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Palladium-Catalyzed Aminomethylation of Nitrodienes and Dienones via Double C-N Bond Activation

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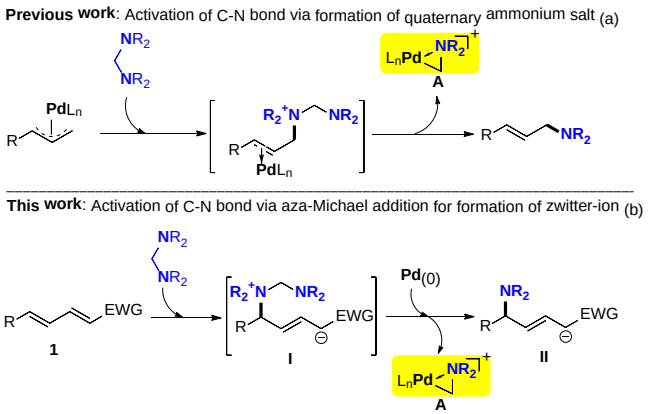
Summary of main observation and conclusion: A new strategy for the generation of the active Pd-alkyl species from aminal via C-N bond activation has been established, in which the formation of zwitterionic intermediate through aza-Michael addition of aminal to nitrodienes and dienones is identified as a key step for the activation of the C-N bond. The efficient strategy has enabled a new palladium-catalyzed α-aminomethylation of nitrodienes and dienones via double C-N bond activation. The scope and versatility of the reaction were demonstrated and a broad range of substrates bearing electron-donating and -withdrawing groups on the aromatic rings were all compatible with this reaction to furnish the desired α-aminomethylated products in moderate to good yields with excellent regioselectivities and *E*/*Z* selectivities.

Background and Originality Content

The dienyl allylic amines and their derivatives are not only important building blocks for the synthesis of various nitrogen-containing compounds, but also widely found in natural products as well as biologically active molecules.[1-6] It is a surprise to find that the catalytic reactions for constructing such a kind of scaffolds remain largely undeveloped, and only few Ir-catalyzed allylic aminations of dienyl allylic carbonates or alcohols have been reported.[7-8] On the other hand, the reaction of activated functionalized dienes with imines or iminium salts under the Morita-Baylis-Hillman (MBH) conditions is another promising approach to functionalized dienyl allylic amines.[9-12] However, the poor *E*/*Z* selectivity observed in most of these reactions restricted the practicality of these reactions. Therefore, it is highly desirable to explore a new and efficient catalytic reaction to prepare functionalized dienyl allylic amines. Recently, we have reported an efficient approach to dienyl allylic amines via palladium-catalyzed aminomethylation of simple dienes with aminals via double C-N bond activation.[13] Inspired by this work and in connection with our work on aminal chemistry, herein, we reported a palladium-catalyzed aminomethylation of activated 1,3-conjugated dienes with aminals to synthesize functionalized dienyl allylic amine.

Recently, our research group has demonstrated that aminals can serve as useful electrophiles undergoing oxidative addition with Pd(0) to form the unique electrophilic cationic cyclopalladated complex **A** (Huang-complex) in the presence of a catalytic amount of acids.[14] Further experiments disclosed that the cyclopalladated complex **A** could be also generated via the reaction of aminal with allylpalladium species, in which the allylic quaternary ammonium salt was formed as the key intermediate (Scheme 1a). The electron-deficient dienes containing a withdrawing substituent at the diene terminus like **1** are good Michael acceptors, which are prone to be attacked by nucleophiles. Tertiary amines are good nucleophiles and have been utilized as the catalyst for MBH reaction via aza-Michael addition[15-16]. Aminals contain two tertiary amine moieties, which could be an excellent nucleophile to react with the electron-deficient diene **1** to form the zwitterionic intermediate through aza-Michael addition. In this context, we envisioned that the in-situ formed zwitterionic intermediate would be capable of undergoing oxidative addition with Pd(0) to generate the cyclopalladated complex **A** together with the intermediate **II**. The highly reactive amine-containing allyl anion would undergo further transformations with the cyclopalladated complex **A** to establish new reactions.

