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Palladium-Catalyzed Intermolecular Aminocarbonylation of Alkenes: Efficient Access of β-Amino Acid Derivatives

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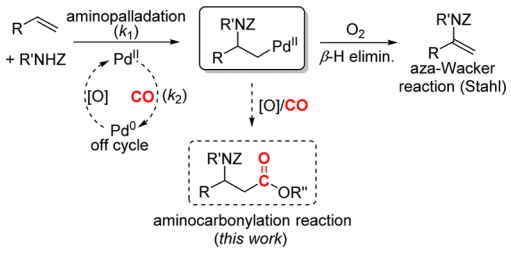
Supporting Information

ABSTRACT: A novel palladium-catalyzed intermolecular aminocarbonylation of alkenes has been developed in which the employment of hypervalent iodine reagent can accelerate the intermolecular aminopalladation, which thus provides the successful catalytic transformation. The current transformation presents one of the most convenient methods to generate β-amino acid derivatives from simple alkenes.

β-Amino acids have been identified as essential components in bioactive natural products and broadly utilized for development of peptide-based pharmaceutical compounds due to their biological metabolism property.[1] For example, β-amino acid-containing peptides exhibited better stability than natural peptides in the proteolysis degradation.[2] Thus, exploration of efficient synthesis of β-amino acid and related derivatives has received much attention.[3] In general, most of these methodologies relied on the manipulations of prefunctionalized substrate such as amination of α,β-unsaturated carboxylic acids (esters), hydrogenation of β-carboxylic enamide, etc.[4] However, more attractive method that started from the simple nonactivated alkenes still remained unexplored.

Transition metal-catalyzed amination of alkenes has provided straightforward methods for the synthesis of nitrogen-containing molecules.[5] Compared to intramolecular reactions, the *intermolecular* amination of alkenes reactions is not only much more attractive, but also much more challenging due to the high kinetic barrier.[5a,d,e] Stahl and co-workers have reported pioneering studies on the palladium-catalyzed intermolecular Aza-Wacker type oxidation of nonactivated alkenes[6] in which an alkyl-Pd(II) species generated from aminopalladation was involved as key intermediates (Scheme 1). We speculated that if reduced carbon monoxide (CO) atmosphere is compatible with the intermolecular oxidative amination condition, then subsequent carbonylation of alkyl-Pd(II) intermediate might be expected to deliver β-amino acid derivatives from simple alkenes. However, to the best of our knowledge, there are no reports on the *intermolecular aminocarbonylation* reaction.[7] Herein, we reported the first intermolecular aminocarbonylation of alkenes by using palladium catalyst.

Scheme 1. Pd-catalyzed Intermolecular Amination of Alkenes



As we know, palladium-catalyzed intramolecular aminocarbonylation of alkenes has been well established by using benzoquinone or Cu(II) salts as oxidants.[8] Among them, fast aminopalladation initiated by Pd(II) catalyst is the key to successful catalytic cycle. In contrast, the aminopalladation step in the *intermolecular* reaction is much slower than that in the *intramolecular* case, which renders a competitive reduction of Pd(II) catalyst by CO to terminate the catalytic cycle. In fact, when styrene **1a**, 2-oxazolidone (HN-Oxa) **2a**, catalytic Pd(II) catalyst, and a stoichiometric amount BQ or Cu(II) were mixed under CO atmosphere, we indeed observed immediately the palladium black precipitate, and only small amount of the desired aminocarbonylation product **3a** was obtained. Increasing palladium catalyst loading or the amount of oxidants was proven to be ineffective. These observations revealed that reduction of Pd(II) catalyst to Pd(0) by CO (k_2) is much faster than aminopalladation (k_1), which then resulted in a predominate off-cycle pathway (Scheme 1). *Thus, the ability to accelerate the intermolecular aminopalladation step or slow down the reduction of palladium catalyst is crucial for successful transformation.* To address this, one solution is to increase the Lewis acidity of palladium center to enhance the nucleophilic attack to the coordinated C=C bond. Recently, Szabó,[9a,b] Stambuli,[10] and our group,[11] respectively, demonstrated that employing hypervalent iodine reagents can *significantly accelerate* allylic C–H activation compared with other oxidants, such as dioxygen and BQ. Meanwhile, the White group discovered that Pd-catalyzed dehydrogenation of ketone also could be greatly improved by addition of $PhI(OAc)_2$.[12] Although the detailed mechanism is unclear, we predicted that palladium catalyst reacted with I(III) reagent could enhance its electrophilic reactivity. Guided by this thought, we speculated that this interaction between I(III) and Pd catalyst might be helpful to accelerate the *intermolecular* aminopalladation step. Then, the intermolecular aminocarbonylation of alkenes might be expected to deliver β-amino acid derivatives.

