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Triple-Bond Insertion Triggers Highly Regioselective 1,4-Aminomethylamination of 1,3-Enynes with Aminals Enabled by Pd-Catalyzed C−N Bond Activation

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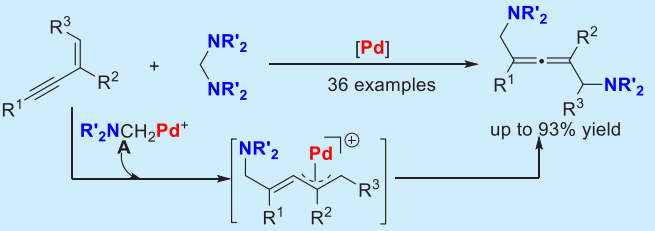
Supporting Information

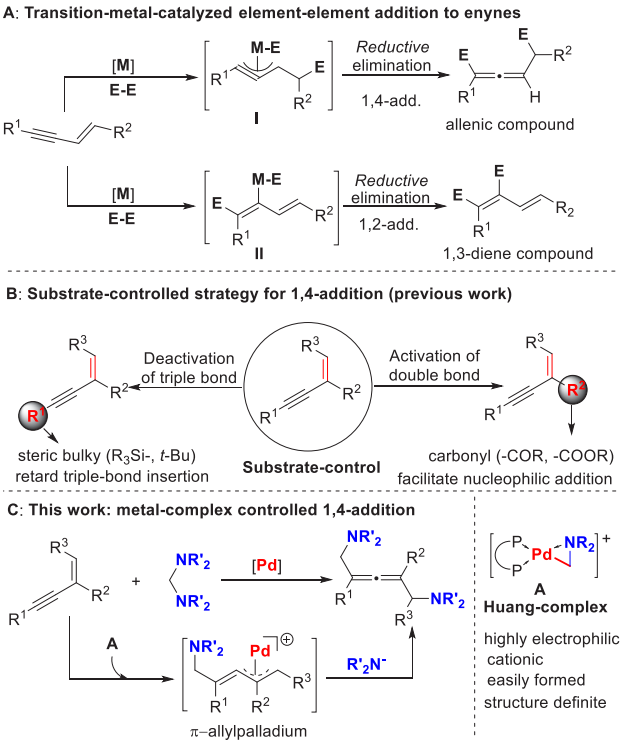
ABSTRACT: A highly chemo- and regioselective 1,4-aminomethylamination of simple enynes with aminals to allenic 1,5-diamines by taking advantage of C−N bond activation has been reported. The reaction proceeds under mild reaction conditions and can be performed under lower catalyst loading (0.1 mol %) with high efficiency and broad substrate scope.



The addition of element−element linkages to unsaturated C−C bonds is a fundamental synthetic strategy that provides direct and efficient access to a wide range of valuable molecules from simple and abundant sources of hydrocarbons.[1,2] In this context, the catalytic conjugate 1,4-addition to 1,3-enynes proceeding through intermediate **I** is a straightforward approach to functionalized allenes,[3−8] which are useful building blocks for natural products and bioactive compound synthesis.[9−18] However, because the alkyne function usually exhibits higher reactivity than that of olefinic bond, the 1,2-addition across the C−C triple bond through intermediate **II** preferentially takes place, leading to the generation of 1,3-diene products (Scheme 1A).[19−29] To improve the regioselectivity, substantial efforts have been devoted to developing efficient strategies to exclusively produce the allenic products. As such, reactions were thought to have to be initiated via double-bond addition (via intermediate **I**), and only a handful of catalytic systems have been demonstrated to achieve the 1,4-addition reaction with special enynes in which either steric bulky substituents were installed into the terminus of the alkyne moiety to thwart the triple-bond insertion or carbonyl groups have to be installed into the terminus of the alkene moiety to facilitate double-bond addition (Scheme 1B).[5,7,8] Thus, the limited substrate scope has been a significant deterrent to the reaction's widespread synthetic use. One attractive and direct approach to circumvent this problem is to develop a conceptually distinct strategy that enables the 1,4-addition reaction to be triggered by triple-bond insertion; thus, the regioselectivity would be independent of the structure of the enynes.

