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Article

Simplifying the Synthesis of Nonproteinogenic Amino Acids via Palladium-Catalyzed δ-Methyl C−H Olefination of Aliphatic Amines and Amino Acids

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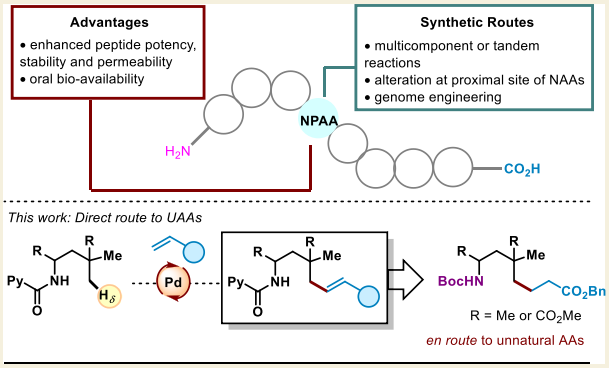
ABSTRACT: Transition metal-catalyzed directing group assisted C−H functionalizations provide a straightforward access to a wide variety of nonproteinogenic amino acids. While altering the side chain of an existing natural amino acids is one way, introducing a functional group to an aliphatic amine to synthesize versatile unnatural amino acids is another exciting avenue. In this work, we explore both the possibilities by the palladium-catalyzed δ-C(sp^3)−H olefination of aliphatic amines and amino acids. A diverse substrate scope including sequential difunctionalizations followed by post synthetic transformations were achieved to understand the applicability of the current protocol. An in-depth mechanistic study was carried out to learn the mode of the reaction pathway.



KEYWORDS: *C−H activation, non proteinogenic amino acids, palladium catalysis, δ-C(sp^3)−H olefination, aliphatic amines*

1. INTRODUCTION

Amino acids (AAs), being the fundamental component of peptides, have significantly influenced the entire fraternity of modern drug discovery.[1] High site selectivity and facile synthesis of peptides make them alluring drug candidates. While native amino acids (NAAs) contribute most in the structural diversity of the peptides, their inadequate bioavailability and brief circulating plasma half-life impede their use as therapeutics and often demand further structural tuning. To surpass this issue, substantial efforts have been devoted in the last few decades to expand the genetic code by selectively incorporating several functional groups into NAAs. These analogues of NAAs or popularly known as "unnatural" or "nonproteinogenic" amino acids (NPAAs) offer a wave of appealing applications in drug discovery.[2,3] However, unlike the NAAs, most NPAA analogues must be synthesized by means of chemical or enzymatic pathways.[4−7] While biologists have their own tricks to synthesize these unnatural amino acids,[8,9] alkylation of amino acid side chain is the most appreciated methodology so far. Although multicomponent or tandem reactions proceeding via highly reactive intermediates seem to be the most approachable route, often they suffer from multiple synthetic steps, low productivity, and poor stereoselectivity. In this context, transition metal-catalyzed C−H functionalization can offer a simple and straightforward solution.[10−19] Particularly, palladium-catalyzed α-, β-, and γ-C(sp^3)−H functionalizations of different proteinogenic αAAs have come up as a very powerful tool in the last 10 years.[20−35]

Very recently, our group has explored arylation[32] and borylation[33] at the distal δ- position of leucine. In 2021, Carretero and co-workers also demonstrated δ-arylation of different γ-unblocked αAA derivatives using a sulfonamide linker.[34]

However, all such transformations to produce NPAAs are achieved by incorporating different functional groups in the side chain of an existing αAA. While this could be one exciting way out for synthesizing NPAAs, introducing a new functional group with a free ester or acid to a simple aliphatic amine can overall lead to a novel NPAA itself on the contrary (Figure 1). In a stark contrast to aromatic C(sp^2)−H olefination,[36] distal C(sp^3)-H olefination is still an underexplored territory due to its intrinsic problem[37−39] and is mostly restricted to aliphatic acids as substrates.[40−44] Although in 2016 Shi and co-workers reported δ-alkenylation of leucine and its derivatives, internal alkynes were used as the source of olefin.[35] While olefins are widely used in cycloaddition chemistry,[45−48] distal aliphatic olefination possess two-fold issues: (i) requirement of six-membered metallacycle overriding thermodynamically stable five membered cycle[49] and (ii) postsynthetic easy cyclization in

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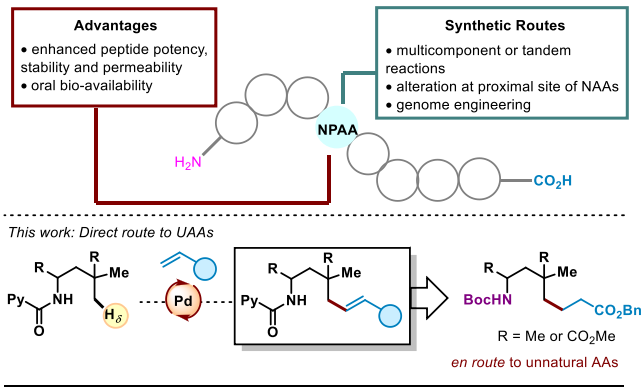

Figure 1. Direct access to NPAAs.

the presence of a more nucleophilic directing group which eventually diminishes the versatility of the olefin group inserted.[50]

In this work, we report a novel route to synthesize an array of long chain NPAAs by means of direct δ-C(sp^3)−H olefination of aliphatic amines with acrylic acid derivatives in the presence of pyridone/quinoline-based ligands. Interestingly, direct olefination of leucine further expands the scope to generate a new set of NPAAs.