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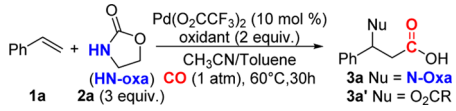
To test the above hypothesis, $PhI(OAc)_2$ was first employed to test the possibility. Gratifyingly, a significant amount of desired product **3a** was obtained in the presence of palladium catalyst, and $Pd(OTFA)_2$ provided **3a** in 80% yield (Table1, entries 1−4).

Table 1. Optimization of Reaction Conditions[a]



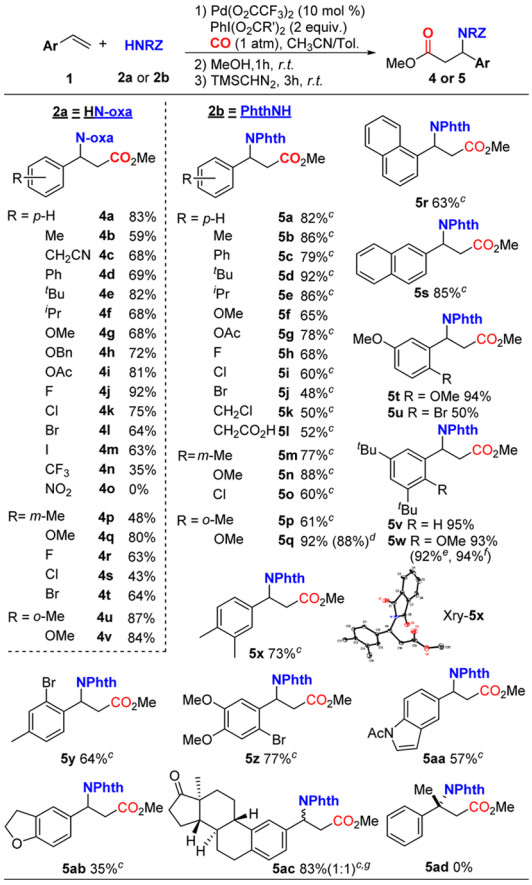
entry	Pd catalyst	oxidant	yield (%)[b] 3a	3a′ (R)
1	$Pd(OAc)_2$	$PhI(OAc)_2$	45	4 (Me)
2	$Pd(CH_3CN)_2Cl_2$	$PhI(OAc)_2$	65	5 (Me)
3	$Pd(acac)_2$	$PhI(OAc)_2$	36	3 (Me)
4	$Pd(OTFA)_2$	$PhI(OAc)_2$	80	5 (Me)
5	$Pd(OTFA)_2$	$PhI(OPiv)_2$	55	5 (^{t}Bu)
6	$Pd(OTFA)_2$	$PhI(O_2CAd)_2$	90 (83)[f]	5 (Ad)
7[c]	$Pd(OTFA)_2$	$PhI(O_2CAd)_2$	80	13 (Ad)
8[d]	$Pd(OTFA)_2$	$PhI(O_2CAd)_2$	85	10 (Ad)
9	$Pd(OTFA)_2$	$(NH_4)_2S_2O_8$	31	0
10	$Pd(OTFA)_2$	oxone	27	0
11[e]	$Pd(OTFA)_2$	35% aq H_2O_2	21	0
12	none	$PhI(O_2CAd)_2$	0	0

[a]All reactions were run at 0.2 mmol scale. [b]Yield obtained by ^{1}H NMR with CF_3-DMA as internal standard. [c]**2a** (1.2 equiv). [d]**2a** (2.0 equiv). [e]Oxidant (5.0 equiv). [f]Isolated yield of ester **4a**.