To this end, we reasoned that once a coordinative unsaturated cationic alkylpalladium complex was formed after triple-bond insertion, the intermediate **II** generated in situ would be prone to converting to the corresponding η^3-allylic complex.[30,31] Further interception of the η^3-allylic complex with a nucleophile in an outer-sphere manner would afford the

Scheme 1. Palladium-Catalyzed Regioselective 1,4-Addition to Enynes



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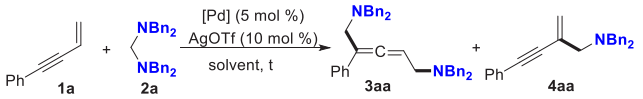
desired allenic adducts. Given these considerations, we speculated that the palladium-catalyzed C−N bond activation recently reported in our group might be an ideal platform for realization of the above hypothesis.[32−39] Specifically, the unique highly electrophilic and cationic Pd−alkyl complex **A** (Huang complex) generated via the oxidative addition of aminal to Pd(0) might be prone to react with the triple bond of enynes to give the corresponding π-allylpalladium species for facilitating the desired 1,4-addition. Herein, we report a conceptually new strategy to turn the regioselectivity of conjugate addition of simple enynes, which enables the development of a novel palladium-catalyzed 1,4-aminomethylamination of simple enynes with aminals to allenic diamines via C−N bond activation (Scheme 1C).[40,41] Diamines are highly valuable molecules from a medicinal and material chemistry perspective.[42] Moreover, the unsaturated diamines containing a C−C double bond such as vinylic, allylic, and allenic functionalities are especially versatile because these moieties in the products exhibit orthogonal reactivity and can be transformed into a wide range of functionalities, thereby facilitating further elaboration. Although a series of elegant approaches to other unsaturated 1,3-diamines and allenic monoamines have been reported,[43,44] the catalytic methods to allenic 1,5-diamines remain elusive, perhaps because of the difficulty in preparing such molecules. The present protocol provides an unusual and reliable approach to little known allenic 1,5-diamines, which should find broad applications in medicinal chemistry.

To examine the feasibility of the proposed strategy, we initiated our investigations with the reaction of but-3-en-1-yn-1-ylbenzene (**1a**) and *N*,*N*,*N*′,*N*′-tetrabenzylmethanediamine (**2a**) in TBME at 80 °C by using $Pd(CH_3CN)_2Cl_2$ as a catalyst precursor. According to our previous results,[32] Xantphos was first utilized as ligand and AgOTf served as an additive to generate the cationic palladium complex to test the feasibility. To our delight, the desired product **3aa** was obtained in 88% yield (Table 1, entry 1). The structure of the desired product **3aa** was unambiguously confirmed by single-crystal X-ray diffraction analysis. In addition, the undesired allylic amine **4aa** was detected, which might result from the off-cycle aminomethylation reaction. Other phosphine ligands including typical bidentate phosphines and monophosphines were then examined (Table 1, entries 1−7), and Xantphos with the steric bulky and larger bite angle stood out as the best ligand. Inspired by this promising result, we next sought to improve the efficiency of the reaction. Various palladium precursors were then screened in combination with Xantphos and AgOTf, and the transformation was found to be sensitive to the palladium precursor (entries 7−12). Catalysts derived from $PdCl_2$, $Pd(TFA)_2$, and $Pd(OAc)_2$ resulted in lower conversion into the desired product **3aa**. However, when $PdBr_2$ and PdI_2 were utilized as palladium sources, product **3aa** was obtained in more than 90% yield with good chemoselectivities and complete regioselectivity, respectively. Screening of some representative solvents disclosed that the reaction was most efficient in TBME (see the Supporting Information). Further optimization of this reaction was performed, and it was found that raising the temperature to 100 °C or decreasing the reaction temperature to room temperature diminished the reactivity (entries 13−16). Notably, no 1,2-addition product was observed in all cases, thus showing the unique features of our method. Control experiments in the absence of Pd catalyst,

Table 1. Optimization of Reaction Conditions[a]