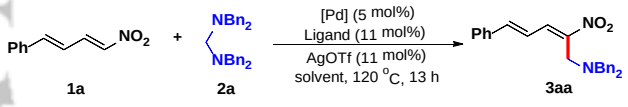


Scheme 1. The strategies for the formation of cyclopalladated complex with aminal.

Results and Discussion

To verify the feasibility of the above strategy, we started our research with the reaction of nitrodiene **1a** and aminal **2a** in DCM at 120 °C by using $Pd(CH_3CN)_2Cl_2$ as a catalyst precursor. When Xantphos was used as the bidentate ligand, the α-aminomethylated product **3aa** was isolated in 13% yield (Table 1, entry 1). Furthermore, we investigated the effects of other phosphine ligands, including typical bidentate phosphines and mono-phosphines (Table 1, entries 2-5). It was a surprise to find that the desired product **3aa** was obtained in 72% yield when $P(4\text{-}CF_3C_6H_4)_3$ was employed as the ligand (Table 1, entry 6). With the best ligand in hand, we next hope to further improve the efficiency of the reaction by examining the palladium precursors in combination with $P(4\text{-}CF_3C_6H_4)_3$ and AgOTf. The results showed that the reaction system was sensitive to the palladium precursor (Table 1, entries 7-11). When $Pd(COD)Cl_2$ was utilized as the palladium source, the desired product **3aa** was obtained in 81% yield with complete regioselectivity. Screening of some representative solvents disclosed that the reaction was most efficient in 1,4-dioxane (Table 1, entry 15). Subsequently, we examined the loading of catalyst and the amount of **2a**, but the yield of **3aa** could not be further improved (Table 1, entries 16-17). Notably, in the absence of palladium catalyst, no desired product was obtained (Table 1, entry 18).

Table 1 Optimization of reaction conditions [a]