Further screening of oxidant revealed that $PhI(O_2CAd)_2$ (Ad: adamantyl) was the best (entries 5−6). Furthermore, changing the amount of 2-oxazolidone **2a** has a slight effect on the yield of **3a**. It is notable that the reaction afforded product **3a** in 80% yield even with 1.2 equiv **2a**, but the 3 equiv **2a** provided the best yield (entries 6−8). In these reactions, small amount of oxycarbonylation side product **3a′** was also provided and could not be completely suppressed. Compared to I(III) reagent, other strong oxidants were proved to be less efficient to provide the desired product (21−31%, entries 9−11). Finally, no product **3a** was observed in the absence of palladium catalyst (entry 12). With regard to the convenient purification, the crude product **3a** in entry 6 was treated with MeOH followed by $TMSCHN_2$ to give the corresponding methyl ester **4a** in 83% yield. It is worth noting that the aminooxygenation product was not observed in all these reactions.

With the optimized reaction conditions in hand, substrate scope of the styrenes was first examined, and the results are summarized in Table 2. Styrenes with various substituents on the *para*-, *meta*-, and *ortho*-position, such as alkyl-, aryl-, alkoxy-, ester-, and halogen groups, were suitable to give the corresponding products **4a**−**4m** and **4p**−**4v** in moderate to good yields (59−92%). However, styrenes bearing strong electron-withdrawing groups were less effective. Substrate **1n** bearing CF_3 group afforded product **4n** in 35% yield, and substrate **1o** with NO_2 group failed to yield product **4o**. For more substituted styrenes, the reactions also afforded corresponding products **4** in good yields (see Supporting Information). Inspired by these results, we turn our attention to more easily removable phthalimide as nitrogen source. When styrene **1a** and phthalimide **2b** were treated under standard condition (entry 6, Table 1), **5a** was obtained in 52% yield combined with a significant amount of oxycarbonylation product **3a′** (~20%). Further optimization of reaction conditions (see Supporting Information) revealed that, when slightly excess amount of styrene was employed, the reaction afforded product **5a** in excellent yield in the presence of $PhI(OAc)_2$ and catalytic amount of CF_3CO_2H. Similar to **2a**, a range of styrenes could react with **2b** to provide the corresponding products **5a**−**5q** in moderate to excellent yields. Electron-rich styrenes were more reactive than electron-poor substrates. In addition, vinylnaphthylenes were suitable to provide amino acid derivatives **5r**−**5s** in good yields. Furthermore, styrenes bearing two- or three-substituents on the arene rings could also be converted to corresponding products **5t**−**5z** in moderate to excellent yields. Steric-hindered substrates showed excellent reactivity to give products **5v** and **5w**. Notably, the reaction could be scaled up to provide product **5w** in excellent yield (92% in 3.0 mmol, 94% in 5.0 mmol). Furthermore, we found that vinylheteroarenes substrates were good for the reaction to deliver products **5aa**−**5ab**. Finally, substrate bearing estrone motif also afforded the corresponding amino acid derivative **5ac** in 83% yield. Unfortunately, because of the steric effect, 1,1- and 1,2-disubstituted styrenes exhibited very poor reactivity toward this aminocarbonylation reaction.

Table 2. Substrate Scope of Styrenes[abc]



[a]Condition A for **2a**: $Pd(O_2CCF_3)_2$ (10 mol %), substrate **1** (0.2 mmol), **2a** (0.6 mmol), $PhI(O_2CAd)_2$ (2.0 equiv) in the mixture solvent of CH_3CN/Toluene (1:1, 1 mL) at 60 °C with CO balloon; Condition B for **2b**: $Pd(O_2CCF_3)_2$ (10 mol %), substrate **1** (0.4 mmol), **2b** (0.2 mmol), $PhI(OAc)_2$ (2.0 equiv). [b]Isolated yield. [c]Italic supercripted letters in table body indicate the following: (*c*) CF_3CO_2H (10 mol %); (*d*) 1.0 mmol scale; (*e*) 3.0 mmol scale; (*f*) 5.0 mmol scale; (*g*) *d.r.* ratio. PhthNH = phthalimide.

