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Title: Access to α-Amino Acid Esters via Palladium-Catalyzed Oxidative Amination of Vinyl Ethers Using Hydrogen Peroxide as Oxidant and Oxygen Source

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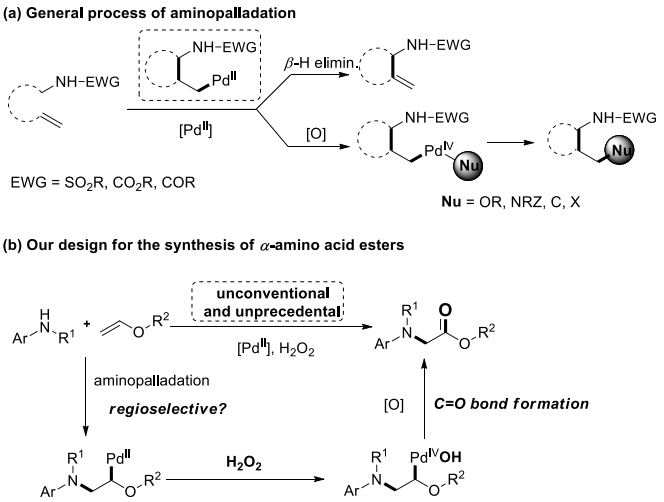
Access to α-Amino Acid Esters via Palladium-Catalyzed Oxidative Amination of Vinyl Ethers Using Hydrogen Peroxide as Oxidant and Oxygen Source **

Lu Ouyang, Jianxiao Li, Jia Zheng, Jiuzhong Huang, Chaorong Qi, Wanqing Wu and Huanfeng Jiang**

Abstract: *A novel and convenient palladium catalytic system to achieve α-amino acid esters with simple starting materials has been reported. Hydrogen peroxide not merely acts as the green oxidant, but also the oxygen source. This new strategy salient merits attention the simplicity of experimental procedure, mild reaction conditions, high atom economy, scalability and practicability, which can convert the amines and vinyl ethers to highly functionalized and structurally diverse α-amino acid esters.*

α-Amino acid, the backbone of proteins, which is one of the most important amino acids in every organism.[1] The biologically significant α-amino acid and the derivatives have been extensively used as medical intermediates, artificial sweetener, food additives, cosmetic additives, mineral flotation additives, germicides,[2] *etc*. Despite its great importance, methods for the direct synthesis of α-amino acid esters, the most important α-amino acid derivatives, are relatively rare.[3] Therefore, a simple and efficient procedure for the synthesis of α-amino acid esters with abundant and accessible starting materials is still highly demanded.

As we know, alkenes can be activated via coordination with transition metal catalysts, which have been focused continuous attention due to the high efficiency in building up molecular complexity.[4] As a Lewis-acidic transition metal, the palladium catalyst effectively facilitates the addition of nucleophiles to alkenes for the difunctionalization.[5] In general, amines (especially for aromatic amines and aliphatic amines) can coordinate with the palladium salts more strongly than alkenes, which will reduce the electrophilicity of palladium to form the stable bis(amine)-Pd intermediate, thus affects the reactivity of the catalyst.[6] Therefore, examples about the nucleopalladation with simple aromatic amines are quite few.[7] To overcome this problem, chemists found that nonbasic nitrogen nucleophiles,[8] such as carbomates, carboxamides, and sulfonamides, can be activated by Pd^{II} to form alkyl-Pd^{II} *via* the nucleopalladation process. The key intermediate of alkyl-Pd^{II} would go through the direct β-H elimination and complete the catalytic cycle.[9] Also, the alkyl-Pd^{II} can be oxidized to alkyl-Pd^{IV} to form C-O, C-N, C-C, C-X bonds (Scheme 1a).[10]



Scheme 1. Process of aminopalladation and our design for the synthesis of α-amino acid esters

Based on our continuous interests in palladium-catalyzed oxidation reactions with green oxidants,[11] we envisioned that the aromatic amines could serve as the nucleophiles to attack the alkenes directly to produce the alkyl-Pd^{II} species under mild conditions, followed by the oxidation to form the alkyl-Pd^{IV}(OH) intermediate in the presence of oxidant such as H_2O_2(Scheme 1b).[12] Herein, we present a novel palladium-catalyzed intermolecular aminopalladation triggered oxidative amination of electron-rich olefins, wherein hydrogen peroxide is functioned as the sole oxidant and oxygen source, which is undoubtedly eco-friendly and inexpensive.[13] This protocol relies on simple and readily available materials to deliver useful α-amino acid esters under mild reaction conditions.

