C–N Activation

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Palladium-Catalyzed Insertion of an Allene into an Aminal: Aminomethylamination of Allenes by C–N Bond Activation**

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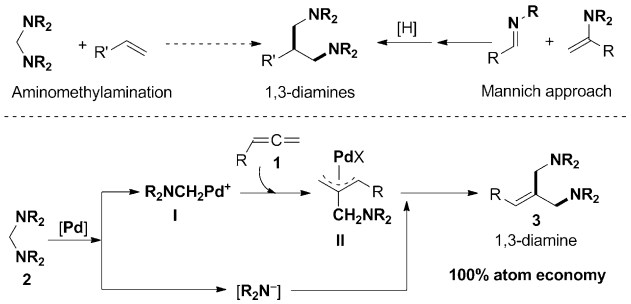
Abstract: *A new and atom-economic palladium-catalyzed aminomethylamination of allenes with aminals by C–N bond activation is described. This direct and operationally simple method provides a fundamentally novel approach for the synthesis of 1,3-diamines. Mechanistic studies suggest that a unique cationic π-allylpalladium complex containing an aminomethyl moiety is generated as a key intermediate through the carbopalladation of the allene with a cyclometalated palladium–alkyl species.*

The 1,3-diamines are important structural motifs in many natural products and pharmaceuticals.[1] As a result, much effort has been devoted to the development of effective methods to access these compounds.[2] However, unlike their 1,2-diamine counterparts, few methods for the direct synthesis of 1,3-diamines have been described.[3] An unusual and direct synthetic method to produce this class of compounds could be the insertion of a C=C bond into an aminal by C–N bond activation under transition-metal catalysis, which is potentially an atom- and step-economical process. This alkene aminomethylamination could be an alternative to the classic Mannich reaction/reduction sequence, which generally utilizes stoichiometric amounts of a reductant (Scheme 1).[4] To realize the proposed alkene difunctionalization reaction with palladium catalysis, the inherent β-hydride elimination of the resulting Pd–alkyl species must be suppressed to enable the second bond construction.[5] Over the past decades, elegant strategies, such as the formation of π-allyl or π-benzyl complexes,[6a–k] and the oxidation of the Pd^{II}–alkyl intermediates to a Pd^{IV} species, have been developed to circumvent this issue.[6l–q] The formation of a π-allylpalladium species by the carbometalation of allenes, a useful strategy for suppressing the β-hydride elimination of metal–alkyl species, has been extensively used and successfully applied in the synthesis of various compounds.[7] However, to the best of our knowledge, the use of these strategies for the synthesis of 1,3-diamines has remained unexplored, which is presumably due to the lack of efficient methods to simultaneously generate both a nitrogen nucleophile and a carbon nucleophile (containing an amine moiety) in the same reaction step.



Scheme 1. Palladium-catalyzed difunctionalization of allenes.

In seeking to address this limitation, we recently found that aminals could serve as useful electrophiles for an oxidative addition with a Pd^0 species to form a unique electrophilic cationic Pd–alkyl species **I** (a carbon nucleophile) while simultaneously releasing one molecule of a nitrogen nucleophile.[8a] The cationic Pd–alkyl species, which contains an aminomethyl group, was highly reactive towards the formation of allylic amines or aminoacetals with alkenes,[8] which suggested that a palladium-catalyzed aminomethylamination process between aminals and allenes might be possible. It was expected that the desired π-allylpalladium species **II** with an aminomethyl group would be facilely generated by the carbopalladation of allene **1** with the active Pd–alkyl species **I**. Subsequent allylic amination with the amine nucleophile should give the desired 1,3-diamine products. Herein, we describe the successful implementation of the first palladium-catalyzed insertion of an allene into an aminal by C–N bond activation for the construction of 1,3-diamines with high atom economy (Scheme 1). These studies represent the first example of the insertion of an allene into a C–N bond that is catalyzed by an isolated Pd^{II} complex.

In accord with our hypothesis, we used propa-1,2-dienylbenzene (**1a**) and *N*,*N*,*N*′,*N*′-tetrabenzylmethanediamine (**2a**) for screening the reaction conditions. When these substrates were treated with $[Pd(Xantphos)(CH_3CN)_2](OTf)_2$ (5 mol%), which has been shown to be highly effective for the generation of Pd–alkyl complex **I**, in toluene at 110 °C for twelve hours, 1,3-diamine **3aa** was obtained in 70% yield (Table 1, entry 1). The structure of **3aa** was confirmed by single-crystal X-ray analysis (see the Supporting Information).[9] In addition, the undesired allylic amine **4aa** was isolated in 22% yield, which might result from the off-cycle