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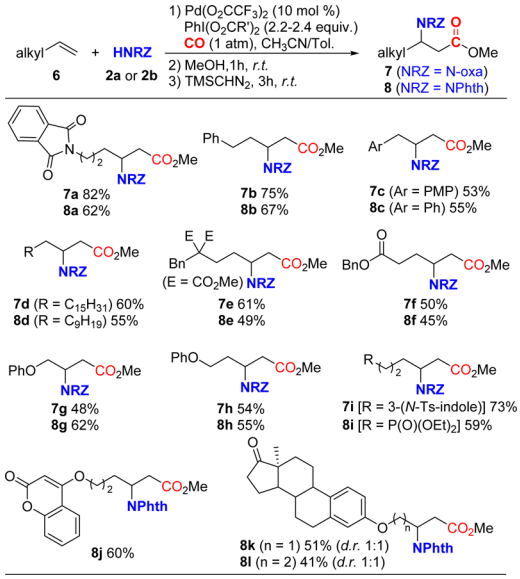
nitrogen source of **2a** and **2b**. When substrates **6a** and **2a** were treated under standard condition (entry 6, Table 1), **7a** could be obtained in 60% yield. Further optimization of reaction conditions (see Supporting Information) revealed that slightly increased amounts of amide nucleophile **2a** and hypervalent iodine were beneficial for the reaction, and the yield of **7a** was finally increased to 82% yield (Table 3). Various unactivated

Table 3. Substrate Scope of Unactivated Alkenes[ab]



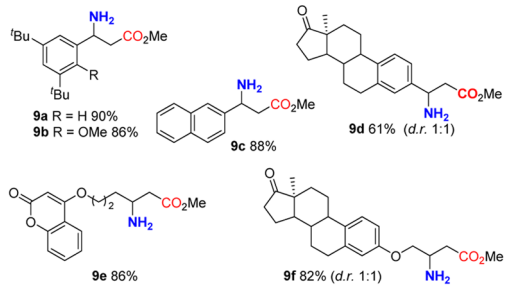
[a]Condition A for **2a**: $Pd(O_2CCF_3)_2$ (10 mol %), **6** (0.2 mmol), **2a** (4.0 equiv), $PhI(O_2CAd)_2$ (2.4 equiv) in the mixture solvent of CH_3CN/Toluene (1:1, 1 mL) at 70 °C with CO balloon. Condition B for **2b**: $Pd(O_2CCF_3)_2$ (10 mol %), **6** (0.2 mmol), **2b** (4.0 equiv), $PhI(OAc)_2$ (2.2 equiv), CF_3CO_2H (10 mol %). [b]Isolated yield.

alkenes were treated by modified reaction condition. As shown in Table 3, alkyl substituted olefins **6b**−**6d** were suitable for the reaction to give products **7b**−**7d** in 53−75% yields. Other olefins bearing functional groups, such as ether, ester, and indole, could be successfully transformed to the corresponding products **7e**−**7i** in moderate yields. Similar to **2a**, phathalimide **2b** exhibited good reactivity to afford the desired products **8a**−**8i** in moderate yields. Notably, the complex substrates bearing coumarin and estrone motifs were compatible under these reaction conditions to yield the desired products **8j**−**8l** in satisfactory yields. Again, these reactions presented excellent regioselectivity to give *β*-amino acid derivatives.

Because of the facile deprotection of phthalimide unit, products **5** and **8** could be easily converted to the corresponding free amino acid esters. For example, more complex amino acid esters **9a**−**9f** were obtained in good to excellent yields under treatment with $(NH_2CH_2)_2$ in MeOH (Table 4).

