Palladium-Catalyzed Three-Component Selective Aminoallylation of Diazo Compounds

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KEYWORDS: aminoallylation; diazo compounds; α,α-disubstituted α-amino acid; palladium catalysis; selectivity

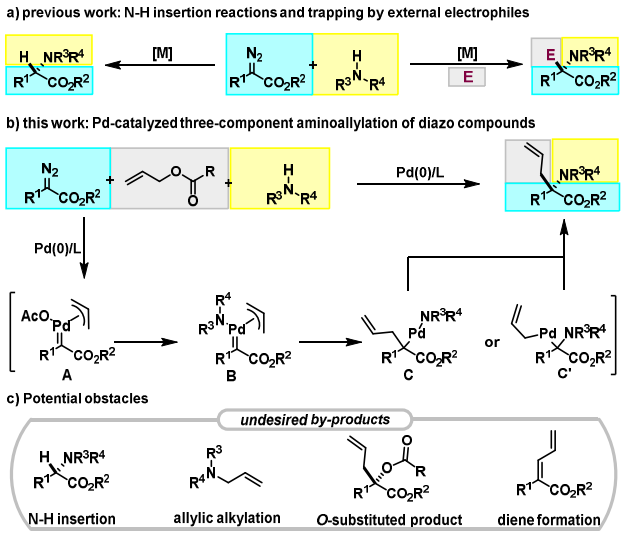
ABSTRACT: In spite of the valuable perspective on rapid accessing α,α-disubstituted α-amino acid derivatives, a three-component reaction of diazo compounds, amines and allyl esters remains as an unexplored challenge, probably because of the foreseeable side reactions arising from each two reactants. In this work, we describe a novel Xantphos-containing dinuclear palladium complex enabled geminal aminoallylation of diazocarbonyl compounds, which provides a range of quaternary α-amino esters selectively. Direct N-H insertion, allylic alkylation of amino nucleophiles and diene formation were not observed under standard conditions. Mechanistic studies indicated that the Xantphos-containing palladium complex with a Pd/P ratio of 1/1 was optimal to enable the reaction to achieve high selectivity. A relayed pathway via allylation of N-H insertion product or [2,3]-sigmatropic rearrangement of a ylide intermediate was unlikely. We believe that the current strategy on palladium-catalyzed selective carbene difunctionalization could be general to construct quaternary carbon centers, and inspire more transformations in related field.

INTRODUCTION

Amino acids and their derivatives play a central role in the design of life. They often serve as building blocks to make up peptides and proteins. The replacement of α-proton with an alkyl group results in increased stability of the corresponding α-amino acid towards hydrolysis and enzymatic degradation, while maintaining the activities on recognizing and binding with the receptor on the cell membrane.[1] These properties have motivated extensive research interests on development of concise methods for their efficient preparation.[2-14]

N-H insertion of a donor-acceptor carbene intermediate is versatile for accessing α-mono substituted α-amino acid derivatives (Scheme 1a, left)[15-24]. Hu and others developed elegant approaches on trapping ammonium ylides by suitable electrophiles (Scheme 1a, right).[25-27] In spite of their high efficiency, the development of a facile and mechanistic distinct synthetic route to access these valuable compounds is still in high demand. To our knowledge, palladium-catalyzed three-component amination and alkylation of carbenic carbon center, which could lead to fully substituted α-amino acid derivatives, is hitherto unknown.

Scheme 1. Hypothesis on Accessing α,α-Disubstituted α-Amino Acid Derivatives through Palladium-Catalyzed Aminoallylation.



In line with our research interests in diazo chemistry[28-39,40-50], we wonder whether a cascade reaction on amination and allylic alkylation of a transient palladium carbene[51-60] intermediate could take place. If such a three-component-reaction is feasible, compounds embedded with α,α-

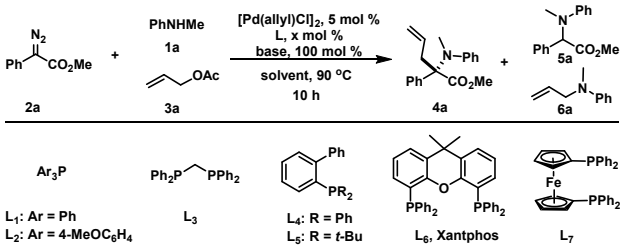
disubstituted α-amino acid motif could also prepared in a modular manner[61] (Scheme 1b). It is envisioned that the palladium(II) intermediate generated in situ would promote the decomposition of donor-acceptor type diazo compound to form a palladium carbene intermediate. Ideally, the establishment of an effective catalytic system would lead to selective formation of α,α-disubstituted α-amino acid derivatives.