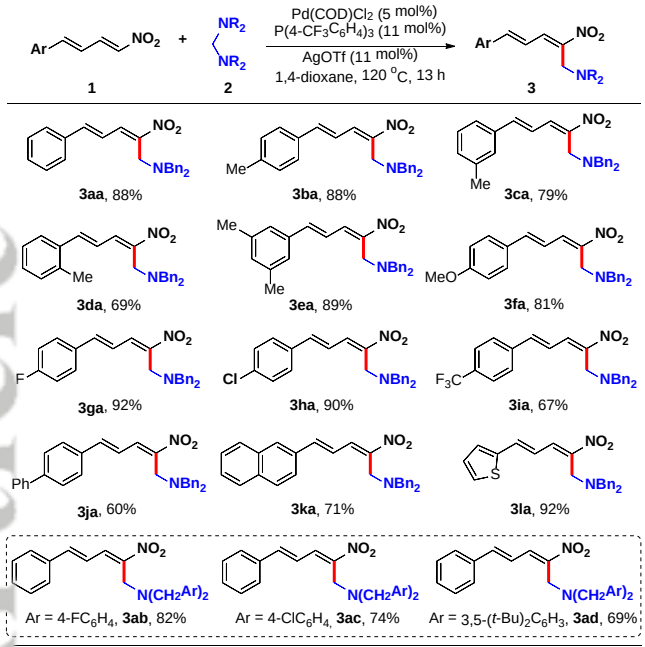
1a 2a 3aa

entry	[Pd]	Ligand	solvent	yield (%)
1[b]	$Pd(CH_3CN)_2Cl_2$	Xantphos	DCM	13
2[b]	$Pd(CH_3CN)_2Cl_2$	DPPE	DCM	14
3	$Pd(CH_3CN)_2Cl_2$	PPh_3	DCM	24
4	$Pd(CH_3CN)_2Cl_2$	$P(4\text{-}MeC_6H_4)_3$	DCM	20
5	$Pd(CH_3CN)_2Cl_2$	$P(C_6F_5)_3$	DCM	13
6	$Pd(CH_3CN)_2Cl_2$	$P(4\text{-}CF_3C_6H_4)_3$	DCM	72
7	$PdCl_2$	$P(4\text{-}CF_3C_6H_4)_3$	DCM	34
8	$Pd(OAc)_2$	$P(4\text{-}CF_3C_6H_4)_3$	DCM	64
9	$Pd(COD)Cl_2$	$P(4\text{-}CF_3C_6H_4)_3$	DCM	81
10	$[Pd(ally)Cl]_2$	$P(4\text{-}CF_3C_6H_4)_3$	DCM	75
11	$Pd(COD)Cl_2$	$P(4\text{-}CF_3C_6H_4)_3$	DCE	58
12	$Pd(COD)Cl_2$	$P(4\text{-}CF_3C_6H_4)_3$	THF	75
13	$Pd(COD)Cl_2$	$P(4\text{-}CF_3C_6H_4)_3$	CH_3CN	63
14	$Pd(COD)Cl_2$	$P(4\text{-}CF_3C_6H_4)_3$	toluene	84
15	$Pd(COD)Cl_2$	$P(4\text{-}CF_3C_6H_4)_3$	1,4-dioxane	88
16[c]	$Pd(COD)Cl_2$	$P(4\text{-}CF_3C_6H_4)_3$	1,4-dioxane	62
17[d]	$Pd(COD)Cl_2$	$P(4\text{-}CF_3C_6H_4)_3$	1,4-dioxane	83
18	-	$P(4\text{-}CF_3C_6H_4)_3$	1,4-dioxane	0
19	$Pd(COD)Cl_2$	-	1,4-dioxane	Trace

[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), [Pd] (5 mol%), Ligand (11 mol%), AgOTf (11 mol%), solvent (2.0 mL), 120 °C, 13 h, isolated yield. [b]Ligand (5.5 mol%). [c][Pd] (2.5 mol%). [d]**1a** (0.20 mmol), **2a** (0.24 mmol).

With the optimized reaction conditions in hand, various substituted nitrodienes **1** were tested to examine the generality of our strategy. As shown in Table 2, the nitrodienes with different substituents on the aromatic ring underwent aminomethylation reaction smoothly, delivering corresponding target products in good yields with excellent regioselectivities and *E*/*Z* selectivities. Besides, this reaction was unbiased toward both the electronic properties of the aromatic moiety and the substitution pattern. Both electron-donating and -withdrawing groups on the rings were smoothly converted to the desired products in moderate to good yields (**3aa**-**3ka**). Notably, the substituents at the *meta*-position or *ortho*-position of the aromatic ring were also tolerated, albeit in slightly lower yields (**3ca** and **3da**). Typical functional groups such as fluoro, chloro, trifluoromethyl were well tolerated under the optimized reaction conditions (**3ga**-**3ia**). Furthermore, naphthyl-substituted nitrodiene and thienyl-substituted nitrodiene were also compatible with this new reaction, generating α-aminomethylated nitrodienes in good yields with excellent regioselectivities and *E*/*Z* selectivities (**3ka**-**3la**). Unfortunately, the aliphatic nitrodiene failed to produce the desired product and the starting material was intact, which might be ascribed to the lower reactivity of the substrate to react with the aminal. In addition, the scope of the aminal was also explored for this aminomethylation. Aminals derived from benzylamines containing different substituents afforded the desired products in moderate to good yields (**3ab**-**3ad**). Either electron-donating or electron-withdrawing groups on phenyl moiety were tolerated well.

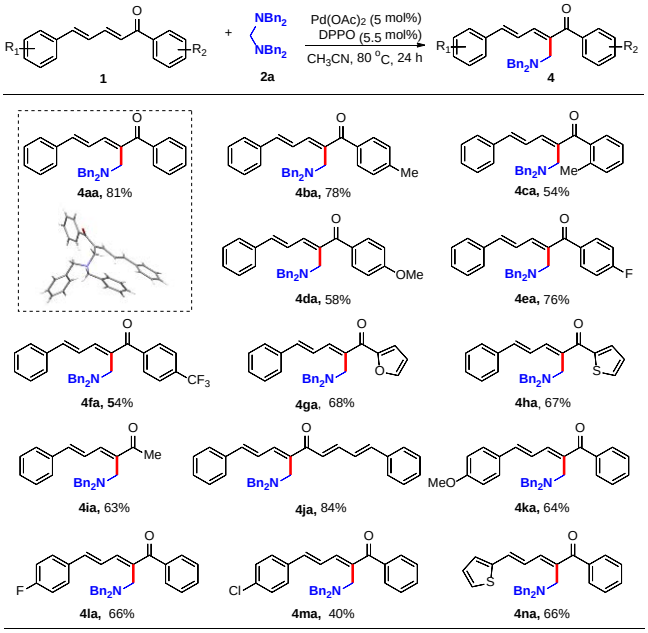
Table 2 Scope of the substrates [a]