entry	[Pd]	ligand	T (°C)	3/4	yield (%)
1	$Pd(CH_3CN)_2Cl_2$	Xantphos	80	90:10	88
2	$Pd(CH_3CN)_2Cl_2$	DPEphos	80	94:6	62
3	$Pd(CH_3CN)_2Cl_2$	DPPF	80	>20:1	51
4	$Pd(CH_3CN)_2Cl_2$	DPPPen	80	>20:1	29
5	$Pd(CH_3CN)_2Cl_2$	DPPH	80		<5
6[b]	$Pd(CH_3CN)_2Cl_2$	$P(t\text{-}Bu)_3$	80		<5
7[b]	$Pd(CH_3CN)_2Cl_2$	PPh_3	80	>20:1	59
8	$PdCl_2$	Xantphos	80	>20:1	64
9	$PdBr_2$	Xantphos	80	>20:1	93
10	PdI_2	Xantphos	80	92:8	92
11	$Pd(TFA)_2$	Xantphos	80		5
12	$Pd(OAc)_2$	Xantphos	80	95:5	71
13	$PdBr_2$	Xantphos	100	84:16	51
14	$PdBr_2$	Xantphos	60	>20:1	78
15	$PdBr_2$	Xantphos	40	>20:1	73
16	$PdBr_2$	Xantphos	25	>20:1	67
17		Xantphos	80		NR
18	$PdBr_2$		80		NR
19[c]	$PdBr_2$	Xantphos	80		NR

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), [Pd] (5 mol %), Xantphos (6 mol %), AgOTf (10 mol %), solvent (1.0 mL), 12 h, isolated yield of **3aa** based on **1a**. [b]Ligand (12 mol %). [c]Without AgOTf.

Xantphos, or AgOTf revealed that all these parameters were necessary for the reaction to occur (entries 17−19).

With an efficient protocol in hand for the synthesis of the allenic diamines, we turned our attention to validating the generality of our strategy. As shown in Scheme 2, a variety of enynes derived from aromatic alkynes reacted smoothly with **2a**, demonstrating that the reaction is unbiased toward both electronic properties of the aromatic moiety and the substitution pattern (**3aa**−**ka**). Notably, similar results were obtained regardless of the steric parameters of the substituents on the alkyne terminus, which was in sharp contrast to the previous reports that the steric hindered substituent on the alkyne terminus is essential for enabling the 1,4-addition reaction.[3,21] Electron-neutral, electron-deficient, and electron-rich functional groups, such as fluoro, chloro, bromo, nitro, alkyl, and methoxyl, were well tolerated under the reaction conditions, affording the corresponding allenic 1,5-diamines in good to excellent yields. In addition to phenyl-substituted enynes, the naphthyl-substituted enyne (**1k**) was also compatible with this new reaction, generating the corresponding 1,5-diamine **3ka** in 51% yield. As illustrated in **3la** and **3ma**, the reaction could be extended to disubstituted enynes with methyl and hydroxymethyl functional groups attached in the β-position of the alkene moiety, producing tetrasubstituted allenes in good yields. In addition, the substituent on the alkene terminus was also tolerated, albeit in slightly lower yields (**3na**). We attributed the lower reactivity to the steric hindrance of the corresponding η^3-allylic complex formed in the course of this transformation. Gratifyingly, the 1,4-addition reaction could also be applied to enynes with a heteroaromatic substituent on the alkyne terminus (**3oa**−**qa**). Moreover, the 1,4-addition reaction proved not to be restricted to aromatic enynes. When aliphatic enynes **1r**, **1s**, and **1t** were reacted with

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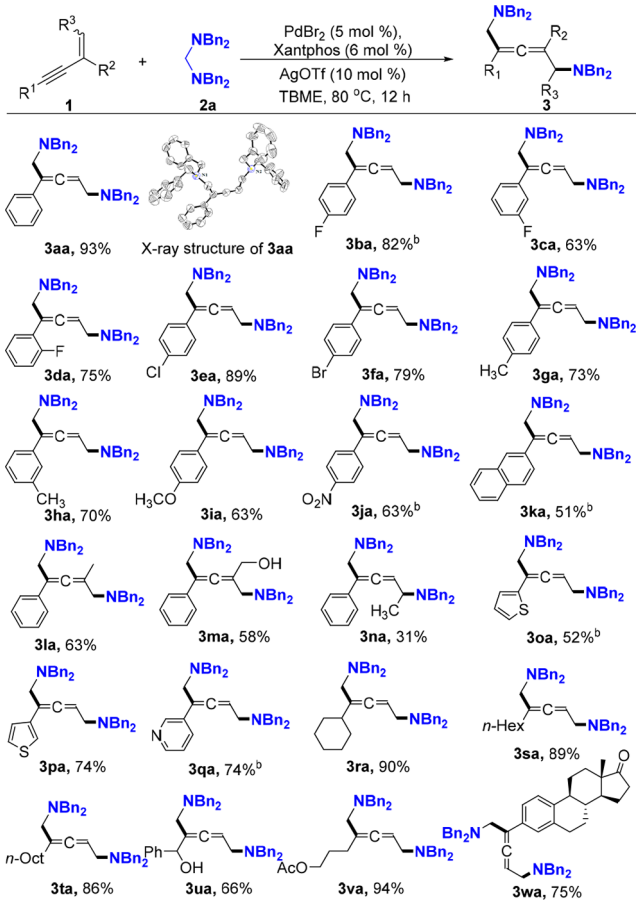
Scheme 2. Substrate Scope of Enynes[a]