While the above strategy could be viewed as an attractive approach to prepare α,α-disubstituted α-amino acid derivatives, several potential obstacles are foreseeable (Scheme 1c). First, α-mono substituted α-amino ester may be produced via N-H insertion reaction.[19,22] Second, a direct allylic alkylation of the amino nucleophile could potentially lead to the formation of allylic amine. Third, formal C-O bond insertion of allylic ester to diazo compound could give α,α-disubstituted α-oxygenated ester.[62] Fourth, a competing pathway through β-hydride elimination of palladium intermediate **C** to form diene may override the requisite C-N bond reductive elimination.[63-66] Therefore, achieving selective formation of α,α-disubstituted α-amino esters through palladium-catalyzed three-component coupling of allyl esters, amines and aryl diazo esters still remains an unexplored challenge. Herein, we describe our preliminary results on execution of this three-component aminoallylation.[67]

RESULTS AND DISCUSSION

To initiate our study, a palladium-catalyzed three-component reaction of *N*-methylaniline **1a**, methyl 2-diazo-2-phenylacetate **2a** and allyl acetate **3a** was tested to verify our hypothesis. As expected, to achieve selective aminoallylation of **2a** is rather challenging. As can be seen from the results compiled in Table 1, the ligands employed were crucial for the chemoselectivity. When the reaction was carried out in the reaction media of ethyl acetate at 90 °C, K_2CO_3 was employed as the base, $[Pd(allyl)Cl]_2$ was selected as the palladium source, and triphenyl phosphine (L_1) was selected as the ligand, product **4a** was indeed observed with a GC yield of 16%, but favouring the formation of N-H insertion type adduct **5a** (Table 1, entry 1). The reaction using tris(4-methoxyphenyl)phosphine (L_2) or dppm (L_3) as the ligand gave allylic amine **6a** as the major product (Table 1, entries 2 and 3). Further experiments on testing the effects of ligands (Table 1, entries 4-7) revealed that the catalyst employing Xantphos (L_6) as ligand could alter the selectivity, leading to the formation of **4a** in 53% GC yield (Table 1, entry 6). A brief examination of base and the reaction media led to the discovery of a set of condition that favoured the formation of **4a** over **5a** and **6a** with a ratio of 21:1:5 (Table 1, entry 14). A pre-reaction of palladium salt with ligand L_6 in DCM at room temperature was beneficial. The yield of **4a** could be enhanced to 65% upon isolation (Table 1, entry 15). Pleasingly, the N-H insertion and allylic amination reaction were almost supressed, when diazo compound **2a** and allyl ester **3a** were added to the reaction mixture at 0 °C, and the aminoallylation product **4a** was isolated in 92% yield (Table 1, entry 16). Altering the ratio of **1a**, **2a** and **3a** to 1:1.5:2.5, or lowering the loading of the catalyst, high selectivity and efficiency were maintained (Table 1, entries 17 and 18). Several chiral ligands were also examined under otherwise identical conditions; however, no promising outcomes were obtained at present.[68]

Table 1. Evaluation of Reaction Conditions.



