Palladium-Catalyzed Formal Insertion of Carbenoids into Aminals via C−N Bond Activation

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S *Supporting Information*

ABSTRACT: A new strategy for selective insertion of metal carbenes into C−N bond has been developed via Pd-catalyzed C−N bond activation. A series of aminals and α-diazoesters with different substituents were successfully incorporated even in 0.1 mol % of catalyst under mild conditions, affording a wide range of α,β-diamino acid esters with quarternary carbon-centers. Preliminary mechanistic studies uncovered that the unique electrophilic cyclopalladated species could easily react with diazoacetates to generate a Pd-carbenoid intermediate which was involved in the catalytic cycle.

Transition-metal-catalyzed insertion of metal carbenes into X−H (X = B, N, O, S, Si, et al) bonds, which involves the stepwise ylide formation and proton transfer, is one of the most reliable methods for constructing carbon−heteroatom bonds and has received considerable developments.[1] However, when the H is replaced with a carbon, the more useful corresponding C−X insertion reactions via the same stepwise ylide mechanism would become intricate, as it is hard to control the selectivity for the migration of two distinct carbon moieties attached to a heteroatom (Scheme 1, eq 1).[2] Previous studies showed that highly selective C−X insertion only can be realized with special substrates, in which some special groups such as benzyl, allyl, and strain carbocycle have to be installed onto the heteroatom to facilitate the selective [2,3]-sigmatropic or Stevens rearrange-

ment.[3] Thus, its further application is significantly restricted. One attractive and direct approach to circumvent this problem is to develop a conceptually distinct strategy, in which the C−X bond was selectively cleaved by a metal prior to the step for formation of metal-carbene species and both cleaved fragments should be successfully incorporated into the carbene moiety (Scheme 1, eq 2). However, such a process has never been realized, although considerable progress had been achieved on the transition-metal-catalyzed coupling reactions with carbenes as coupling partners.[4,5]

The cleavage of a C−N bond of simple nitrogen-containing building blocks and installing the cleaved carbon and nitrogen fragments onto a coupling partner via simultaneously forming a new C−C and C−N bond is perhaps one of the most direct and promising pathways for the synthesis of nitrogen-containing functional molecules.[6] In this respect, the selective insertion of a carbenoid into a C−N bond with the formation of a C−C and C−N bond offers an attractive method for the preparation of amino acid esters. However, it is highly challenging to establish such a protocol due to the lack of a facile and general method that not only can facilitate the rate of the C−N bond cleavage to be faster than the formation of metal-carbene species suppressing the formation of ammonium ylide but also can simultaneously generate both a reactive carbon nucleophile and a usable nitrogen nucleophile. Previously, we have disclosed that palladium(0) could readily insert into the C−N bond of aminal via oxidative addition to afford a unique cationic cyclopalladated complex **I** and one molecule of nitrogen nucleophile.[7] The aminomethyl moiety ($R_2NCH_2^-$) contained in the cyclopalladated complex and the amino nucleophile (R_2N^-) have been successfully incorporated into the unsaturated double bond when allenes were utilized as coupling partners.[6i] Inspired by this success, we envisaged that the preformed cationic cyclopalladated complex **I** might be prone to react with α-diazoesters **2** to give the corresponding Pd-carbenoid intermediate **II**,[8] which would further react with the released nucleophilic R_2N^- to provide the desired α,β-diamino acid esters **3**. Herein, we report the first example of an efficient formal insertion of carbenoids into a C−N bond via transition-metal-catalyzed C−N bond activation. Notably, this protocol provides an unusual and reliable approach to α,β-diamino acid esters, which not only are key structural motifs in a myriad of natural products but also serve as important building blocks for the synthesis of important pharmaceuticals.[9]