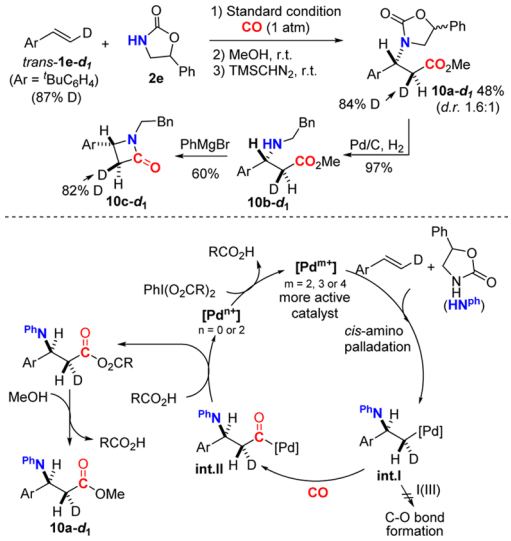
To illustrate the reaction mechanism, the stereochemistry was first investigated by employing deuterium labeling substrate *trans*-**1e**-d_1. The reaction afforded product **10a**-d_1 with 1.6:1 *d.r.* ratio in 48% yield, and its configuration was assigned from compound **10c**-d_1 via sequential hydrogenation and cyclization (see Scheme 2 and Supporting Information). The selective formation of *syn*-amino-carbonylation product **10a**-d_1 suggested that the reaction is initiated from *cis*-aminopalladation of alkenes.[13] Then, CO insertion into alkyl-Pd complex **int.I** and nucleophilic attack of carboxylate at acyl-Pd species **int.II** yielded

Table 4. Deprotection of Products[ab]



[a]Condition: compound **5** or **8** with $(NH_2CH_2)_2$ (10 equiv) in MeOH. [b]Isolated yield.

Scheme 2. Stereochemistry and Proposed Mechanism



the anhydride product, which could further undergo hydrolysis to give carboxylic acid or alcoholysis to give carboxylic ester.

As mentioned previously, the employment of hypervalent iodine reagent is crucial for the successful aminocarbonylation. To probe the role of I(III) reagent, some controlling experiments were conducted with the model reaction of **1a** and **2a** under CO atmosphere (Figure 1). Compared to the catalytic reaction with BQ (green), the catalytic system of [Pd]/$PhI(O_2CAd)_2$ exhibited a much faster rate (red). More importantly, this catalytic system presented a faster rate over the stoichiometic reaction (red versus blue). These interesting observations implied that $PhI(O_2CAd)_2$ should play an important role to accelerate the aminopalladation step rather than simple oxidant

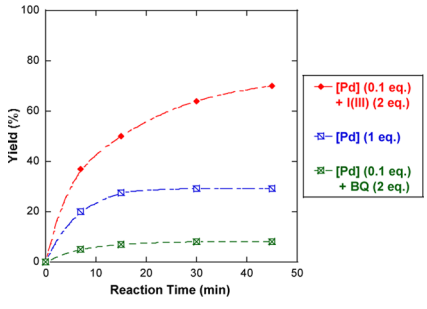


Figure 1. Time course of controlling experiments. [Pd] = Pd-$(O_2CCF_3)_2$, I(III) = $PhI(O_2CAd)_2$, BQ = benzoquinone.

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for Pd(II) catalyst regeneration.[14] We speculated two scenarios: (1) the Lewis acidic character of I(III) reagent facilitates displacement of anionic ligand from Pd(II) by the alkenes and favors a faster aminopalladation process;[15] and (2) the reaction is possibly initiated by a highly electrophilic high-valent Pd species, such as Pd^{III} or Pd^{IV}, which also facilitates to accelerate the aminopalladation step.[16,17] However, it is difficult to differentiate the above two pathways at this stage.

In conclusion, we have developed the first Pd-catalyzed *intermolecular aminocarbonlylation* reaction of alkenes in which broad substrate scope was observed. The current methodology presents a facile synthesis of β-amino acid derivatives from simple olefins. Further mechanistic studies and synthetic application are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) If I(III) only acts as oxidant to regenerate Pd(II) catalyst, the catalytic reaction should have a slower rate than stoichiometric reaction.

(15) Nevado reported that hypervalent iodine CF_3^+ regent (Togni's reagent) could react with I^-. Thus, it is possible that $PhI(O_2CR)_2$ could react with $CF_3CO_2^-$ of Pd catalyst to release more reactive cationic $Pd(OCCF_3)^+$. For details, see: Kong, W.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13086.

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