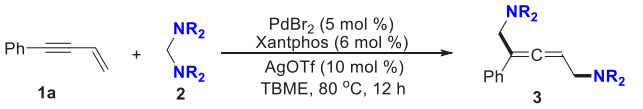
[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), $PdBr_2$ (5 mol %), Xantphos (6 mol %), AgOTf (10 mol %), TBME (1.0 mL), 12 h, isolated yield. [b]$Pd(CH_3CN)_2Cl_2$ (5 mol %), THF (1.0 mL).

aminal **2a**, the corresponding products **3ra**, **3sa**, and **3ta** were efficiently accessed (86−90% yield). In particular, the hydroxyl and ester functional group could be tolerated well under these reaction conditions to provide the corresponding products (**3ua** and **3va**) in good to excellent yields. To further demonstrate the synthetic utility of our method, the estrone-derived enyne **1w** was subjected to our protocol. The substrate was effectively converted into the corresponding 1,5-allenic diamine **3wa** in 75% yield.

We then evaluated the scope of aminals that could be used in this protocol (Table 2). Using simple but-3-en-1-yn-1-ylbenzene **1a** as a model enyne, we observed that a number of dibenzylamine derived aminals were successfully accommodated (**3aa**−**aj**). A variety of electron-withdrawing and electron-donating substitutents on the phenyl ring of the aminals, including halides (F, Cl, Br), CF_3, CH_3, and sterically hindered *t*-Bu, were well tolerated. Aminals derived from simple acyclic aliphatic amines, such as dipropylamine and dibutylamine, could react smoothly with but-3-en-1-yn-1-ylbenzene **1a** to give the corresponding products (**3ak** and **3al**) in 53% and 68% yields, respectively. Cyclic secondary amine derived aminals were also viable substrates, although with somewhat diminished yields relative to the aminals derived from benzylamines.

In addition, this palladium-catalyzed 1,4-addition process proved to be scalable in the presence of a very low catalyst

Table 2. Substrate Scope of Aminals[a]

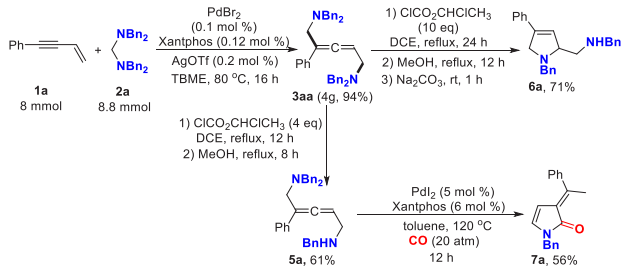


entry	R	3	yield (%)
1	$C_6H_5CH_2$	**3aa**	93
2	$2\text{-}FC_6H_4CH_2$	**3ab**	77
3	$3\text{-}FC_6H_4CH_2$	**3ac**	91
4	$4\text{-}FC_6H_4CH_2$	**3ad**	70
5	$4\text{-}ClC_6H_4CH_2$	**3ae**	81
6	$2\text{-}BrC_6H_4CH_2$	**3af**	83
7	$4\text{-}CF_3C_6H_4CH_2$	**3ag**	74
8	$3,5\text{-}(CF_3)_2C_6H_3CH_2$	**3ah**	78
9	$4\text{-}MeC_6H_4CH_2$	**3ai**	81
10	$4\text{-}t\text{-}BuC_6H_4CH_2$	**3aj**	77
11	$CH_3CH_2CH_2$	**3ak**	52
12	$CH_3CH_2CH_2CH_2$	**3al**	68
13	$-CH_2(CH_2)_3CH_2-$	**3am**	54
14	$-(CH_2)_2O(CH_2)_2-$	**3an**	68

[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.36 mmol), $PdBr_2$ (5 mol %), Xantphos (6 mol %), AgOTf (10 mol %), TBME (1.0 mL), 12 h, isolated yield based on **1a**.