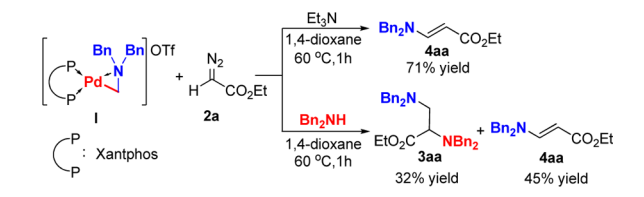**Scheme 1. A New Strategy for Insertion of C−N Bond to Metal Carbene**
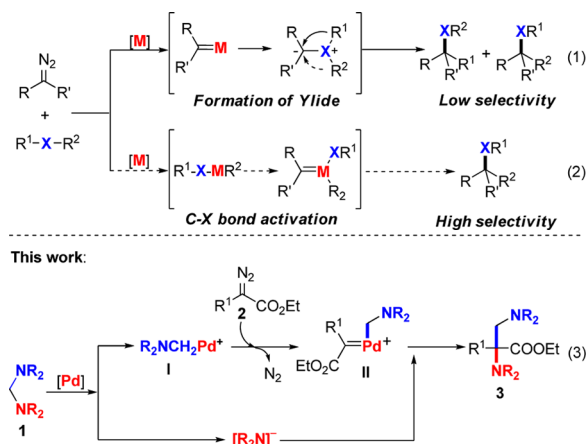
To validate our hypothesis, we initially investigated a stoichiometric reaction of the cyclopalladated complex **I** (confirmed by X-ray analysis)[7a] with α-diazoacetate **2a** in the presence of Et$_3$N at 60 °C (Scheme 2). To our delight, the

Scheme 2. Stoichiometric Reaction of Metal-Complex I and Diazoacetate

aminoacrylate **4aa** was isolated in 71% yield. This result suggested that the cationic Pd-alkyl species **I** could be trapped by diazoacetate to generate the carbene intermediate **II**, which was followed by migratory insertion and β-H elimination facilitated by Et$_3$N to produce **4aa**. By replacing Et$_3$N with Bn$_2$NH, the three-component stoichiometric coupling reaction took place to furnish the desired C−N insertion product **3aa** in 32% yield together with **4aa** as a byproduct and no N−H insertion product was observed. Although the **3aa** was isolated in relative lower yield, these data supported the intermediacy of the complex **I** in the catalytic cycle. These results intrigued us to study the catalytic C−N insertion reaction with aminal and α-diazoacetate according to the proposed reaction pathway. Initial studies were focused on the reaction of *N,N,N′,N′*-tetrabenzyl-methanediamine **1a** with ethyl α-diazoacetate **2a** in the presence of a catalytic amount of a palladium catalyst. We were delighted to find the desired C−N insertion product **3aa** quickly formed in 72% yield together with byproduct **4aa** when the cyclopalladated complex **I** served as a catalyst (Table 1, entry 1). To circumvent the formation of byproduct **4aa** and to maximize the efficiency of the process, an extensive screening of various reaction parameters (palladium, ligand, solvent, and temperature) was conducted (see Supporting Information (SI)). The evaluation of ligands revealed that the bidentate phosphine dppb is superior to all other phosphine ligands. The reaction proceeded well with Pd$_2$(dba)$_3$ as the palladium source in the presence of dppb, suggesting that Pd(0) was involved in the present reaction (Table 1, entry 6; see SI). We then examined the effect of temperature and found that the reaction could proceed smoothly at room temperature to give the desired product in good yield (Table 1, entry 10). To maintain the productivity of this reaction, we chose 60 °C as the optimal temperature. The desired product **3aa** could be obtained in 81% yield by prolonging the reaction time to 6 h (Table 1, entry 11). It is worth noting that after reducing the catalyst loading to 1.0 mol %, the reaction still reacted well to give **3aa** in 80% yield (Table 1, entry 12). 1,4-Dioxane provided the best results among solvents we screened (see SI), and the yield of **3aa** was increased to 82% when the solvent decreased to 1.0 mL. Furthermore, the impact of the counterions over the reactivity and selectivity of the process were investigated (entries 13−17). PF$_6^-$ emerged as the anion of choice to give the desired product in highest yield together with perfect chemoselectivity (entry 15), while comparable results in terms of reactivity were obtained also in the presence of OTf$^-$, accompanied by lower chemoselectivity. Moreover, the desired reaction virtually stopped with Cl$^-$ as the counterion (Table 1, entry 17). In the absence of a Pd-catalyst, the desired product **3aa**