[a]Reaction conditions: **1** (0.6 mmol), **2a** (0.5 mmol), $Pd(COD)Cl_2$ (5 mol%), $P(4\text{-}CF_3C_6H_4)_3$ (11 mol%), AgOTf (11 mol%), 1,4-dioxane (2.0 mL), 120 °C, 13 h, isolated yield.

Having identified that the nitrodienes are adequately substrates for the aminomethylated reaction, we aimed to expand the substrate scope to other activated dienes bearing different electron-withdrawing groups. Dienones are important skeletons for the synthesis of biologically active molecules, especially nitrogen-containing heterocyclic compounds.[17-20] Studies have shown that some of them exhibit significant anticancer activity and the selectivity index is superior to that of doxorubicin.[17] Therefore, (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one **1m** and *N*,*N*,*N*′,*N*′-tetrabenzylmethanediamineaminal **2a** were selected as the benchmark substrates to optimize the reaction conditions. After an extensive screening of the reaction conditions, the best result was obtained when the combination of $Pd(OAc)_2$/DPPO was employed as the catalyst system. The desired product **4aa** was obtained in 81% isolated yield when the reaction was conducted in CH_3CN at 80 °C for 24 hours (see the Supporting Information).

Table 3 Substrate scope of dienones [a]



[a]Reaction conditions: **1** (0.48 mmol), **2a** (0.40 mmol), $Pd(OAc)_2$ (5 mol%), DPPO (5.5 mol%), CH_3CN (1.5 mL), 80 °C, 24 h, isolated yield.

Based on the optimal reaction conditions for the synthesis of the α-aminomethylated dienones, we turned our attention to examine the scope of dienones. As shown in Table 3, a variety of dienones derived from aromatic acetophenone reacted smoothly with aminal **2a**, demonstrating that the reaction is unbiased toward electronic properties of substituents (**4aa**-**4fa**). The structure of product **4aa** was determined by single-crystal X-ray crystallographic analysis. Notably, the reaction efficiency of the dienones bearing methyl-substituent at *ortho*-position was significantly reduced, which may be due to the effect of steric hindrance, and the corresponding products could only be obtained in 54% yield. In addition, heterocycle-substituted dienones were also compatible with this reaction and gave the desired products in good yields (**4ga**-**4ha**). To our delight, the dienone derived from acetone also provided the desired products in good yield with excellent regioselectivity and *E*/*Z* selectivity (**4ia**). Moreover, the α-mono-aminomethylated product **4ja** could be obtained in 84% yield when a symmetrical dienone derived from acetone and cinnamaldehyde was used as the substrate. Next, we evaluated the scope of dienones derived from cinnamaldehydes containing different substituents. Typical functional groups such as methoxy, fluoro-, chloro-, and thienyl were also tolerated under the reaction conditions (**4ka**-**4na**). However, the corresponding α-aminomethylation process could only be achieved in 40% yield when using 4-chlorocinnamaldehyde-derived dienone to carry out this reaction (**4ma**).

On the base of the previous studies[13-14,21-29] and our experimental results, a plausible mechanism for this α-aminomethylation is proposed (Figure 1). Firstly, the aza-Michael addition reaction takes place between the aminal **1a** and the nitrodiene **2a** to form the key intermediate **I**. Subsequently, the S_N2-type oxidative addition of allyl ammonium salt **I** to Pd(0) delivers the allylic amine **II** together with generating the active palladium-complex **A**. The intermediate **II** reacts with the palladium-complex A through S_N2-type reductive elimination to give the complex **B**. Cleavage of the C-N bond of the allylic amine **B** via oxidative addition to give the π-allylpalladium species **C**, which isomerizes to intermediate **D**. Finally, β-H elimination of intermediate **D** provides the α-aminomethylated nitrodienes **3aa** together with regenerating the Pd(0) to complete the catalytic cycle. HRMS analysis of the reaction mixture showed a peak at m/z 582.3135, which corresponded to the mass of $[\mathbf{I}+H]^+$ or $[\mathbf{B}\text{-Pd}+H]^+$. This result supported that the intermediates **I** or **B** might be involved in the catalytic cycle of this transformation.

