.0 equiv of $NaHCO_3$, and 3.0 equiv of LiF in a mixture of 1,1,2,2-tetrachloroethane (TCE) and hexafluoroisopropanol (HFIP) at 100 °C for 18 h under O_2 atmosphere (Table 1, entry 1), and starting material **1** was recovered in 28% yield. Control experiments showed that no alkenylation product was observed in the absence of the palladium catalyst (entry 2). The yield was significantly reduced in the absence of $NaHCO_3$ (entry 3). The reaction proceeded more effectively under O_2 atmosphere (entries 5 and 6), and the addition of silver salts decreased the yield (entry 7, 44%). DMBQ was found to promote the reaction, probably acting both as a ligand and as a co-oxidant (entry 8), while 1,4-benzoquinone (BQ) only slightly improved the yield (entry 9). The yield was reduced to 44% in the absence of HFIP (entry 10), and no desired product was observed when HFIP was replaced with ^{i}PrOH, which could improve the yield in nickel-

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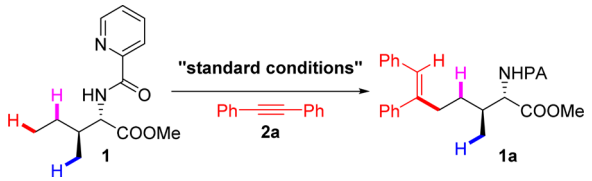
Table 1. Optimization of Site-Selective δ-C(sp³)−H Alkenylation[a]



entry	deviation from standard conditions	yield (%)[b]
1	none	66[c]
2	no $Pd(OAc)_2$	0
3	no $NaHCO_3$	31
4	no LiF	56
5	N_2 instead of O_2	43
6	air instead of O_2	49
7	add 0.1 equiv Ag_2CO_3	44
8	no 2,6-DMBQ	50
9	BQ instead of 2,6-DMBQ	55
10	no HFIP	44
11	^{i}PrOH instead of HFIP	0

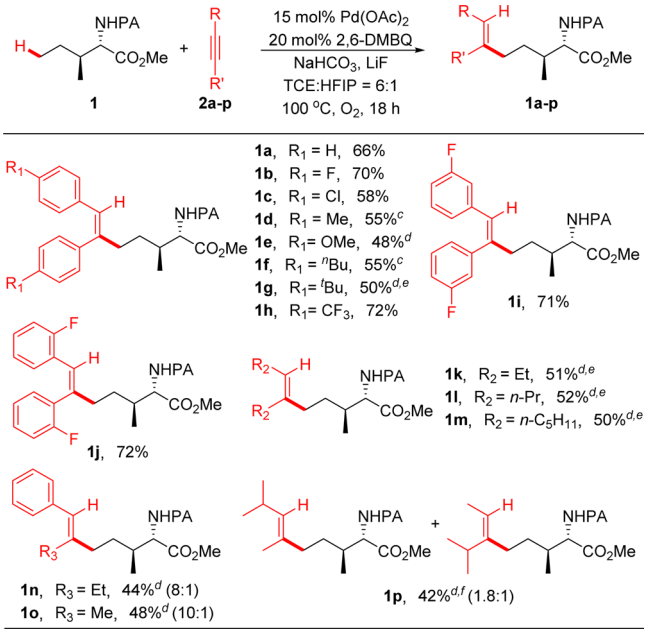
[a]Standard conditions: **1** (0.1 mmol, 1.0 equiv), alkyne **2a** (1.2 equiv), $Pd(OAc)_2$ (15 mol %), 2,6-DMBQ (0.2 equiv), $NaHCO_3$ (1.0 equiv), and LiF (3.0 equiv) in TCE (0.6 mL) and HFIP (0.1 mL) at 100 °C under O_2 for 18 h. [b]^{1}H NMR yield using CH_2Br_2 as the internal standard. [c]Isolated yield.

catalyzed alkenylation of C(sp³)−H bonds with alkynes (entry 11).[13a] Finally, we also evaluated the influence of different protecting groups under the standard conditions, including various PA-based protecting groups and other reported amide-type directing groups.[2d−h,3a,8b] As a result, PA was found to be the optimal directing group (see Supporting Information).