Table 1. Optimization of Reaction Conditions[a]
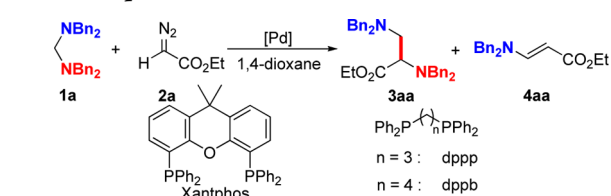
entry	[Pd]	T (°C)	t/h	yield (%) 3aa	yield (%) 4aa
1	Pd(Xantphos)(CH$_2$NBn$_2$)(OTf)	100	2	72	26
2	Pd(Xantphos)(CH$_3$CN)$_2$(OTf)$_2$	100	2	78	15
3	Pd(PPh$_3$)$_2$(CH$_3$CN)$_2$(OTf)$_2$	100	2	69	21
4	Pd(dppp)(CH$_3$CN)$_2$(OTf)$_2$	100	2	68	25
5	Pd(dppb)(CH$_3$CN)$_2$(OTf)$_2$	100	2	81	13
6[b]	Pd$_2$(dba)$_3$/dppb	100	2	58	29
7	Pd(dppb)(CH$_3$CN)$_2$(OTf)$_2$	80	2	77	13
8	Pd(dppb)(CH$_3$CN)$_2$(OTf)$_2$	60	2	78	13
9	Pd(dppb)(CH$_3$CN)$_2$(OTf)$_2$	40	2	75	12
10	Pd(dppb)(CH$_3$CN)$_2$(OTf)$_2$	25	2	63	8
11	Pd(dppb)(CH$_3$CN)$_2$(OTf)$_2$	60	6	81	16
12[c]	Pd(dppb)(CH$_3$CN)$_2$(OTf)$_2$	60	6	80	16
13[c,d]	Pd(dppb)(CH$_3$CN)$_2$(OTf)$_2$	60	6	82	17
14[c,d]	Pd(dppb)(CH$_3$CN)$_2$(BF$_4$)$_2$	60	6	64	29
15[c,d]	Pd(dppb)(CH$_3$CN)$_2$(PF$_6$)$_2$	60	6	88(84)	<5
16[c,d]	Pd(dppb)(CH$_3$CN)$_2$(ClO$_4$)$_2$	60	6	38	24
17[c,d]	Pd(dppb)Cl$_2$	60	6	0	0
18[d]	–	60	6	0	0

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), [Pd] (2.5 mol %), 1,4-dioxane(1.5 mL); yields based on GC analysis by using *n*-cetane as an internal standard; isolated yield was given in parentheses. [b]Pd$_2$(dba)$_3$ (1.25 mol %), dppb (2.75 mol %), HOTf (5.0 mol %). [c][Pd] (1.0 mol %) was used. [d]1,4-Dioxane (1.0 mL).

was not observed under otherwise identical conditions (Table 1, entry 18).

Upon establishing the optimized reaction conditions for the insertion of the C−N bond of aminals to carbenoids, the substrate scope was next investigated. First, the reactions of a variety of aminals with ethyl α-diazoacetate were conducted. As shown in Table 2, the benzyl aminals with both an electron-withdrawing and -donating group underwent the reaction smoothly with good to excellent yields (62−91% yields, **3aa**–**3da**). Substrate **1b** with a sterically demanding *tert*-butyl group on the *meta*-position of phenyl ring afforded the desired product in 62% yield. Aminals derived from simple alkyl amines, such as diethyl amine, dipropylamine, and dibutylamine, could react smoothly with ethyl α-diazoacetate to give the corresponding products (**3ea**–**3ga**) in 79−82% yields. Moreover, aminals prepared from cyclic amines were used as reaction partners, giving the corresponding products (**3ha** and **3ia**) in good yields in the presence of 2.5 mol % of catalyst.

After investigating the generality of aminals, various substituted α-diazoesters were employed in the reaction with *N,N,N′,N′*-tetrabenzylmethanediamine **1a**. As shown in Table 3, the desired reaction was amenable to a broad range of α-diazoesters. The higher reaction temperature was required to prepare a series of α,β-diamino acid esters with a quarternary carbon center. For the aryl diazoacetate, both electron-rich and -deficient aryl groups gave the products in good to excellent yields. Typical functional groups such as alkyl (**2c** and **2d**), methoxyl (**2e**−**2g**), fluoride (**2h** and **2i**), and chloride (**2j**−**2l**)