2. RESULTS AND DISCUSSION

To materialize our hypothesis of synthesizing NPAAs, feasibility of palladium-catalyzed ligand-enabled δ-C(sp^3)−H olefination of the methyl ester of leucine **1a** was studied. We commenced with studying the extraordinary effect of substituted pyridone, pyridine, and quinoline based ligands in site-selective distal C(sp^3)−H functionalizations (Figure 2).[51−53] It is prevalent from the literature that substituted pyridones or 2-hydroxy pyridines (X-type ligands) can effectively coordinate with the palladium catalyst and make the C−H bond activation step quite facile by lowering the energy barrier of that particular step.[53] Studies indicate that the formation of Pd-ligand dimer complexes in the case of pyridone ligands is quite feasible due to a $\pi-\pi$ stacking interaction between two pyridone ligands which enables a thermodynamically stable Pd-ligand system in the first place. Interestingly, the efficacy of such ligands further enhances when there is a strong electron-withdrawing group (such as $-NO_2$ or $-CF_3$) present at the 3- or sometimes 3,5- positions of pyridones. As the major focus of this optimization study was achieving high δ-selectivity with a synthetically useful yield, we were pleased to find 3-nitro-2(1H)-pyridone (**L8**) as the best ligand to attain an exclusive δ-selectivity over an equally accessible γ-C(sp^3)−H bond in substrate **1a**. After carefully scrutinizing other reaction parameters, it was found that the use of 10 mol % $Pd(OPiv)_2$ and 20 mol % **L8** along with 2 equiv of CF_3CO_2Na and 2.5 equiv of Ag_2CO_3 as oxidant in DCE at 110 °C provided 51% yield of product **2a** (Figure 2). In this context, it is also worth mentioning that the use of both $Pd(OPiv)_2$ and CF_3CO_2Na were found immensely crucial for the increase of the yield compared to other Pd catalysts and metal salts. Since the use of mono *N*-protected amino acid (MPAA) ligands is quite well investigated in palladium-catalyzed C−H activation reactions,[54−56] we studied several MPAAs (see Supporting Information section S6) to improve the yield of the δ-alkenylated product **2a**. However, none of them could outperform **L8**. Finally, several directing groups

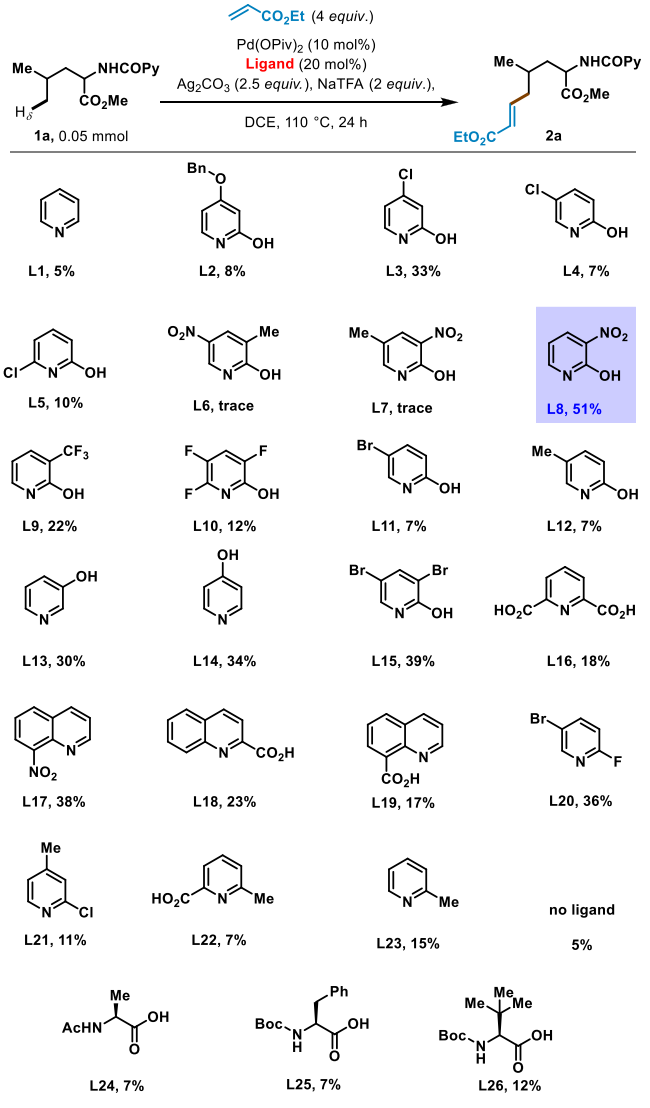

Figure 2. Ligands for δ-C(sp^3)−H olefination of leucine.

(DGs) with diverse electronic environments and coordination strengths were also tested, but **PG1** turned out to be the most suitable DG for this protocol (Figure 3).

Under this optimized condition, we further varied a series of acrylates which in turn produced δ-olefinated leucine derivatives with preparatively useful yields (**1**−**7**) (Scheme 1). Apart from leucine, analogous AA isoleucine also led to the formation of δ-olefinated product **8** with 63% (δ:γ = 2.4:1) overall yield under a slightly modified reaction condition. Additionally, structurally comparable other open chain aliphatic amines and alicyclic amines (**9**−**11**) with multiple competing reaction sites such as δ- *vs* γ-C(sp^3)−H bond or primary methyl vs secondary methylene (in the case of **11**) also selectively led to δ- alkenylated product. Even substrate having three equally accessible δ-C−H bonds in **12** exclusively produced δ-specific olefin product under a modified reaction condition. Unfortunately, amines with no α-substitution failed to deliver any olefinated products probably because of difficulty in forming the required palladacycle due to the absence of an additional α-alkyl effect. Despite our rigorous