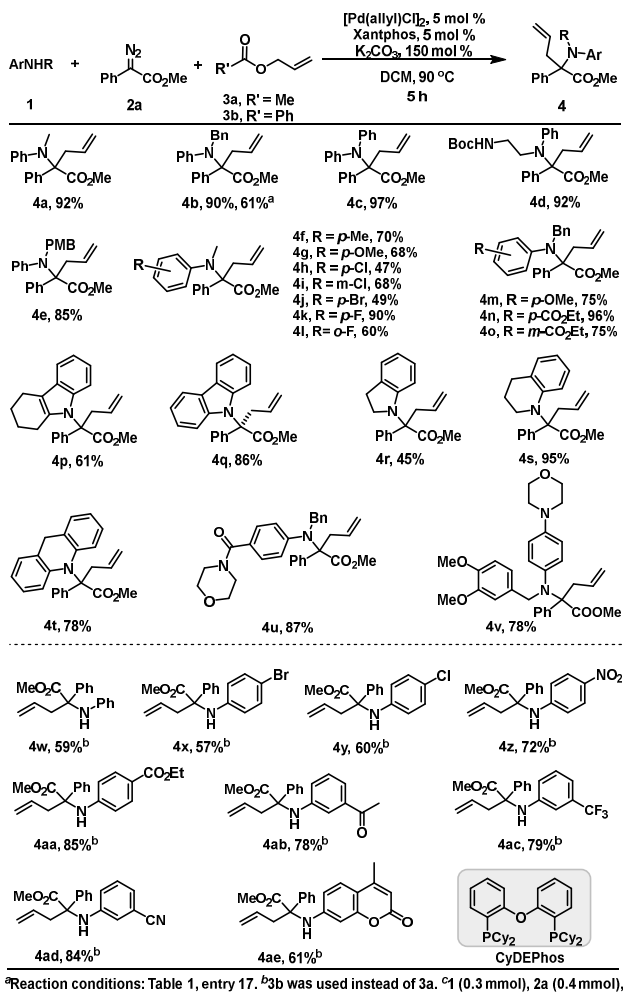
entry [a]	solvent	L/x	base	**4a/5a/6a**	yield/% [b]
1	EA	L_1/15	K_2CO_3	1/5/0	16
2	EA	L_2/15	K_2CO_3	1/1.4/8.7	3
3	EA	L_3/7.5	K_2CO_3	1/3.3/15	-
4	EA	L_4/15	K_2CO_3	1/1.7/0.2	26
5	EA	L_5/15	K_2CO_3	1/10/0	3
6	EA	L_6/7.5	K_2CO_3	2.0/1/0.6	53
7	EA	L_7/7.5	K_2CO_3	1/2/6.2	4
8	EA	L_6/7.5	Cs_2CO_3	3.0/1/1.2	46
9	EA	L_6/7.5	K_3PO_4	1/1.7/1	24
10	EA	L_6/7.5	Et_3N	0/1/0	-
11	dioxane	L_6/7.5	K_2CO_3	-	-
12	PhMe	L_6/7.5	K_2CO_3	-	2
13	DCE	L_6/7.5	K_2CO_3	1/2.5/0	22
14	DCM	L_6/7.5	K_2CO_3	21/1/5	63
15[c]	DCM	L_6/7.5	K_2CO_3	10/1/1	69(65)
16[c,d]	DCM	L_6/5.0	K_2CO_3	-	(92)
17[c-e]	DCM	L_6/5.0	K_2CO_3	-	(92)
18[c-f]	DCM	L_6/2.5	K_2CO_3	-	(88)

[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.4 mmol), [Pd]/L = 1/1.5, base (100 mol%) in solvent (2.0 mL), stirring under atmosphere of Argon. [b]yields of **4a** and the ratio of **4a**/**5a**/**6a** was determined by GC using *n*-decane as internal standard; numbers in parentheses are referred to isolated yields; [c]palladium salt and ligand were pre-reacted at RT for 30 min; [d]150 mol% K_2CO_3 was employed; **1a** and **2a** were added to the reaction mixture at 0 °C; [e]**2a** (0.3 mmol), **3a** (0.5 mmol) were added; [f]2.5 mol% $[Pd(allyl)Cl]_2$ was employed. EA = ethyl acetate, DCM = dichloromethane.