Preliminary investigation to the Pd-catalyzed oxidative amination was conducted with *N*-methylaniline (**1a**), ethyl vinyl ether (**2a**), and the green oxidant H_2O_2. Pleasingly, 61% consumption of **3a** was found when **1a** was treated with 5 mol % of $Pd(OAc)_2$, 4 equivalents of 35% aqueous H_2O_2 at 70 °C under air in 1,4-dioxane (Table 1, entry 1). Subsequently, the exploration of different solvents led to the discovery that DMF was the best choice for this process and the desired product **3aa** could be obtained in 83% yield (Table 1, entry 2). However, solvents such as THF, MeCN, DCE, were not compatible for this reaction (Table 1, entries 5-7). Screening of other Pd salts, such as $Pd(PPh_3)_2Cl_2$, $Pd(MeCN)_2Cl_2$, $Pd(PhCN)_2Cl_2$, $Pd(dba)_2$ and $Pd(PPh_3)_4$, revealed that $Pd(OAc)_2$ was the optimal (Table 1, entries 8-13). Notably, no desired product was detected when the reaction was performed without metal catalyst (Table 1,

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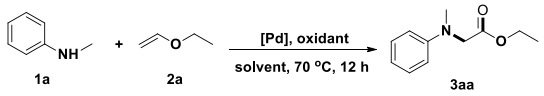
entry 14). Compared to the aqueous H_2O_2, other strong oxidants including TBHP (70% aq.), DTBP and $K_2S_2O_8$ were inefficient to provide the desired product (Table 1, entries 15-17).

Table 1. Optimization of the reaction conditions [a]

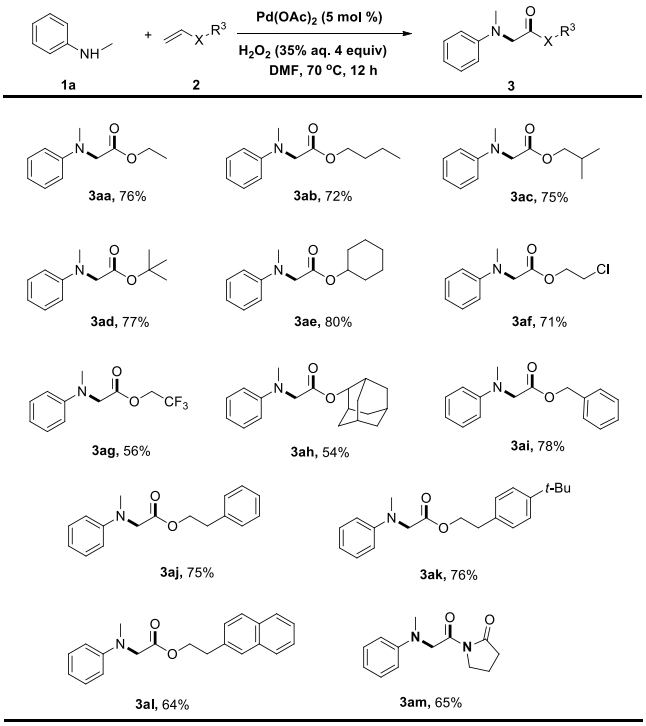


entry	Pd catalyst	oxidant	solvent	yield (%)
1	$Pd(OAc)_2$	35% aq. H_2O_2	1,4-dioxane	61
2	$Pd(OAc)_2$	35% aq. H_2O_2	DMF	83 (76)
3	$Pd(OAc)_2$	35% aq. H_2O_2	DMA	74
4	$Pd(OAc)_2$	35% aq. H_2O_2	EtOH	57
5	$Pd(OAc)_2$	35% aq. H_2O_2	THF	trace
6	$Pd(OAc)_2$	35% aq. H_2O_2	DCE	n.d.
7	$Pd(OAc)_2$	35% aq. H_2O_2	MeCN	trace
8	$PdCl_2$	35% aq. H_2O_2	DMF	trace
9	$Pd(PPh_3)_2Cl_2$	35% aq. H_2O_2	DMF	n.d.
10	$Pd(MeCN)_2Cl_2$	35% aq. H_2O_2	DMF	12
11	$Pd(PhCN)_2Cl_2$	35% aq. H_2O_2	DMF	57
12	$Pd(dba)_2$	35% aq. H_2O_2	DMF	50
13	$Pd(PPh_3)_4$	35% aq. H_2O_2	DMF	69
14	--	35% aq. H_2O_2	DMF	n.r.
15	$Pd(OAc)_2$	70% aq. TBHP	DMF	n.d.
16	$Pd(OAc)_2$	DTBP	DMF	n.d.
17	$Pd(OAc)_2$	$K_2S_2O_8$	DMF	n.d.