Table 2. Substrate Scope of Aminals[a]
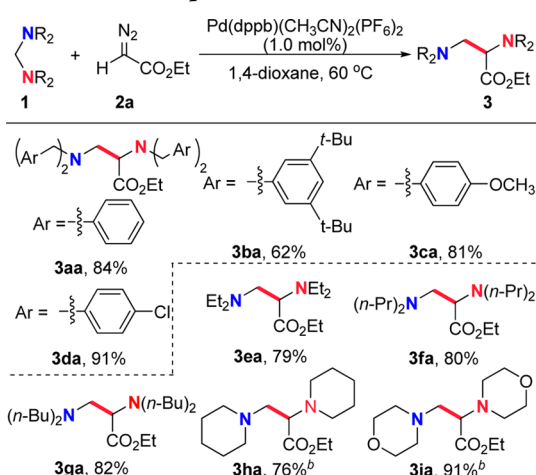
[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), [Pd] (1.0 mol %), 1,4-dioxane (1.0 mL), under N_2 at 60 °C for 6 h, isolated yield. [b][Pd] (2.5 mol %).

Table 3. Substrate Scope of α-Diazoesters[a]
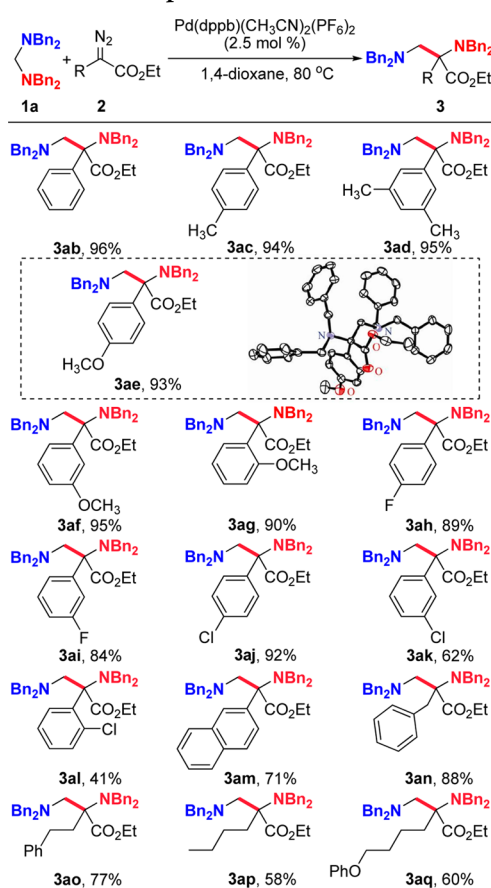
[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), [Pd] (2.5 mol %), 1,4-dioxane (1.0 mL), under N_2 at 80 °C for 12 h, isolated yield.

were well tolerated under the reaction conditions. In general, α-aryl-α-diazoacetates bearing electron-donating groups on the phenyl ring displayed higher reactivity than those with electron-deficient substituents. All the substrates examined here with electron-donating groups gave over 90% yields. The solid state structure of **3ae** was unambiguously determined by single-crystal X-ray crystallographic analysis (see SI).[10] In addition to

substituted phenyl diazoacetates, naphthyl-substituted diazoacetate was also compatible with this new reaction, generating the corresponding diamino acid ester **3am** in 71% isolated yield. After the exploration of the reaction scope of aryl diazoacetates, we turned our attention to more challenging alkyl diazoacetates. The ethyl 2-diazo-3-phenylpropanoate was initially studied, producing the corresponding adduct in 88% yield. Other simple alkyl diazoacetates with a long chain and functional group converted to **3ao–3aq** in 58–77% yields. An enantioselective reaction of **1a** with **2b** has been tried with chiral diphosphine as a ligand; only 37% ee was obtained for **3ab** (see SI).[11]