Substrate scope. With a set of conditions for selective aminoallylation of diazo compound **2a** established, we then explored the substrate scope with respect to the amination reagents **1** (Table 2). As can be seen, a variety of disubstituted aniline analogues could participate in current three-

component reaction well. Beside methyl group, anilines bearing other groups on the nitrogen atom, including phenyl, benzyl or substituted benzyl groups, could act as amination reagents to react with diazo compound **2a** and allyl acetate **3a**, giving corresponding aminoallylation products in high yields (**4a**-**4e**, **4r** and **4s**, 78-97%). When ethane-1,2-diamine derivative **1d** was employed, the reaction was selectively taking place at aniline site, leaving the Boc protected amine moiety intact, and the aminoallylation product **4d** was obtained in 92% yield upon isolation. Electron-varied substituents on the phenyl ring were well tolerated and gave the corresponding products (**4f**-**4l**) in moderate to excellent yields (60-96%). Functional groups including halogens, ester and amide were compatible and delivered a range of α,α-disubstituted α-amino esters successfully, which provided synthetic handles for further downstream synthetic applications. Indole, carbazole, indoline, tetrahydroquinoline and dihydroacridine were viable amination reagents, and the corresponding α-amino esters with fully substituted carbon centers were obtained in moderate to excellent yields (**4p**-**4t**, 45-95%).

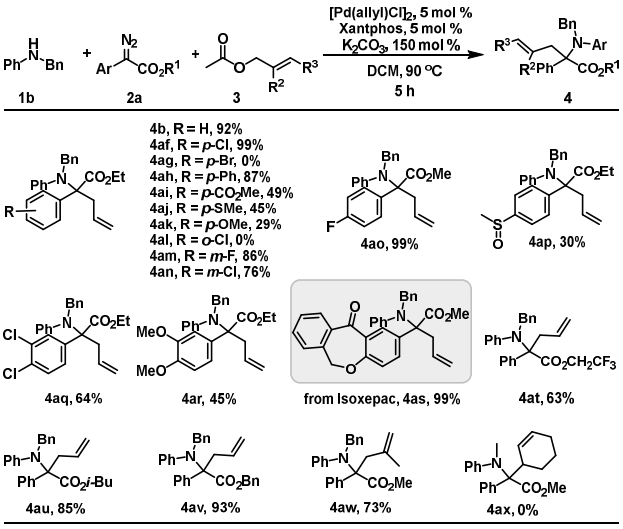
Table 2. Reaction Scope with Respect to Anilines 1.[a]



[a]Reaction conditions: Table 1, entry 17. [b]3b was used instead of 3a. [c]1 (0.3 mmol), 2a (0.4 mmol), 3 (0.2 mmol), $[Pd(allyl)Cl]_2$ (5 mol %), CyDEPhos (5 mol %), K_2CO_3 (0.6 mmol) in anhydrous DCM (2.0 mL), stirred under an atmosphere of argon at 90 °C. PMB = p-methoxybenzyl.

To our delight, free aniline could also be employed as amination reagent under slightly modified conditions. As depicted, replacing the ligand with CyDEPhos ((oxybis(2,1-phenylene))bis(dicyclohexylphosphane)), and enhancement the mount of K_2CO_3 to 3.0 equiv., the desired adduct **4w** was obtained in 59% isolated yield after purification by column chromatography. Similarly, functional moieties like bromo, chloro, nitro, ester, ketone, trifluoromethyl and cyano groups were tolerated; the corresponding aminoallylation products (**4x**-**4ad**) were obtained from 57% to 85% yields. Aniline containing a coumarin scaffold could react with **2a** and **3a** as well, and the desired product **4ae** was isolated in 61% yield.

Table 3. Reaction Scope with Respect to 2 and 3.[a]



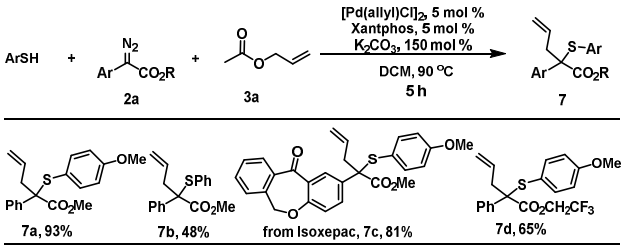
[a]Reaction conditions: Table 1, entry 17