With the optimized reaction conditions in hand, we next evaluated the scope of alkynes (Table 2). Both the symmetrical alkynes (**2a**−**m**) and unsymmetrical alkynes (**2n**−**p**) were tested for the reaction. In general, diarylacetylenes bearing both electron-donating groups (**2d**−**g**) and an electron-withdrawing group (**2h**) were compatible with this reaction. Halogen-substituted diarylacetylenes (*p*-F, **2b**; *m*-F, **2i**; *o*-F, **2j**; and *p*-Cl, **2c**) were well-tolerated, giving the desired alkenylation products in good yields. It was found that the coordination property of the alkynes had an effect on the reaction. We were pleased to find that dialkylacetylenes also reacted with **1** to afford the desired products in moderate yields. Symmetrical alkynes, such as 3-hexyne (**2k**), 4-octyne (**2l**), and 6-dodecyne (**2m**), could furnish the alkenylation products in moderate yields (50−52%). When unsymmetrical alkynes were used, the alkenylation products (**1n**, **1o**, and **1p**) were also obtained, albeit giving a mixture of regioisomers.

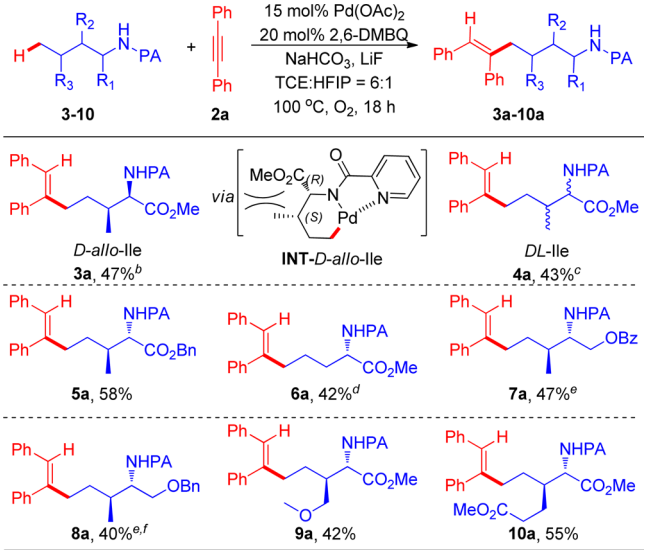
The scope of aliphatic amines was next explored using diphenylacetylene **2a** as the alkenylation reagent (Table 3). δ-Alkenylation of L-Ile **1** afforded the desired product **1a** in 66% yield; while D-*allo*-Ile derivative **3** and DL-Ile derivative **4** gave reduced yields (**3a**, 47%; **4a**, 43%). We reasoned that the stereochemistry of isoleucine derivatives could have a significant influence on the reactivity, due to the unfavorable sterics in palladacycle **INT**-D-*allo*-Ile. Benzyl ester of Ile **5** also reacted smoothly to give **5a** in 58% yield. The L-norvaline derivative **6** was also reactive, albeit in low yield (**6a**, 42%). Benzoyl-protected and benzyl-protected amino alcohols (**7** and **8**) were also compatible with this reaction. Aliphatic amines bearing γ-methoxy (**9**) and δ′-ester (**10**) could also react with **2a** to provide

Table 2. Substrate Scope of the Alkynes[a,b]



[a]Standard conditions. [b]Isolated yields. The values in parentheses indicate ratios of the regioisomers that were determined by ^{1}H NMR. [c]$Pd(OAc)_2$ (20 mol %). [d]$Pd(OAc)_2$ (20 mol %), alkynes (2.0 equiv), 2-Me-BQ instead of 2,6-DMBQ. [e]2,5-di-Cl-BQ instead of 2-Me-BQ. [f]2-Cl-BQ instead of 2-Me-BQ.

Table 3. Substrate Scope of Aliphatic Amines[a]



[a]Standard conditions. Isolated yields. [b]2,5-di-Cl-BQ instead of 2,6-DMBQ. [c]A mixture of two stereoisomers; 2-Cl-BQ instead of 2,6-DMBQ. [d]$Pd(OAc)_2$ (20 mol %), alkynes (2.0 equiv), 2,5-di-Ph-BQ instead of 2,6-DMBQ, NaOAc instead of $NaHCO_3$, 120 °C. [e]$Pd(OAc)_2$ (20 mol %), alkynes (2.0 equiv), 2,2,2-trifluoroethanol instead of HFIP. [f]2,6-di-Cl-BQ instead of 2,6-DMBQ.

the desired δ-alkenylation products (**9a**, 42%; **10a**, 55%). It is noteworthy that no γ-alkenylated products were observed among all substrates listed above.