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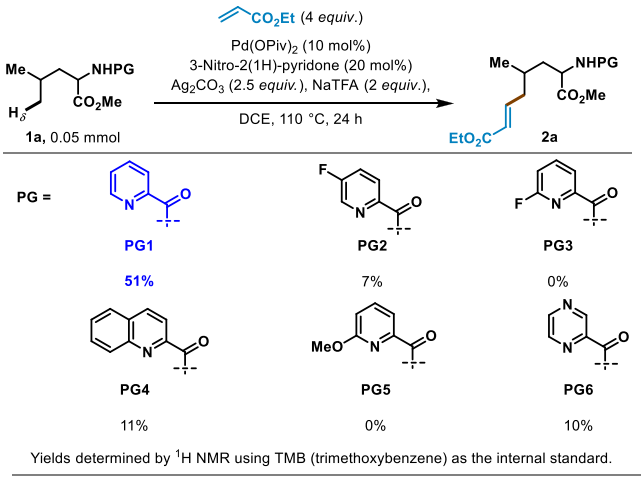
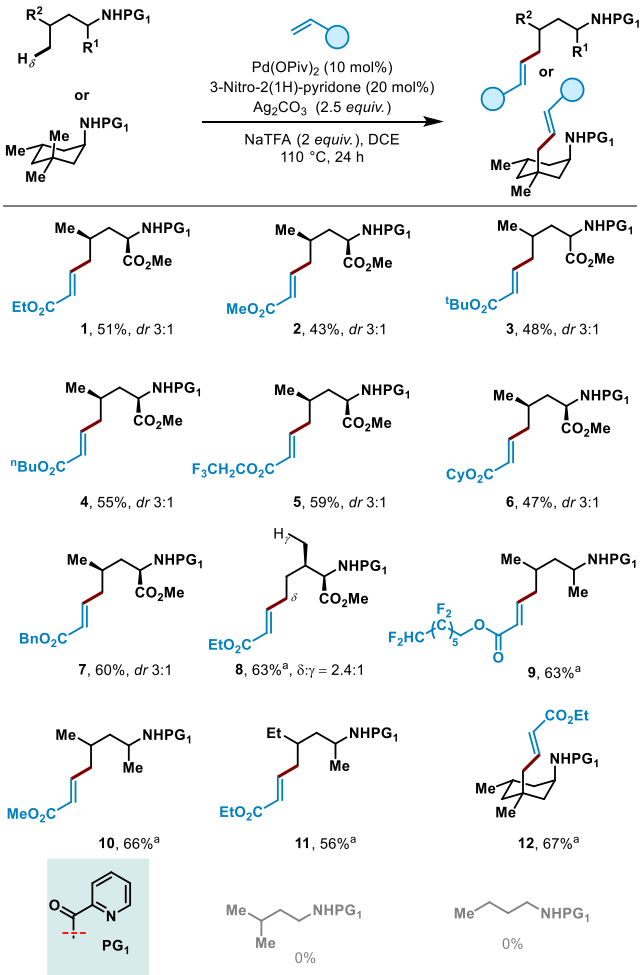


Figure 3. DGs for δ-C(sp^3)−H olefination of leucine.

Scheme 1. δ-C(sp^3)−H Olefination of Leucine and Unbiased Aliphatic Amines

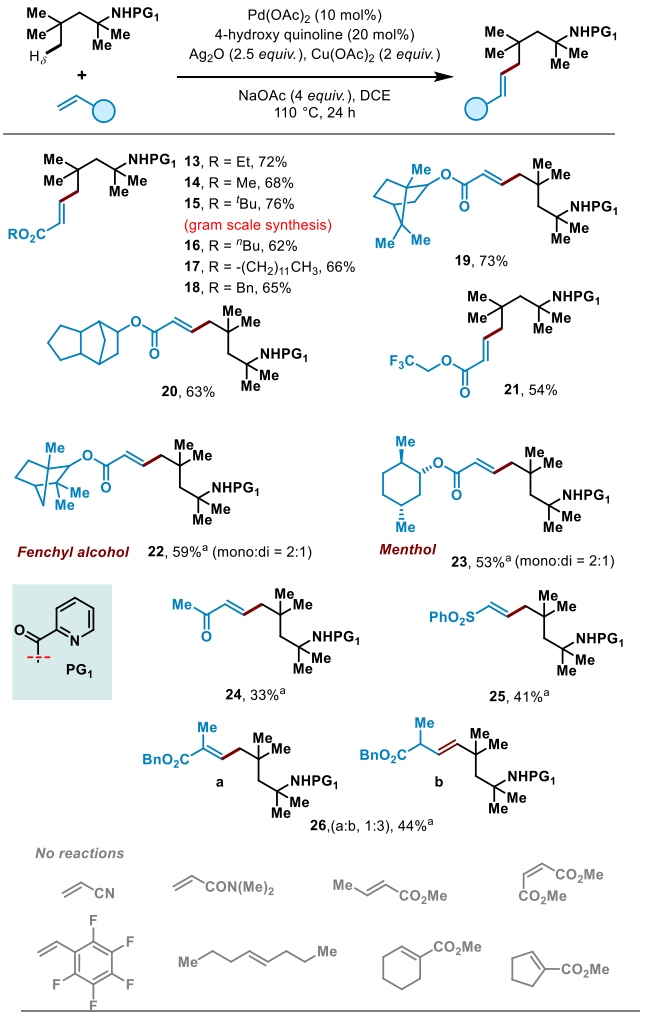


[a]2-Chloro quinoline was used as the ligand (20 mol %), Ag_2O (2.5 equiv) instead of Ag_2CO_3, and TFT (1 mL) instead of DCE. Isolated yields are reported.

optimization, we were unable to obtain δ-olefination of completely unbiased aliphatic amines.