Taking the results described above and our previous report into consideration,[6] we proposed the following catalytic cycle for this novel reaction (Figure 1). The catalyst precursor Pd(II) was
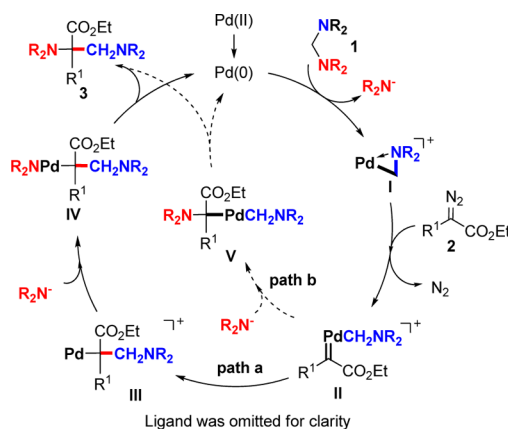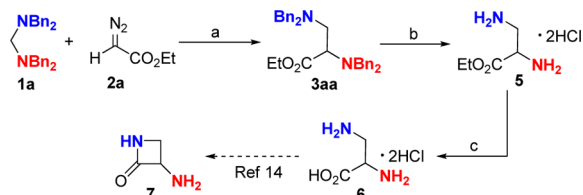

Figure 1. Plausible reaction mechanism.

reduced to Pd(0) which reacted with aminal **1** through oxidative addition to produce the cyclopalladated complex **I** together with one molecule of R_2N^-.[12] The metal complex **I** was then trapped by diazoacetate **2** to generate the Pd-carbenoid **II**. Subsequently, the migratory insertion of the aminomethyl group may take place and intermediate **III** formed, which was then attacked by R_2N^- to afford the intermediate **IV**. Reductive elimination released the desired α,β-diamino acid ester **3** and regenerated the active Pd(0) for the next catalytic cycle (path a). Alternatively, the intermediate **II** might be attacked by R_2N^- to generate the intermediate **V**, which undergoes reductive elimination to give the desired α,β-diamino acid ester **3** and regenerate the active Pd(0) (path b). Since no N–H insertion product was observed in the stoichiometric reaction of complex **I**, diazoacetate **2**, and dibenzylamine (Scheme 2), path b might be ruled out.

The synthetic versatility of the present catalytic system was demonstrated through a large-scale reaction and the simple functional group transformation. The reaction of **1a** with **2a** on a 10 mmol scale completed in 48 h, even in the presence of 0.1 mol % catalyst, yielding 3.64 g of the corresponding product in 74% yield. The benzyl groups of **3aa** were quickly removed to give ethyl α,β-diaminopropanoate dihydrochloride **5** in 93% yield via hydrogenolysis in the presence of a catalytic amount of $Pd(OH)_2/C$.[13] The subsequent acid hydrolysis of **5** provided the α,β-diaminopropanoic acid dihydrochloride **6**, which is a common constituent of the amino acid pool of seeds from various species of Mimosa and Acacia.[15] Compound **6** could be facilely transferred to 3-aminoazetidin-2-one **7**, which is a common building block for synthesis of a variety of antibiotics, such as Penicillins and Cephalosporins.[16]

Scheme 3. Synthetic Utility of the α,β-Diamino Acid Ester[a]

[a](a) Pd(dppb)(CH$_3$CN)$_2$(PF$_6$)$_2$ (0.1 mol %), 1,4-dioxane, 60 °C, 48 h, 74%. (b) CH$_2$ClCHCl$_2$, 20% Pd(OH)$_2$/C (10 wt %), MeOH, H$_2$ (5 atm), 25 °C, 8 h, 93% yield. (c) HCl (6 N), 110 °C, 6 h, 84% yield.

In summary, we have established an unprecedented insertion of carbenoids into the C−N bond of aminals on the basis of palladium catalyzed C−N bond activation, which provided a valuable and efficient method for synthesis of α,β-diamino acid esters under mild conditions. Various aminals and diazoesters are compatible with the reaction conditions to give a broad range of α,β-diamino acid esters with a quaternary carbon-center. Further investigation will be focused on the asymmetric catalysis and other types of C−X bond insertion reactions involving transition-metal-catalyzed C−X bond activation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08476.

　　Crystallographic data for **3ae** (CIF)
　　Experimental details and full spectroscopic data for all new compounds (PDF)

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Notes
The authors declare no competing financial interest.

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(10) CCDC 1405248 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(11) Many commercially available chiral phosphine ligands have been tried; only (*R*)-(6,6′-dimethoxy-[1,1′-biphenyl]-2,2′-diyl)bis(diisopropylphosphine) can give the desired product **3ab** in 37% ee. Further studies to establish a highly enantioselective reaction is needed.

(12) A stoichiometric reaction monitored with in situ NMR further demonstrated that the cyclopalladated complex **I** is produced in the catalytic cycle (see SI for details).

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