Next, the generality and limitation of diazo compounds **2** were examined (Table 3). Aryl diazoesters bearing chloro (**4af**, **4an** and **4aq**) fluoro (**4am** and **4ao**) and ester (**4ai**) groups at the *para* or *meta* position on the benzene ring could react with benzyl substituted aniline **1b** and **3a** smoothly, giving the corresponding difunctionalized products in 49% to 99% yields. Setting a chloro group at *ortho* position of the phenyl ring resulted in a sluggish reaction, which was probably attributed to steric hindrance nature of the corresponding diazo ester. A bromo group decorating on the benzene ring was not compatible under current conditions (**4ag**). Sulfoxide, which proved to be apt to react with transition metal carbene intermediate, was also tolerated (**4ap**). It was found that the outcome of the reaction was marginally affected the electron-donating nature of the groups on the phenyl rings of the aryl diazoesters. As depicted, the reactions of diazo compounds bearing methoxyl and thiomethyl groups gave the desired products in low yields (**4aj**, **4ak** and **4ar**). Pleasingly, aryl diazoester derived from isoxepac was a competent substrate, which could react with **1b** and **3a**, giving the corresponding amino ester **4as** in nearly quantitative yield. We have also examined the reactivity of diazo compounds containing other esters groups, and these reactions provided the corresponding products in 63% (**4at**), 85% (**4au**) and 93% (**4av**) isolated yields, respectively. Simple ethyl diazoester without an aryl group was not compatible to react to furnish the corresponding aminoallylation product under standard conditions. The reaction of allylic acetate bearing a methyl group on the alkene moiety could

also proceed well, giving **4aw** in 73% yield upon isolation. The reaction of acetate **3** containing internal allylic ester group failed to give **4** under current conditions.

After identifying a set of condition for aminoallylation of aryl diazoesters, a challenging thioallylation was tested subsequently (Table 4). A brief examination of various thiophenols revealed that *para*-methoxylthiophenol was an excellent substrate for the desired transformation, and gave the α,α-disubstituted thioester **7a** in 93% isolated yield. By contrast, unsubstituted thiophenol could also react, but gave the corresponding product **7b** in diminished yield. The major by-product was arising from the formal C-O bond insertion of allyl acetate **3a** to the palladium carbene intermediate, which led to oxylallylation of carbenic carbon center. Diazo ester derived from isoxepac was also thioallylated successfully, giving the desired product **7c** in 81% isolated yield. Diazo compound containing a trifluoroethyl ester moiety was viable substrate as well, and the corresponding product **7d** was isolated in 65% yield.

Table 4. Thioallylation of Aryl Diazoesters.[a]