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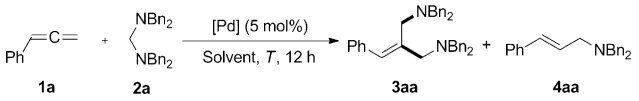
Table 1: Optimization of the reaction conditions.[a]

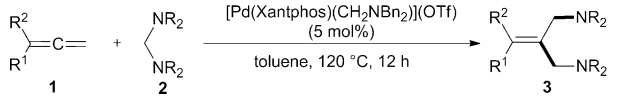


1a 2a 3aa 4aa

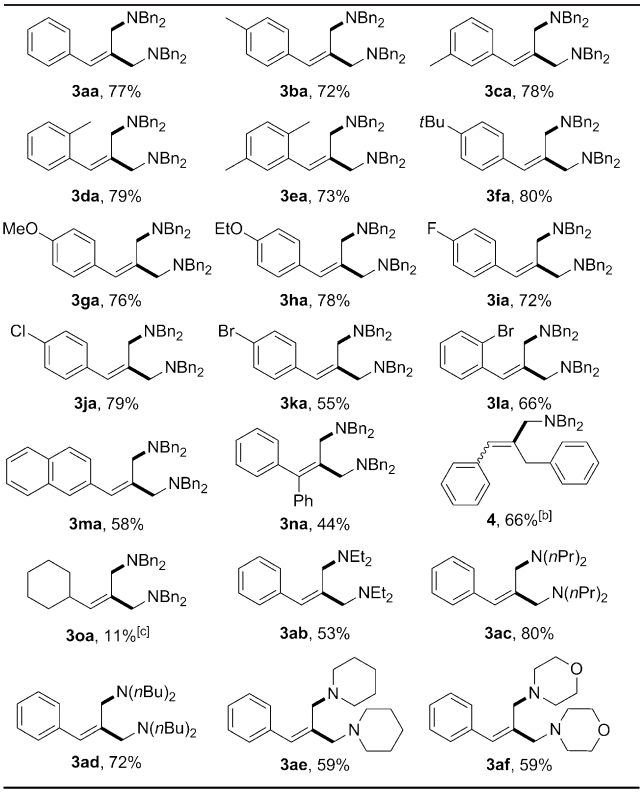
Entry	Palladium precursor	Solvent	T [°C]	Yield [%] 3aa	4aa
1	$[Pd(Xantphos)(CH_3CN)_2](OTf)_2$	toluene	110	70	22
2	$[Pd(Xantphos)(CH_3CN)_2](OTf)_2$	benzene	110	56	21
3	$[Pd(Xantphos)(CH_3CN)_2](OTf)_2$	CH_2Cl_2	110	55	26
4	$[Pd(Xantphos)(CH_3CN)_2](OTf)_2$	THF	110	43	14
5	$[Pd(Xantphos)(CH_3CN)_2](OTf)_2$	CH_3CN	110	42	29
6	$[Pd(Xantphos)(CH_3CN)_2](OTf)_2$	DMF	110	62	15
7	$[Pd(Xantphos)(CH_3CN)_2](OTf)_2$	*i*PrOH	110	48	15
8	$[Pd(Xantphos)(CH_3CN)_2](OTf)_2$	toluene	110	70	19
9	$[Pd(Xantphos)(CH_3CN)_2](OTf)_2$	toluene	80	66	20
10	$[Pd(Xantphos)(CH_3CN)_2](OTf)_2$	toluene	120	74	15
11	$[Pd(Xantphos)(CH_3CN)_2](PF_6)_2$	toluene	120	38	25
12	$[Pd(Xantphos)(CH_3CN)_2](SbF_6)_2$	toluene	120	43	11
13	$[Pd(Xantphos)(CH_3CN)_2](OTs)_2$	toluene	120	trace	trace
14	$[Pd(Xantphos)Cl_2]$	toluene	120	trace	12
15	$[Pd(BINAP)(CH_3CN)_2](OTf)_2$	toluene	120	trace	trace
16	$[Pd(DPPF)(CH_3CN)_2](OTf)_2$	toluene	120	trace	trace
17	$[Pd(DPPB)(CH_3CN)_2](OTf)_2$	toluene	120	trace	trace
18	$[Pd(DPPPen)(CH_3CN)_2](OTf)_2$	toluene	120	trace	trace
19	$Pd(OAc)_2$	toluene	120	trace	trace
20	$[Pd(Xantphos)(CH_2NBn_2)]OTf$	toluene	120	77	trace

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.4 mmol), palladium precursor (0.02 mmol, 5 mol%), solvent (1.5 mL), 12 h. Yields of isolated products are given. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, DPPB = 1,4-bis(diphenylphosphino)butane, DPPF = 1,1′-bis(diphenylphosphino)ferrocene, DPPPen = 1,5-bis(diphenylphosphino)pentane, OTs = *para*-toluenesulfonate, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