loading (Scheme 3). We were able to conduct an 8 mmol scale reaction to prepare **3aa** using only 0.1 mol % of $PdBr_2$ and 0.12

Scheme 3. Synthetic Utility of the Present Reaction



mol % of Xantphos without lowering the yield of this transformation (4 g, 94% yield). The scalability and robustness of this transformation suggest its potential application in the manufacture of fine chemicals. Furthermore, these synthetically versatile allenic diamines prepared by our method could be easily transformed into a variety of useful molecular architectures. For example, the compound **6a** with a 2,5-dihydropyrrole framework could be obtained in good yields by debenzylation[45] and base-promoted cyclization reaction under the mild reaction conditions.[46,47] On the other hand, the diamine **5a** could be obtained by selectively removing one benzyl group, which can be successfully converted into lactam **7a** via the Pd-catalyzed cyclocarbonylation.[48]

To gain some insight into the reaction mechanism, several experiments were conducted. First, ^{31}P NMR and ESI-MS experiments were conducted to monitor the stoichiometric reaction of cyclopalladated complex **A** with enyne **1a**. At the beginning, two resonances at 2.72 and 14.24 ppm in ^{31}P NMR spectra for the complex **A** appeared.[6] After the resulting mixture was heated at 40 °C for 20 min, two new doublet signals at 4.14, 4.26 ppm and 14.68, 14.86 ppm were detected. At the same time, the ESI-HRMS analysis of the reaction mixture showed a peak at *m*/*z* 1022.2842, which corresponds to the mass of $[C\text{-}OTf]^+$ (see the Supporting Information).

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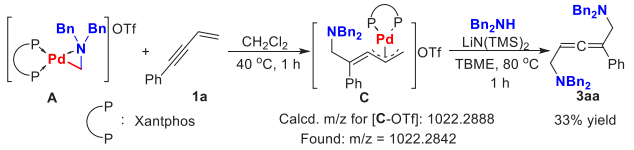
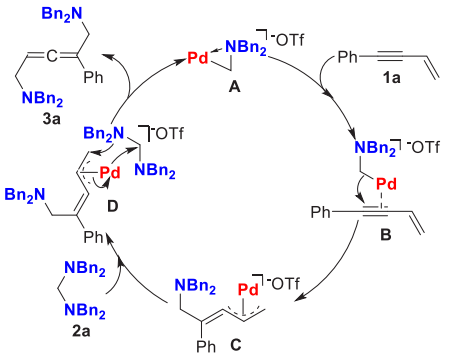
Second, the desired product **3aa** was obtained in 31% yield by sequential treatment of the complex **A** with stoichiometric enyne **1a** and the mixture of Bn_2NH and $LiN(TMS)_2$. Finally, with the cyclopalladated complex **A** as a catalyst, the desired product **3aa** could be exclusively obtained in 72% yield (see the SI). These results indicated that both the cyclopalladated complex **A** and π-allylpalladium species **C** were most likely involved in the present reaction.



On the basis of the above results and our previous work,[32−39] a plausible reaction mechanism for this reaction is exemplified in Scheme 4. Initially, the cyclopalladated complex

Scheme 4. Plausible Reaction Mechanism



A was generated via the oxidative addition of Pd(0) to aminal.[32] The triple bond of the enyne **1a** coordinated to the palladium center to form the intermediate **B**. Subsequently, migratory insertion of the triple bond into the C−Pd bond of complex **A** occurred to give the π-allylpalladium complex **C**, which was then intercepted by aminal **2a** to afford the desired allenic diamine and regenerated the starting cationic Pd−alkyl complex **A** for the next catalytic cycle.

In summary, we have disclosed a fundamentally different approach to control the regioselectivity of palladium-catalyzed 1,4-addition reaction to enynes, which enabled the development of a novel palladium-catalyzed 1,4-aminomethylamination of simple enynes with aminals to highly valuable allenic 1,5-diamines. In this process, the 1,4-addition is not initiated by double-bond insertion, but the requisite π-allyl palladium species is accessed via triple bond insertion with cationic palladium complex generated via C−N bond activation of aminals. This contrasting approach allows for the facile and highly chemoselective and regioselective formation of allenic adducts from simple enynes, where no special substitutents were required in the terminus of the enynes. Further investigation will be focused on the asymmetric catalysis and application of this strategy to many other transition-metal-catalyzed reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03847.

Experimental details and full spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 1874490 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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