To highlight the synthetic utility of the site-selective δ-C(sp³)−H alkenylation, further elaboration of the alkenylation product was conducted. As demonstrated in Scheme 2, **1a** could be hydrogenated to give the alkylated product **11** in 95% yield.

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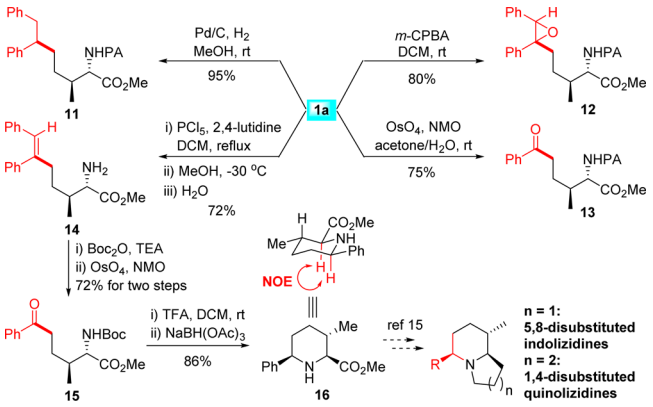
Scheme 2. Application of the Alkenylation Reaction



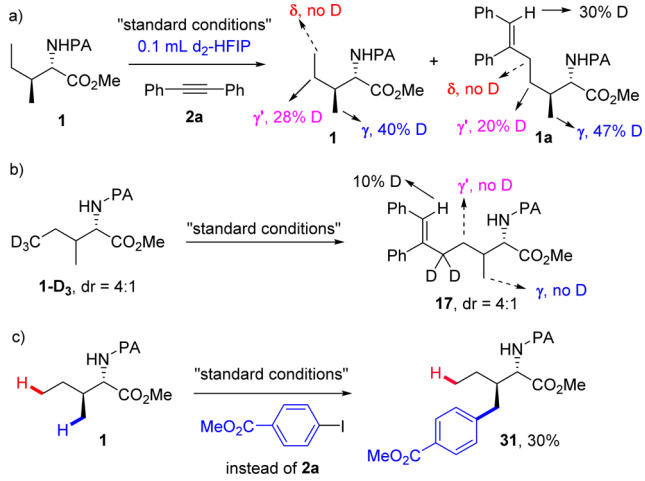
Epoxide **12** was obtained in 80% yield when **1a** was treated with *m*-CPBA. Interestingly, the double bond of **1a** could be over-oxidized to produce the ketone **13** in 75% yield by employing the dihydroxylation method.

Removal of the PA group under mild conditions with good functionality tolerance is crucial for the synthetic application of this reaction. After extensive investigations, we found that the PA group could be easily removed from **1a** by the treatment with PCl_5/2,4-lutidine, followed by conversion of imidoyl chloride intermediate to the imino ether with MeOH. Subsequent aqueous workup gave the free amine **14** in 72% yield.[14] We anticipated that this three-step, one-pot protocol could be generally applied to the removal of PA group after C−H functionalizations. Ketone **15** was obtained by the protection of amine with Boc_2O, followed by oxidative cleavage of the double bonds. After removal of the Boc group and subsequent reductive amination, chiral piperidine **16** was afforded in 86% yield as a single stereoisomer, as evidenced by ^{1}H NMR NOE analysis. The chiral piperidine could be further elaborated to the synthesis of bioactive 5,8-disubstituted indolizidines[15a] and 1,4-disubstituted quinolizidines,[15b] which were found in *Dendrobates* alkaloids.