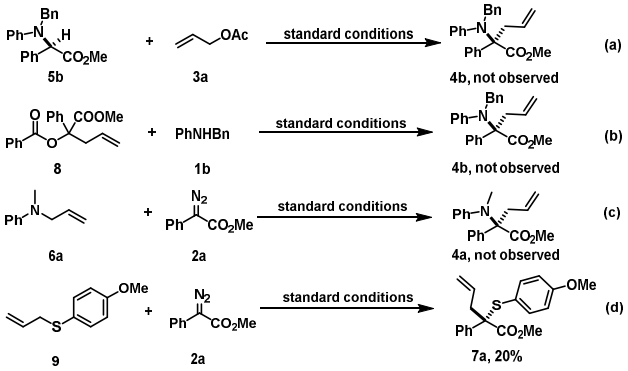


[a]Reaction conditions: Table 1, entry 17

MECHANISTIC STUDIES

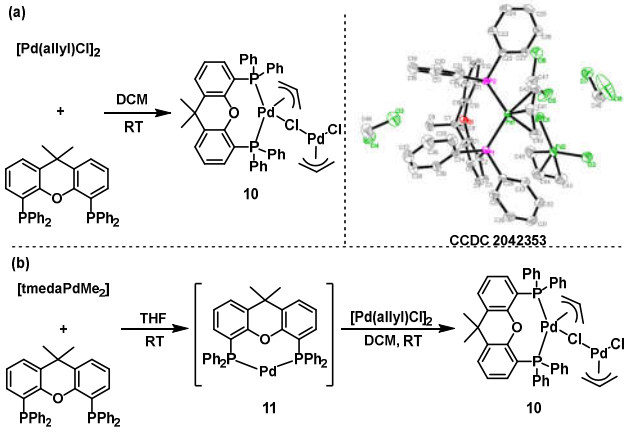
Further experiments were conducted to shed light on the reaction mechanism. First, N-H insertion type product **5b** could not convert to **4b** by reacting with **3a** under standard conditions (Scheme 2a). Second, compound **8** was prepared and subjected to the standard conditions to react with **1b**. However, no conversions of both **8** and **1b** were observed (Scheme 2b). These results suggested that potential side products **5** and **8** were not reaction intermediates for **4**. Moreover, the reaction of allylic amine **6a** with diazo compound **2a** could not give **4a** (Scheme 2c), which also indicated that **6a** was not an intermediate to produce **4a**. This observation further suggests a reaction path through [2,3]-sigmatropic rearrangement[69-71] of ammonium ylides was unlikely. Interestingly, the reaction of sulfide **9** with **2a** gave **7a** but in a much lower yield than three-component thioallylation reaction under standard conditions (Scheme 2d).

Scheme 2. Mechanistic Experiments.



To get more information on the palladium catalyst, the stoichiometric reaction of Xantphos with $[Pd(allyl)Cl]_2$ was monitored by NMR spectroscopy. Surprisingly, treatment of $[Pd(allyl)Cl]_2$ with one equivalent of Xantphos in DCM led to selective formation of a dinuclear palladium complex **10**.[72-74] Although this complex was proved to be air and moisture sensitive, we were able to obtain a crystal in high quality under an atmosphere of argon. The structure of **10** was confirmed by X-ray crystallography, in which one of the palladium atoms coordinated to both arms of the bidentate phosphine ligand (Scheme 3a). The benefit on pre-reaction of $[Pd(allyl)Cl]_2$ with Xantphos may highlight the positive effects of **10** on selective formation of **4a**. Given the fact that the reactions using $Pd_2(dba)_3$•$CHCl_3$ or $Pd(PPh_3)_4$ as palladium sources gave negligible amount of target adduct **4a**,[68] we were thinking about the possibility whether **10** was a precursor to generate Pd(I) species. In this regard, we tried to prepare a potential Pd(I) complex containing Xantphos ligand. A Pd(0) complex **11** was generated in situ[75,76], and then it was treated with $[Pd(allyl)Cl]_2$ (with 1:1 ratio of Pd/P in whole). Interestingly, complex **10** was obtained as main product, together with precipitation of small amount palladium black species (Scheme 3b).

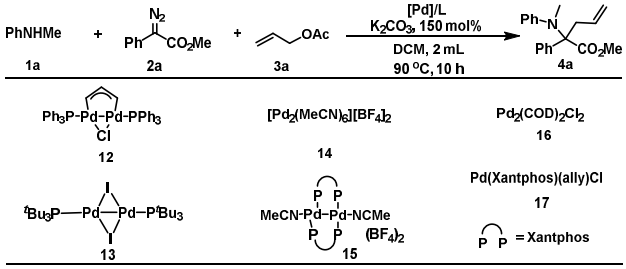
Scheme 3. Mechanistic studies on palladium complexes.



Since we were unable to obtain a stable Pd(I) complex from **10**, the reactivity of a number of well-defined dinuclear Pd(I) complexes **12**-**16** were tested for current three-component reaction. As can be seen, complex **10** has proved to be competent for this three-component reaction (Table 5, entry 1). The reactions catalyzed by palladium(I) dimers **12** or **13** were unselective for the formation of **4a** (Table 5, entries 2 and 3). Delightfully, a catalyst generated from