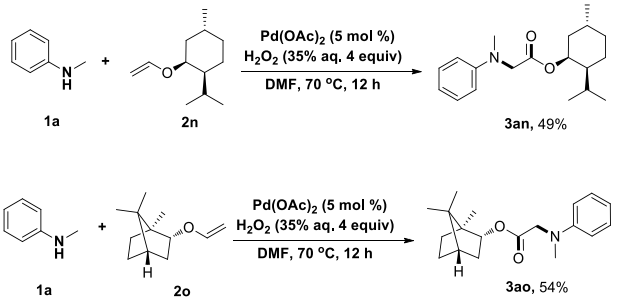
[a] Reaction conditions: *N*-methylaniline (**1a**) as the limiting reagent (0.25 mmol), Pd catalyst (5 mol %), oxidant (4 equiv), ethyl vinyl ether (**2a**, 2 equiv), solvent (0.25 M substrate); under air. Yield was determined by GC with dodecane as internal standard based on **1a**. Isolated yield is in the parentheses. n.r. = no reaction; n.d. = not determined.

A broad range of anilines and electron-rich alkenes were investigated to afford the α-amino acid ester compounds under the optimized conditions. As illustrated in Scheme 2, the oxidative amination of alkenes proceeded well over a wide range of alkenes with moderate to excellent yields. Substrates with different alkoxy groups reacted smoothly, either the alkoxy groups come in chain (**3aa-3ad**) or comes in cyclic (**3ae**). The reaction was also amenable to halogen-substituted vinyl ethers (**3af**, **3ag**), which might change their properties and transfer to different functional groups. It is worth noting that 1-adamantanol vinyl ether which is a rigid molecule performed well to access the *α*-amino acid ester molecule (**3ah**). Furthermore, when benzyl vinyl ether (**3ai**), 2-phenyl ethyl vinyl ethers (**3aj**, **3ak**) and 2-napthyl ethyl vinyl ether (**3al**) were subjected to the reaction system, the reactions proceeded with good efficiency under the conditions used. In order to further improve the versatility of this reaction, different kinds of electron-rich olefins were also examined. Gratifyingly, under the standard reaction conditions, 1-vinyl-2-pyrrolidinone (**2m**) could also react with *N*-methylaniline (**1a**) smoothly to give the desired product **3am** in 65% yield.

In view of the great importance of *α*-amino acid esters in bioactive natural products and pharmaceutical compounds, it is essential to develop late-stage modification of *α*-amino acid esters (Scheme 3). To our delight, the *α*-amino acid esterification process performed well to access different complex products under the standard conditions. For instance, natural alcohol derivatives, such as *L*-menhol, (-)-borneol (**2n**, **2o**), could participate in the present transformation to generate the corresponding *α*-amino acid esters **3an** and **3ao**, respectively.



Scheme 2. The scope of the alkenes for the synthesis of *α*-amino acid esters. Reaction conditions: *N*-methylaniline (**1a**) as the limiting reagent (0.25 mmol), $Pd(OAc)_2$ (5 mol %), H_2O_2 (35% aq., 4 equiv), ethyl vinyl ether (**2a**, 2 equiv), DMF (0.25 M substrate); under air. Yields of isolated products are shown.



Scheme 3. Late-stage modification of *α*-amino acid esters

The scope of the Pd-catalyzed oxidative amination of alkenes leading to *α*-amino acid esters was further investigated to a variety of substituted amines (Scheme 4). Intriguingly, halogen atoms (–F, –Cl, –Br) on the aromatic ring could be applied to this reaction (**3ba-3da**). The methyl substituent at different positions of *N*-methytoluidine (*para*-, *meta*-, and *ortho*-positions) showed steric hindrance effect, and the corresponding products **3ea**, **3fa**, **3ga** were obtained in decreasing yields. It should be noted that the cyclic amines were also tolerated in this process, which gave the corresponding products **3ha** and **3ia** in moderate yields. Moreover, the palladium catalyst was also compatible with primary aromatic amine, and the desired product **3ja** was formed in 60% yield with 8 equivalents of oxidants. Notably, the substrates possessing halogen group could undergo the oxidative amination process, leading to the corresponding *α*-amino acid esters (**3ka-3ma, 3pa**) in moderate yields. The absolute configuration of **3la** was unambiguously characterized by X-ray analysis (see the Supporting Information for details). Additionally, the reaction was amenable to the electron-donating group (isopropyl, methyl, phenoxyl and methoxyl) of amines for further transformations (**3na**, **3oa, 3qa, 3ra**). Different *N*-alkyl substituted amines served well for this transformation (**3sa**, **3ta**). However, the reaction was sensitive to the functional groups