Another class of substrate obtained from 2,4,4-trimethylpentan-2-amine was somewhat less productive under the similar reaction condition as mentioned in Scheme 1. However, replacing silver carbonate by silver oxide in addition to copper acetate as the cooxidant improved the yield of desired product significantly. Interestingly, for this system, quinoline ligands were found to be superior over pyridone ligands. 4-Hydroxy quinoline and 7-chloro-4-hydroxy quinoline were equally effective to obtain the desired δ-olefinated product. Additionally, an acetate combo of cupric acetate, palladium acetate, and sodium acetate was quite essential in boosting the formation of the δ-alkenylated product up to a yield of 72%. Remarkably, this method was found compatible with a diverse range of simple open chain as well as cyclic esters of acrylic acid (**13**−**21**, Scheme 2). Under a slightly

Scheme 2. δ-C(sp^3)−H Olefination of 2,4,4-Trimethylpentan-2-amine



[a]2-Chloro quinoline was used as the ligand (20 mol %); TFT (1 mL) instead of DCE. Isolated yields are reported. [b]Combined yields of the isolated mono-and disubstituted products. Products isolated as mono- and dimixtures.

modified reaction condition, natural product appended acrylates such as fenchyl alcohol (**22**) and menthol (**23**) derivatives were also found compatible albeit with moderate yield. Interestingly, under this modified reaction condition, other activated olefins, for example, methyl vinyl ketone (**24**) and phenyl vinyl sulfone (**25**), also were tolerated. However,

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JACS Au 2023, 3, 1975−1983

olefins such as acrylo nitrile, *N*,*N*-dimethyl acrylamide, or styrenes remained completely silent under both the reaction conditions. When we used benzyl methacrylate, an α-substituted acrylate, as a coupling partner, the desired olefinated product **26a** formed as a minor product along with its isomerized analogue **26b** (major product) where the double bond is migrated. Unfortunately, no internal olefins such as *trans*-4-octene, ethyl *trans*-3-hexanoate, or even methyl cyclopent-1-ene-1-carboxylate worked under similar or in a modified reaction condition. To probe the practical adequacy of the current protocol, compound **15** was synthesized in gram scale in 56% yield (see Supporting Information S17).

Upon mono-olefination, we turned our focus on sequential δ-C(sp^3)−H hetero difunctionalizations of picolyl tethered *tert*-octylamine. At first, we employed our developed protocol[32] to obtain mono δ-arylated amine derivatives which were then used as the substrate for δ-olefination. Undoubtedly, upon monoarylation, the steric and electronic environments of the substrates no longer remained the same. Therefore, the current protocol was solely exposed to a new class of substrates. While sequential functionalizations were attempted before to diversify arenes, consecutive heterofunctionalizations are quite less explored at distal aliphatic sites. It was quite intriguing to see that these new substrates delivered δ-olefinated amine derivatives (**27**−**34**, Scheme 3) with synthetically useful yield.

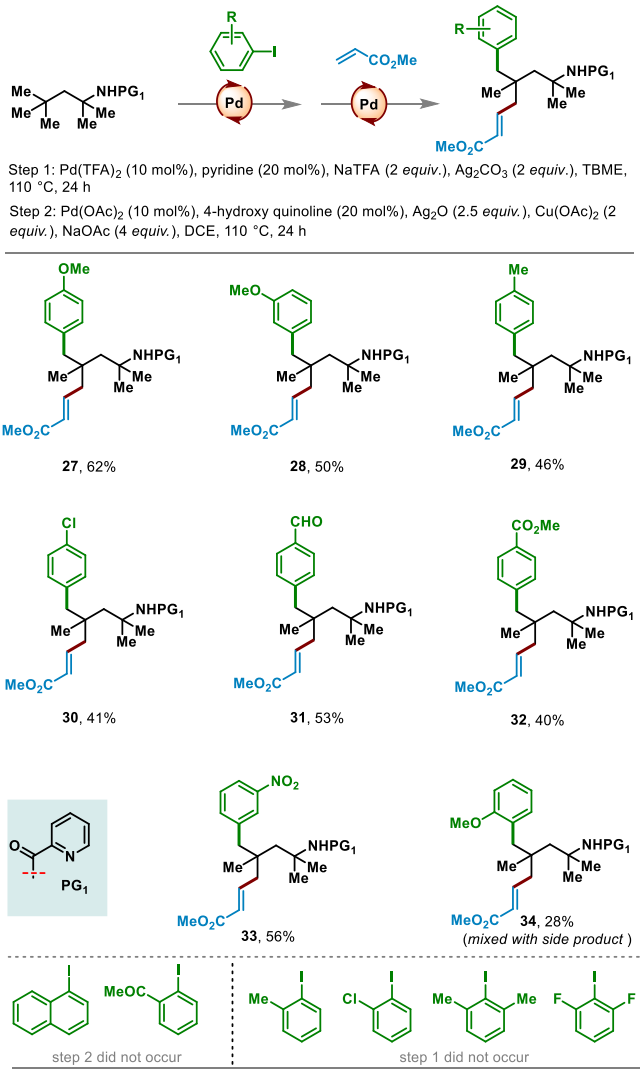
Various substrates, irrespective of *ortho*-, *meta*-, and *para*-substitutions, were found well suitable for a second functionalization. Additionally, we tested seven [1-iodo-2-methoxybenzene, 1-iodo-2-methylbenzene, 1-chloro-2-iodobenzene, 1-(2-iodophenyl)ethan-1-one, 1-iodonaphthalene, 2-iodo-1,3-dimethylbenzene, and 1,3-difluoro-2-iodobenzene] different types of aryl iodides for preparing the δ-arylated substrates. Only two aryl iodides (1-iodo-2-methoxybenzene and 1-iodonaphthalene) were reported in our prior work.[32] However, out of all five mono *ortho*-substituted arylated substrates, only 1-iodo-2-methoxybenzene benzene led to δ-olefinated product **34** (Scheme 3). However, a significant amount of other side product (*arene*-olefination of the anisole) was also observed, and both the products came as an inseparable mixture. On the other hand, with 1-iodo-2-methylbenzene, 1-chloro-2-iodobenzene, 2-iodo-1,3-dimethylbenzene, and 1,3-difluoro-2-iodobenzene, the first step, that is, δ-arylation, did not take place. After mono-olefination, the modified substrate was successfully used for diolefination (**35**, Scheme 4) under the same reaction condition. Further, a series of post synthetic diversifications were done with compound **13** (for an elaborate scheme and other synthetic details, see Figure S1 in Supporting Information, page S17−S19).