cationic complex **14** and Xantphos (Pd/P = 1/1) was capable of inducing the selective formation of **4a**, which was obtained in 65% yield upon isolation (Table 5, entry 4). When the reaction was carried out in a more concentrated solution, the yield of **4a** could be enhanced to 84% (Table 4, entry 6). By contrast, palladium(I) complex **15** bearing two Xantphos ligands was inactive to produce **4a** (Table 5, entry 5). A catalyst generated from palladium(I) dimer **16** bearing transient COD ligand was also competent for selective aminoallylation reaction, and **4a** was isolated in 91% yield (Table 5, entry 7). Interestingly, well-defined palladium(II) complex **17** could also enable the three-component reaction to occur, giving **4a** in 67% isolated yield (Table 5, entry 8). These results suggest that the reactions enabled by palladium complexes **14** (Table 5, entry 6) and **16** (Table 5, entry 7) with Xantphos ligand may have similar reaction profiles to the one with complex **10**, and a common palladium(II) species akin to **17** was produced within the catalytic cycle.

Table 5. Comparison Experiments with Well-Defined Palladium Complexes.

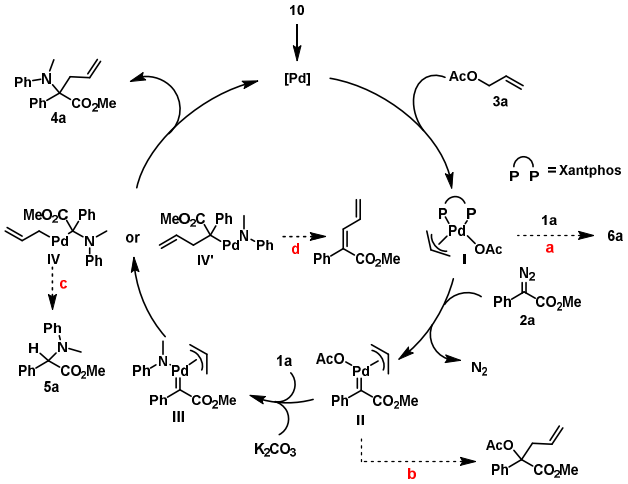


entry	[Pd]/mol%	L/mol%	**4a**/%
1	**10**, 5	-	90
2	**12**, 5	-	25
3	**13**, 5	-	trace
4	**14**, 5	Xantphos, 5	65
5	**15**, 5	-	trace
6[a]	**14**, 5	Xantphos, 5	84
7[a]	**16**, 5	Xantphos, 5	91
8	**17**, 10	-	67

[a] The reaction was run in DCM (1.5 mL).

Although an exact pathway is not clear at present, based on the results obtained above and previous report, a plausible reaction mechanism was proposed (Scheme 4). Taking aminoallylation for example, an active catalyst was produced in situ from complex **10**, and the catalytic cycle started with oxidative addition of low valent palladium catalyst to allyl acetate **3a** to generate a π-allyl palladium intermediate **I**, which might be embeded with a similar core structure as **17**. **I** could further react with diazo compound **2a** to produce a palladium carbene intermediate **II**. Displacement of acetate anion with by an external nucleophile **1a** would furnish another carbene intermediate **III**, which might undergo migratory insertion to produce intermediate **IV** or **IV'**. Reductive elimination would eventually give the final aminoallylation product **4a** with the concomitant regeneration of the active palladium catalyst to enter the next cycle. A related reaction path could dominate for thioallylation reaction, since a significant low yield of **7a** was obtained from the reaction of **9** and **2a**. As depicted, the difficulties on selective formation of **4a** is again highlighted by other potential facile side reactions: (1) direct reaction of intermediate **I** with **1a** to generate **6a** (arrow a); (2) alkoxylation/allylation takes place from palladium carbene intermediate **II** (arrow b)[62]; (3) β-hydride elimination from intermediate **IV** or **IV'** to form N-H insertion type side-product **5a** (arrow c) or diene type side-product (arrow d)[63-66].