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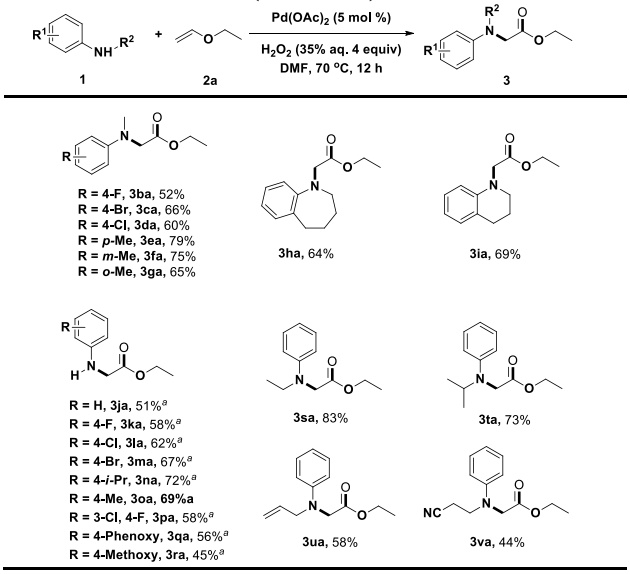
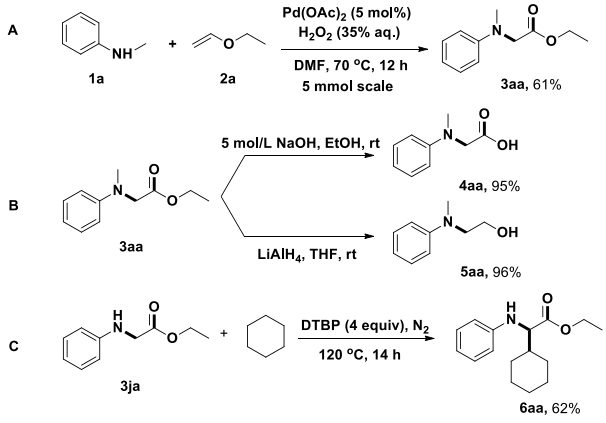
such as allyl and nitrile, affording the corresponding products **3ua** and **3va** in lower yields.

Besides broad functional group tolerance, potential applications of this oxidative amination reaction were tested. A scale-up experiment (**1a**, 5 mmol) was smoothly conducted under the standard conditions with 61% yield of **3aa** obtained (Scheme 5A). Further chemical transformations of the ester functionality in the product molecules make the method more useful and attractive. Hydrolysis of **3aa** could afford *N*-methyl-*N*-phenyl glycine (**4aa**) directly and efficiently. Compounds with glycine skeleton can be observed in many pharmaceutically active drugs, and showed broad biological activities. And the reduction of **3aa** gave α-amino alcohol **5aa** in excellent yields (Scheme 5B). Similarly, amino alcohols are important compounds and have found wide applications in many synthetic molecules and natural products. In addition, **6aa** could be easily obtained from the α-alkylation of α-amino acid ester in 62% yield with the aid of DTBP (Scheme 5C)

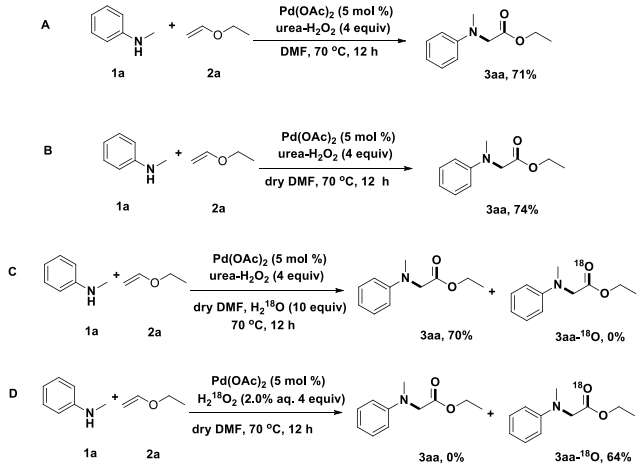


Scheme 4. The scope of amine for the α-amino acid esterification. Reaction conditions: aniline (**1a**) as the limiting reagent (0.25 mmol), $Pd(OAc)_2$ (5 mol %), H_2O_2 (35% aq., 4 equiv), ethyl vinyl ether (**2a**, 2 equiv), DMF (0.25 M substrate); under air. Yields of isolated products are shown. [a] 8 equiv of H_2O_2 (35% aq.) was used.