Following the scope of the current protocol, we wanted to investigate its mode of action. At the onset of our experiment, we synthesized the acetonitrile-coordinated [5,6]-fused organopalladium complex **Int A**.[33] Stoichiometric reaction of **Int A** with ethyl acrylate under otherwise similar condition was done, and compound **13** was obtained in 60% yield (Scheme 5).

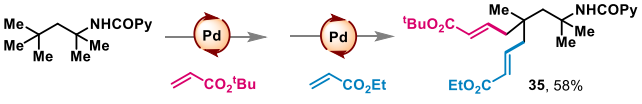
Next, we sequentially studied the interaction of olefin with the synthesized cyclopallada complex **Int** by ^{1}H NMR experiment. The reaction was carried out in a NMR tube using $CDCl_3$ as the solvent (Scheme 6). After mixing ^{t}butyl acrylate with **Int A**, we found that peaks (8.6−7.3 ppm) corresponding to the pyridyl moiety of **PG1** were shifted to a downfield region as we gradually increased the reaction time.

Interestingly, formation of compound **14** was identified within 5 min of the experiment (Scheme 6a−d). Simulta-

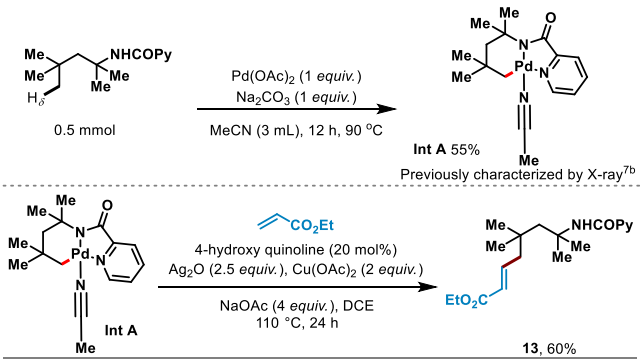
Scheme 3. Iterative δ-C(sp^3)−H Hetero Difunctionalizations of Amines



Scheme 4. Iterative δ-C(sp^3)-H Diolefination of Amines



Scheme 5. Synthesis of Organometallic Intermediate and Its Catalytic Competency



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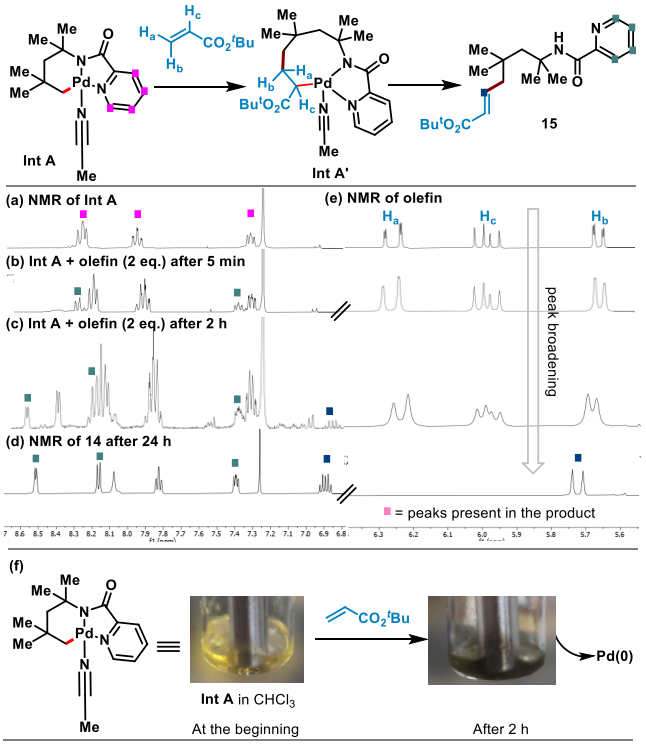
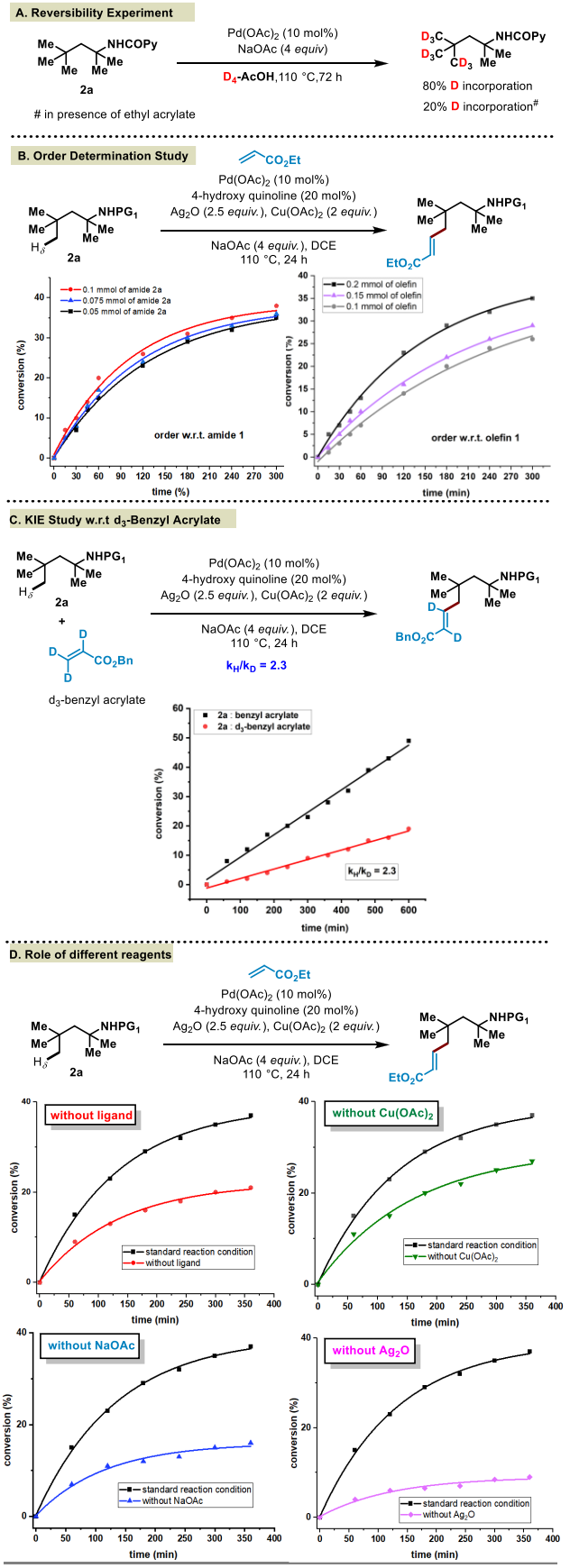
Scheme 6. Interaction of the Olefin with the Carbo-Palladated Intermediate Int A