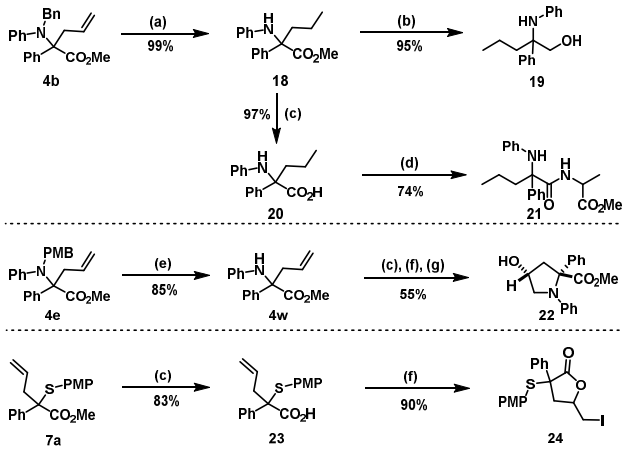
Scheme 4. Plausible Catalytic Cycle. Ligands and counterions were omitted for clarity.



SYNTHETIC APPLICATION

Several experiments were carried out to demonstrate the synthetic utility of current protocol (Scheme 5). The alkene moiety in product **4b** could be hydrogenated in the presence of Pd/C and HCO_2NH_4 to give **18** with a concomitant removal of the benzyl group. Reduction of **18** by LAH could give amino alcohol **19** in 95% isolated yield. Saponification of **18** could lead to the formation of α,α-disubstituted α-amino acid **20** in very high efficiency. **20** was further applied for a dipeptide synthesis, giving **21** in a straightforward manner. The PMB group in **4e** could be removed under mild conditions with the treatment of HBr in HOAc, and gave α-amino ester **4w** in 85% yield. The double bond in the product provides opportunity to increase the structural complexity. For instance, following a three-step, one-pot manipulation, a proline analogue **22** could be obtained as a single isomer in 55% overall yield from **4w**. Similarly, hydrolysis of the thioallylation product **7a** could furnish **23** in 83% yield. Treatment of **23** with elementary iodine and NaI in dark could lead to the formation of γ-lactone **24** as a mixture of diastereoisomers in 90% yield upon isolation.

Scheme 5. Synthetic manipulations. Conditions and reagents: (a) **4b**, HCO_2NH_4, 10% Pd/C, MeOH/H_2O, reflux, 5 h, 99%; (b) $LiAlH_4$, THF, 0 °C, 95%; (c) LiOH, THF/MeOH/H_2O, 0 °C, 5 h, 97%; (d) (*D*/*L*)-methyl alaninate•HCl, DCC, DMAP, $KHCO_3$, DCM, RT, overnight, 74% (dr = 3.8:1); (e) HBr in AcOH, *n*-hexane, 0 °C-rt, 85%; (f) I_2, NaI, $NaHCO_3$, H_2O, rt, dark; (g) NaH, MeOH, rt.



CONCLUSION

In conclusion, a palladium-catalyzed challenging three-component reaction of aniline derivatives with allyl acetates and aryl diazoesters was described, which provided a range of α,α-disubstituted α-amino acid derivatives selectively. This method was amenable for selective thioallylation. Mechanistic experiments revealed that relayed reaction via N-H insertion and allylic alkylation or [2,3]-sigmatropic rearrangement of a nitrium ylide was unlikely. Furthermore, the participation of a Xantphos-containing dinuclear palladium complex with a Pd/P ratio of 1/1 was optimal for the aminoallylation to occur selectively. Further studies on identification the active catalyst and other carbene difunctionalizations in presence of dinuclear palladium complex are on-going in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

SI: Experimental procedures and analysis data for all new compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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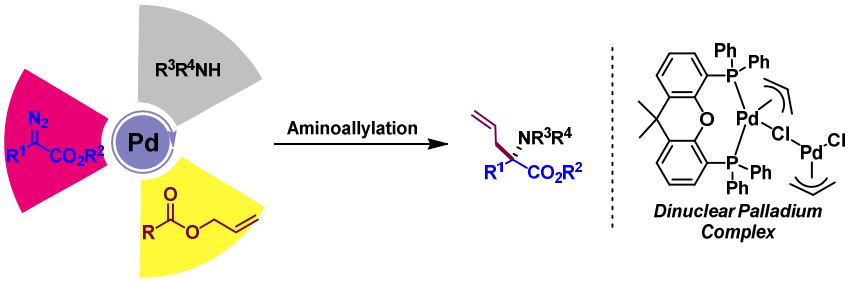
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Dinuclear Palladium
Complex