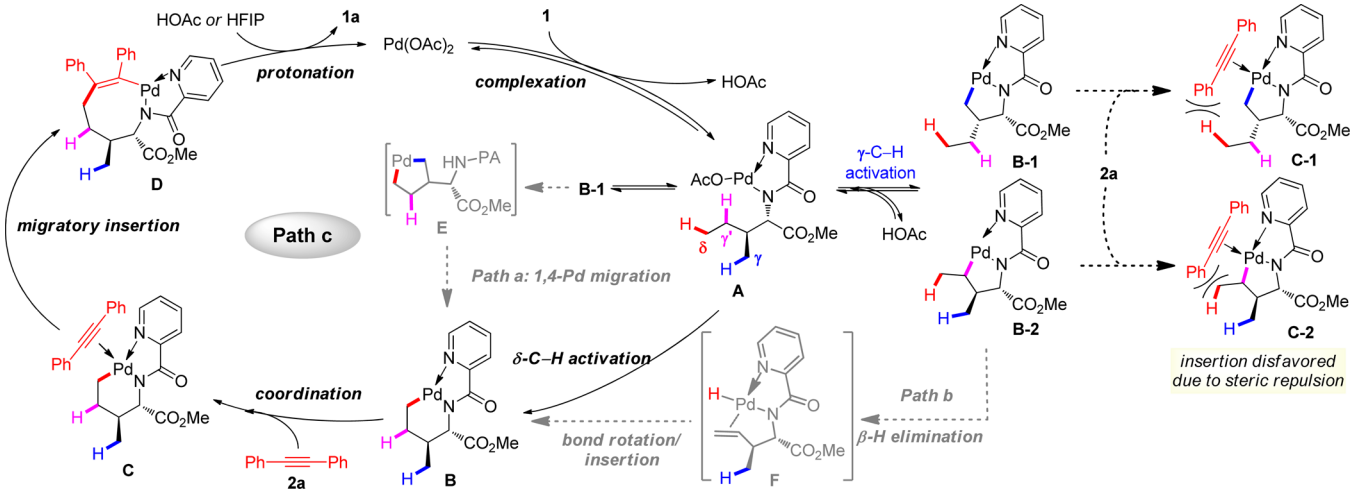
The possible mechanism of this protocol was proposed as shown in Scheme 3. First, complexation of amide **1** with $Pd(OAc)_2$ using the PA group forms a Pd(II) complex **A**. Conventionally, the kinetically favored five-membered palladacycles (**B-1** and **B-2**, via γ-C−H activation) and the kinetically less favored six-membered palladacycle (**B**, via δ-C−H activation) could be generated. Previously, it was observed that both γ- and δ-C−H activation steps are reversible based on the deuteration experiments.[3b,9a] Consistent with these observation, we also found that the cleavage of γ-C−H bonds was reversible under our standard conditions. However, no deuterium incorporation at the δ-position was observed in the presence of alkyne **2a** (Scheme 4a). These results suggested that either δ-C−H activation was irreversible or the migratory insertion of alkyne was significantly faster than the back reaction of the C−H activation step.[16] These observations could be explained by the Curtin−Hammett principle[17] that, due to steric repulsion, it is less favored for palladacycles **C-1** and **C-2** to undergo migratory insertion to lead to the seven-membered complex, while the migratory insertion of **C** to form a unique eight-membered intermediate **D** is a fast and favored process. Finally, intermediate **D** was protonated by HOAc or HFIP to give the δ-alkenylation product **1a**, and $Pd(OAc)_2$ was regenerated to finish a catalytic cycle (path c).

Alternatively, the reaction could also proceed through the generation of palladacycle **E** by 1,4-palladium migration[18] of palladacycle **B-1** (path a). A third possible pathway involves β-H elimination of palladacycle **B-2**, followed by bond rotation/

Scheme 4. Deuteration Experiments



Scheme 3. Proposed Mechanism for δ-Selective C−H Alkenylation



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insertion to form six-membered palladacycle **B** (path b).[19] These two pathways were readily investigated by subjection of δ-deuterated substrate **1-D$_3$** to the standard reaction conditions. Analysis by ^{1}H NMR showed no deuterium incorporation in both γ-methyl and γ′-methylene (Scheme 4b). These observations strongly argue against path a and path b. Therefore, on the basis of these deuteration experiments and our rationale, we tend to favor path c. It is worth noting that the unusual δ-selectivity is linked to the use of alkyne reactant via a selectivity-determining migratory insertion since only γ-arylated product **31** was obtained when methyl 4-iodobenzoate was used as coupling partner instead of alkyne **2a** (Scheme 4c, 30% yield).

In summary, we have developed a Pd-catalyzed site-selective δ-C(sp^3)−H alkenylation of aliphatic amines with internal alkynes. This unique reaction regioselectively occurs at δ-methyl rather than the more accessible γ-methyl position through a kinetically less favored six-membered palladacycle. Further studies toward the application of this novel strategy to other kinds of substrates are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05978.

Experimental procedures, spectra data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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