Scheme 7. Mechanistic Investigation with Amide 2a



neously, another significant change was observed in the 5.5−6.5 ppm region where broadening of the initial sharp peaks of the olefinic double bond of ^{t}butyl acrylate took place. After 2 h following the addition of **Int A**, significant broadening of these signals was observed, which can be attributed to the coordination of the olefin to Pd(II).[57,58] Characteristic aliphatic peaks corresponding to H_c and diastereotopic H_a/H_b were also observed due to the formation of new **Int A′** (Scheme 6c). Interestingly, the initial straw yellow color of **Int A** in $CHCl_3$ gradually converted into dark black in the presence of the olefin (Scheme 6f).

While the NMR titration study revealed the interaction of olefin, a detailed mechanistic investigation with amide **2a** was carried out to understand the mode of C−H activation and other steps. We observed that substrate **2a** having a quaternary γ-center undergoes reversible C−H bond activation and the substrate was recovered with 80% deuterium incorporation (Scheme 7A). Even in the presence of olefin, 20% deuterium incorporation of the starting material **2a** was observed, which further confirms the reversible nature of the C−H activation step in the case of **2a**. A unit order with respect to both amide **2a** as well as ethyl acrylate corroborates that the C−H activation step is not involved in the rate-determining step (RDS) for this class of substrate and olefin is involved in the rate-limiting step (Scheme 7B).Therefore, we assumed that possibly 1,2-migratory insertion or β-hydride elimination step demands higher energy in comparison to the C−H activation step in this case. To gain further evidence, we synthesized deuterated benzyl acrylate (d_3-benzyl acrylate) by following a reported literature procedure[59] and then performed kinetic isotope analysis by running two parallel sets of reactions. A primery KIE value of 2.3 with d_3-benzyl acrylate confirms that β-hydride elimination step is probably the RDS (Scheme 7C), which was also found to be consistent with our prior

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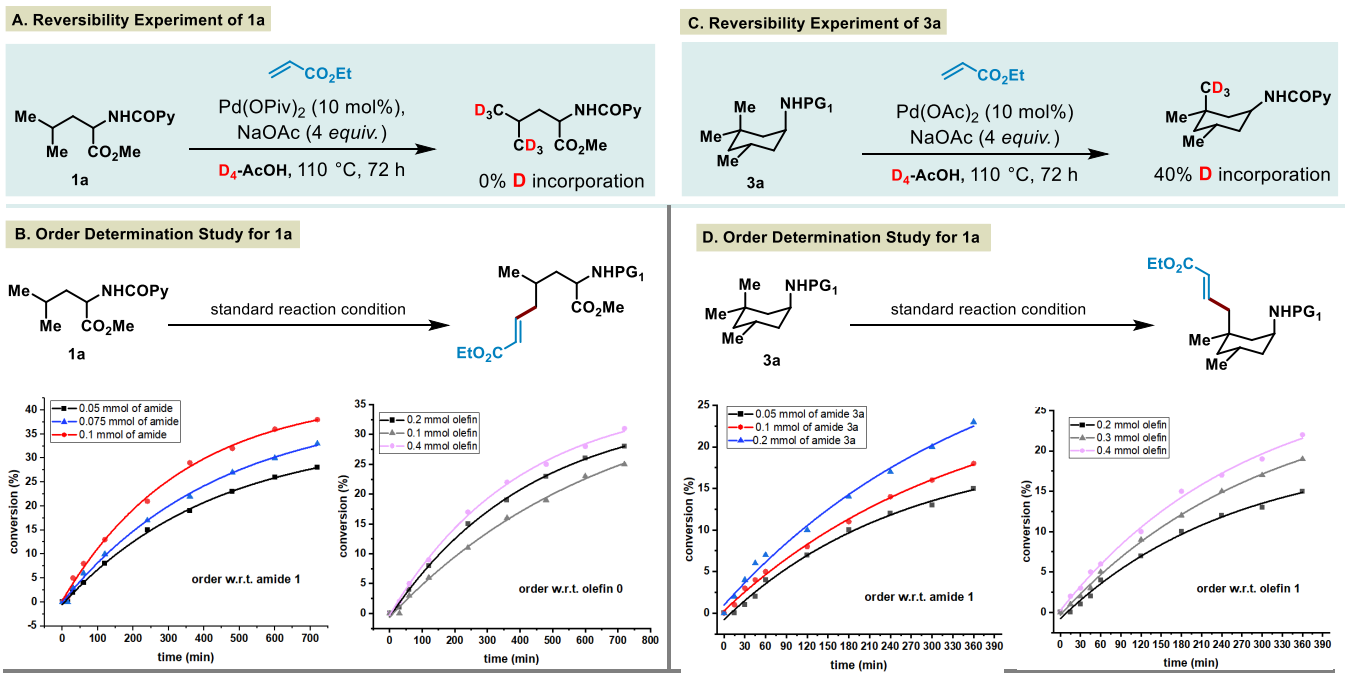
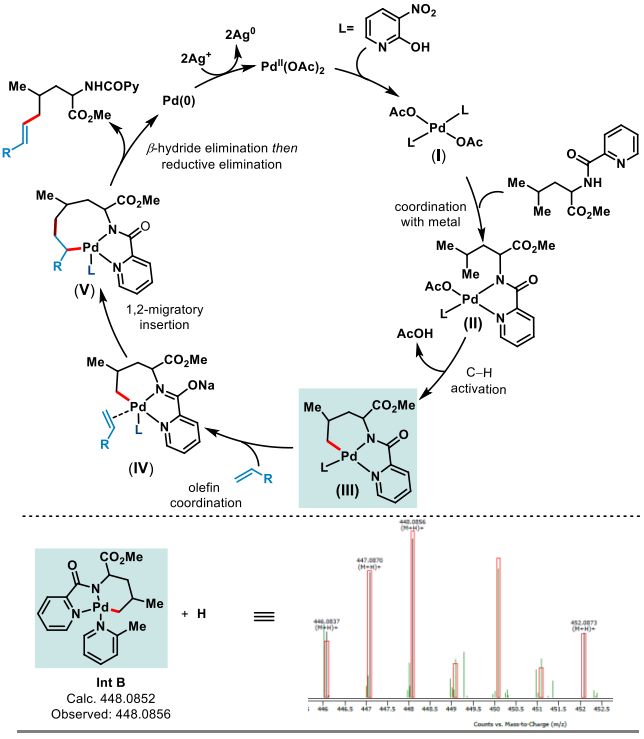