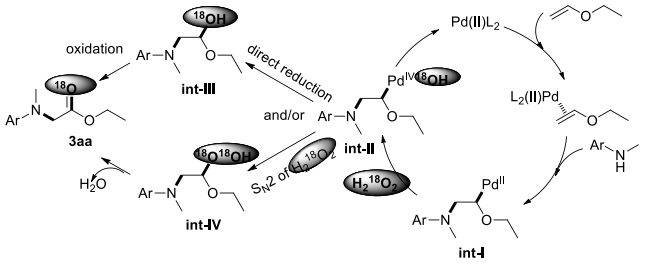


Scheme 5. Synthetic applications

To gain more insight into the C-O bond formation steps, several control experiments were conducted (Scheme 6). The reaction of *N*-methylaniline (**1a**) and ethyl vinyl ether (**2a**) using urea-H_2O_2 as the oxidant proceeded well with DMF as the solvent, giving the product in 71% yield (Scheme 6A). In order to estimate whether the water in the solvent of DMF could serve as a nucleophile involved in the reaction, anhydrous DMF was used as the solvent, and the reaction occurred smoothly to afford the desired product in 74% yield, indicating that the oxygen should not come from H_2O in DMF (Scheme 6B). Critical evidence was obtained in the isotope labeling experiment by adding ten equivalents of $H_2{}^{18}O$ to the anhydrous DMF, which afforded product **3aa** in 70% yield without ^{18}O incorporation product (**3aa-^{18}O**) (Scheme 6C). Moreover, by using $H_2{}^{18}O_2$ (2.0% aq.) as the oxidant, the *N*-methylaniline could be converted to **3aa-^{18}O** in 64% yield instead of **3aa** (Scheme 6D). Oxygen coming from dioxygen was also ruled out (see the Supporting Information for details). Based on the above control experiments, one might draw a conclusion that the oxygen of α-amino acid esters comes from the H_2O_2.



Scheme 6. Mechanistic investigations



Scheme 7. Proposed mechanism

On the basis of the above results, a reasonable mechanism for Pd-catalyzed intermolecular oxidative amination is illustrated in Scheme 7. First, **2a** can be activated via the coordination with the Pd(II) catalyst, suggesting that the aminopalladation process should be involved to give the alkylpalladium **int-I**.[14] Subsequently, the H_2O_2 oxidizes the alkylpalladium **int-I** to form the alkyl $Pd^{IV}(OH)$ (**int-II**), which might go through the direct reductive elimination to generate the **int-III** and then would be oxidized to the final product **3aa**.[12b, 15] Alternatively, H_2O_2 may also act as a nucleophile to attack the **int-II** to produce **int-IV**,[16] which undergoes the dehydration process to afford **3aa**.

In conclusion, we have developed a novel and convenient protocol for the synthesis of functionalized α-amino acid esters via palladium-catalyzed oxidative amination of vinyl ethers. ^{18}O-Labeling experiments demonstrated that H_2O_2 was not only served as a green and inexpensive oxidant, but also the source of oxygen. This method may open up a new viewpoint on the difunctionalization (installing of both amino and ester groups) of alkenes. Moreover, the simple and abundant starting materials without prefunctionalization make this method particularly practical, neutral and mild. Ongoing studies are focused on exploring the applications of the reaction and the detailed mechanism of the reaction.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: palladium-catalyzed ·amination oxidation *α*-amino acid ester · hydrogen peroxide

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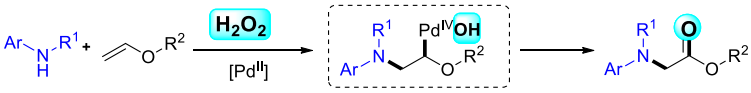

♣ Abundant and readily available building block
♣ Easy operation and high atom economy
♣ H_2O_2 not only sever as the green oxidant but also the oxygen source
♣ Efficient synthesis of a variety of α-amino acid esters

A novel and convenient palladium catalytic system to achieve α-amino acid esters with simple starting materials has been reported. Hydrogen peroxide not merely acts as the green oxidant, but also the oxygen source. This new strategy salient merits attention the simplicity of experimental procedure, mild reaction conditions, high atom economy, scalability and practicability, which can convert the amines and vinyl ethers to highly functionalized and structurally diverse α-amino acid esters.

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