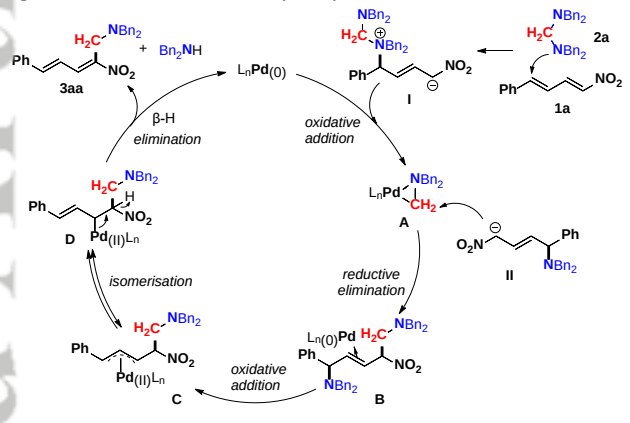


Figure 1 Proposed mechanism.

Conclusions

In summary, we have successfully developed an efficient palladium-catalyzed α-aminomethylation of nitrodienes and dienones with aminals to give the corresponding functional dienyl allylic amines via double C-N bond activation. The reaction proceeded well to give the desired products in moderate to good yields with excellent regioselectivities and *E*/*Z* selectivities. The formation of zwitterionic intermediate through aza-Michael addition of aminal to nitrodienes and dienones is identified as a key step for the C-N bond activation. Further studies to deeply understand the reaction process and apply this strategy are in progress in our laboratory.

Experimental

For the aminomethylation of nitrodienes: A mixture of nitrodiene **1** (0.6 mmol) and aminal **2** (0.5 mmol), $Pd(COD)Cl_2$ (7.2 mg, 0.025 mmol), $P(4\text{-}CF_3C_6H_4)_3$ (25.6 mg, 0.055 mmol), AgOTf (14.2 mg, 0.055 mmol) and 1,4-dioxane (2.0 mL) was added to a Young-type tube in the glove box. The reaction mixture was degassed via the freeze-thaw method and stirred at 120 °C for 13 hours. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (eluted with petroleum ether/diethyl ether = 100/1 - 10/1) on a silica gel to give the desired product **3**.

For the aminomethylation of dienones: A mixture of dienone **1** (0.48 mmol), *N*,*N*,*N*′,*N*′-tetrabenzylmethanediamine **2a** (162.4 mg, 0.4 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), DPPO (10.6 mg, 0.022 mmol), CH_3CN (1.5 mL) was added to a 25 mL flame-dried Young-type tube under nitrogen atmosphere. The reaction mixture was degassed via the freeze-thaw method and stirred at 80 °C for 24 hours. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (eluted with petroleum ether / ethyl acetate = 100/1 - 30/1) on a silica gel to give the desired product **4**.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2020xxxxx.

Acknowledgement

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[30] CCDC 1993112 (**4aa**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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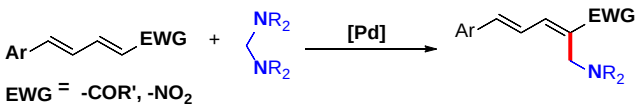

29 examples, up to 92% yield
excellent regioselectivities and E/Z selectivities

A new strategy for the generation of the active Pd-alkyl species from aminal via C-N bond activation has been established, in which the formation of zwitterionic intermediate through aza-Michael addition of aminal to nitrodienes or dienones is identified as a key step for activation of the C-N bond. The efficient strategy has enabled a new palladium-catalyzed α-aminomethylation of nitrodienes and dienones via double C-N bond activation.

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