Figure 4. Mechanistic Studies of δ-C(sp^3)−H Olefination of Leucine and Analogues Aliphatic Amine. (A) Reversibility experiment of **1a**, (B) order determination study for **1a**, (C) reversibility experiment of **3a**, and (D) order determination study for **3a**.

observations. Simultaneously, kinetic studies were performed to investigate the role of individual components in the reaction medium (Scheme 7D). As mentioned earlier, the reaction works best in the presence of a base (NaOAc) with silver oxide as the oxidant and 4-hydroxyquinoline as the ligand. However, a drastic deterioration of yield can be observed in the absence of the base and silver salt. Apart from their usual role, the presence of Na^+ or Ag^+ ions perhaps led to hetero-bimetallic cluster formation which helps in a facile product release and hence contribute to elevate the yield.[60] On the other hand, compared to silver oxide, the absence of copper acetate showed little effect which justified the role of silver oxide as the major oxidant responsible to run the catalytic cycle, while copper acetate might be playing the role of the co-oxidant. Next, the nature of the C−H activation step for the other two types of substrates was also probed separately by the reversibility experiment (Figure 4). Unlike previous case, no deuterium scrambling was observed for amide **1a**, even at 110 °C for 72 h with or without the ligand (Figure 4A). This implies that possibly C−H activation is the rate-limiting step for this class of substrate. Our hypothesis was further strengthened from the order determination study, where a first-order and a zero-order kinetics with respect to amide **1a** and olefin was obtained, respectively (Figure 4B). Similarly, these experiments were run for a cyclic amine-based amide **3a**. In this case, a similar result as in **2a** was obtained albeit with a lower extent of deuterium incorporation (Figure 4C,D). These results clearly indicated that the irreversible nature of the C−H activation step in the case of **1a** can be because of the lack of Thorpe-Ingold effect by the extra methyl groups at the α-position of amide unlike in **2a**.[32]

Based on above studies, a plausible mechanistic blueprint has been corroborated in Scheme 8. The catalytic cycle commences with the formation of metal−ligand complex **I**. Subsequently, complex **II**, upon coordination with substrate **1a**, undergoes C−H activation to generate intermediate **III** in

Scheme 8. Mechanistic Blueprint of δ-C(sp^3)−H Olefination



the presence of a base. The ESI-MS study of the reaction mixture in the absence of olefin using 2-methylpyridine ligand indicated the formation of **Int B** which further suggested the formation of **III**. Next, olefin coordinates with the palladium center to give intermediate **IV** which consequently generates intermediate **V** via 1,2-migratory insertion. Upon β-hydride elimination followed by reductive elimination desired olefinated product, and Pd(0) forms. The catalyst then regenerates in the presence of a silver oxidant.

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3. CONCLUSIONS

To summarize, we have disclosed a strategy to directly synthesize a series of novel long chain unnatural amino acids (NPAAs) via δ-C(sp^3)-H olefination of aliphatic amines as well as leucine and isoleucines. The protocol was further extended to sequential diolefination and hetero difunctionalizations via δ-C(sp^3)-H activation. Postsynthetic modification followed by a series of kinetic studies has further helped to gain a better perception about the developed protocol. A separate investigation for the distal asymmetric aliphatic C−H functionalizations is currently being carried out separately in our lab.

4. METHODS

4.1. General Procedure for Palladium-Catalyzed δ-sp^3 C−H Arylation of Leucine Derivatives (GP1, Scheme 1, Entries 1−7)

A clean, oven-dried screw cap reaction tube with a previously placed magnetic stir bar was charged with picolinamide (0.1 mmol, 1 equiv), olefin (0.4 mmol, 4 equiv), palladium(II) pivalate (0.01 mmol, 10 mol %), 2-hydroxy-3 nitro pyridine **L8** (0.02 mmol, 20 mol %), Ag_2CO_3 (0.3 mmol, 3 equiv), and sodium trifluoroacetate (0.2 mmol, 2 equiv) followed by addition of DCE (1 mL). The reaction mixture was vigorously stirred for 24 h in a preheated oil bath at 110 °C. After the stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (30 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 × 10 mL) followed by water (2 × 10 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4, and the volatiles were removed under vacuum. The crude reaction mixture was purified by column chromatography using silica gel and petroleum-ether/ethyl acetate as the eluent to give the desired δ-olefinated product.

4.2. General Procedure for Palladium-Catalyzed δ-sp^3 C−H Arylation of Leucine Derivatives (GP2, Schemes 1 and 2, Entries 8−12, 22−26)

A clean, oven-dried screw cap reaction tube with a previously placed magnetic stir bar was charged with picolinamide (0.1 mmol, 1 equiv), olefin (0.4 mmol, 4 equiv), palladium(II) acetate (0.01 mmol, 10 mol %), 2-chloro quinoline (0.02 mmol, 20 mol %), and Ag_2O (0.3 mmol, 3 equiv) followed by addition of TFT (1 mL). The reaction mixture was vigorously stirred for 24 h in a preheated oil bath at 110 °C. After the stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (30 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 × 10 mL) followed by water (2 × 10 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4, and the volatiles were removed under vacuum. The crude reaction mixture was purified by column chromatography using silica gel and petroleum-ether/ethyl acetate as the eluent to give the desired δ-olefinated product.

4.3. General Procedure for Palladium-Catalyzed δ-sp^3 C−H Arylation of Aliphatic Amines (GP3, Scheme 2, Entries 13−21)

A clean, oven-dried screw cap reaction tube with a previously placed magnetic stir bar was charged with picolinamide (0.1 mmol, 1 equiv), olefin (0.4 mmol, 4.0 equiv), palladium(II) acetate (0.01 mmol, 10 mol %), 4-hydroxy quinoline (0.02 mmol, 20 mol %), Ag_2O (0.3 mmol, 2.5 equiv), $Cu(OAc)_2$ (2 equiv), and sodium acetate (0.4 mmol, 4 equiv) followed by addition of DCE (1.1 mL). The reaction mixture was vigorously stirred for 24 h in a preheated oil bath at 110 °C. After the stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (30 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 × 10 mL) followed by water (2 × 10 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4, and the volatiles were removed under vacuum. The crude reaction mixture was purified by column chromatography using silica gel and petroleum-ether/ethyl acetate as the eluent to give the desired δ-olefinated product.

4.4. General Procedure for Palladium-Catalyzed δ-sp^3 C−H Sequential Difunctionalization of Aliphatic Amines (GP4, Scheme 3, Entries 27−34)

The monoarylation was carried out by following the reported protocol.[7a] Yields for each of the arylated products were calculated considering the precursor amides obtained from preceding arylations as 100%. A clean, oven-dried screw cap reaction tube with a previously placed magnetic stir bar was charged with monoarylated picolinamide (0.1 mmol, 1 equiv), olefin (0.4 mmol, 4.0 equiv), palladium(II) acetate (0.01 mmol, 10 mol %), 4-hydroxy quinoline (0.02 mmol, 20 mol %), Ag_2O (0.3 mmol, 2.5 equiv), $Cu(OAc)_2$ (2 equiv), and sodium acetate (0.4 mmol, 4 equiv) followed by addition of DCE (1.1 mL). The reaction mixture was vigorously stirred for 24 h in a preheated oil bath at 110 °C. After the stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (30 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 × 10 mL) followed by water (2 × 10 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4, and the volatiles were removed under vacuum. The crude reaction mixture was purified by column chromatography using silica gel and petroleum-ether/ethyl acetate as the eluent to give the desired δ-olefinated product.

4.5. General Procedure for Palladium-Catalyzed δ-sp^3 C−H Sequential Difunctionalization of Aliphatic Amines (GP4) (GP5, Scheme 4, Entry 35)

At first, mono-olefination was carried out by following GP3. Yields for each of the olefinated products were calculated considering the precursor amides obtained from preceding olefins as 100%. Upon mono-olefination, the olefinated amide was again used as the substrate for the second δ-olefination following procedure GP3. For the first olefination, *tert* butyl acrylate was used as the coupling partner, and in the next step, that is, for diolefination, ethylacrylate was used as a coupling partner.

4.6. General Procedure for Scaleup Reaction

A clean, oven-dried screw cap reaction tube with a previously placed magnetic stir bar was charged with monoarylated picolinamide (6 mmol, 1 equiv), olefin (24 mmol, 4.0 equiv), palladium(II) acetate (0.06 mmol, 10 mol %), 4-hydroxy quinoline (0.12 mmol, 20 mol %), Ag_2O (18 mmol, 2.5 equiv), $Cu(OAc)_2$ (12 mmol, 2 equiv), and sodium acetate (24 mmol, 4 equiv) followed by addition of DCE (6 mL). The reaction mixture was vigorously stirred for 24 h in a preheated oil bath at 110 °C. After the stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (50 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 × 10 mL) followed by water (2 × 10 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4, and the volatiles were removed under vacuum. The crude reaction mixture was purified by column chromatography using silica gel and petroleum-ether/ethyl acetate as the eluent to give the desired δ-olefinated product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.3c00215.

Supporting information contains the experimental details including starting material synthesis, optimization details, mechanistic study, characterization data, ^1H, ^{13}C, ^{19}F NMR spectra of all the isolated compounds (PDF)

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Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Trisha Bhattacharya** conceptualization, data curation, formal analysis, investigation, writing-original draft, writing-review & editing; **Prabhat Kumar Baroliya** data curation, formal analysis, writing-review & editing; **Shaeel A. Al Thabaiti** funding acquisition, writing-review & editing; **Debabrata Maiti** conceptualization, funding acquisition, supervision, writing-original draft, writing-review & editing.

Notes

The authors declare no competing financial interest.

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