Table 2: Substrate scope of the aminomethylamination.[a]



1 2 3



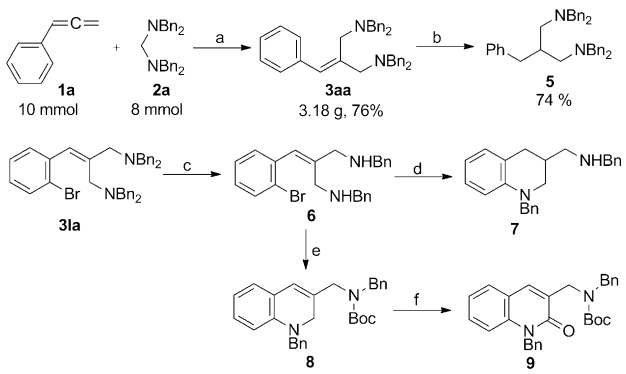
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.4 mmol), [Pd(Xantphos)-(CH_2NBn_2)](OTf) (0.02 mmol, 5 mol%), toluene (1.5 mL), 120°C, 12 h. Yields of isolated products are given. [b] Z/E = 70:30, determined by ^{1}H NMR spectroscopy. [c] The reaction was conducted at 100°C with $[Pd(Xantphos)(CH_3CN)_2](OTf)_2$ (5 mol%).

hydroamination of the allene. Among the solvents tested, toluene was the best in terms of both reactivity and selectivity, even though the reaction was also compatible with common organic solvents (entries 1–7). During further optimization of this reaction, it was found that raising the temperature to 120°C improved the yield without diminishing the selectivity. Variations of the counterion of the palladium complex indicated that the counterion was a key factor. The desired reaction hardly occurred when OTs^- or Cl^- served as the counterion. Several other palladium catalysts with different phosphine ligands, such as BINAP, DPPF, DPPB, and DPPPen, were examined, but most of them furnished poor results. Interestingly, the use of the unique cationic cyclometalated complex $[Pd(Xantphos)(CH_2NBn_2)]OTf$ (**I**) in place of $[Pd(Xantphos)(CH_3CN)_2](OTf)_2$ in toluene completely suppressed the formation of side product **4aa** and furnished **3aa** in 77% yield. In the absence of the Pd catalyst and under otherwise identical conditions, the desired product was not formed.

After establishing these optimized reaction conditions, we examined the scope of this aminomethylamination with respect to variation of the allene (Table 2). A series of either electron-donating or -withdrawing substituents on the aryl ring of the aromatic allene were well tolerated, and the corresponding 1,3-diamines were obtained in moderate to good yields (44–80%). The steric hindrance of the substituents on the aryl ring of the allene did not have a strong influence on the reactivity. For example, the aryl-substituted allenes **1d** and **1e**, which bear *ortho* substituents on the aryl ring, reacted smoothly and gave the desired products in good yields (**3da** and **3ea**). Typical functional groups, such as alkyl, alkoxy, fluoro, chloro, and bromo moieties, were also tolerated under the reaction conditions, providing ample opportunities for further elaboration of the products by transition-metal-catalyzed coupling reactions or other transformations. Aside from aryl-substituted allenes, the naphthyl-substituted allene **1m** was also compatible with this new reaction, generating the corresponding 1,3-diamine **3ma** in 58% yield. The reaction of *gem*-diphenyl-substituted allene **1n** with aminal **2a** afforded the desired product **3na** in 44% yield; the 1,3-diphenyl-substituted allene, however, failed to give the desired product, but afforded the aminomethyl product **4** in 66% yield. Unfortunately, an alkyl-substituted allene (**1o**) was less reactive (**3oa**). The substrate scope was further extended to a wide variety of aminals with different substituents. Several aminals that are derived from simple alkyl amines were also compatible with this process and

afford the desired products in moderate to good yields (**3ab**–**3ad**). Moreover, aminals that are based on cyclic amines could also be used as coupling partners, giving the corresponding products in good yields (**3ae**–**3af**).

We further evaluated the utility of this reaction by performing a large-scale experiment (Scheme 2). The reaction proceeded smoothly on a gram scale even at a lower catalyst loading (2.5 mol%). The double bond of **3aa** could be selectively reduced by Na/NH_3 to give product **5**.[10] Furthermore, the two benzyl groups of **3la** were rapidly removed to give **6** by treatment with CAN in $MeOH/H_2O$ at room temperature; **6** could then be successfully transformed into tetrahydroquinoline **7**, which contains an aminomethyl group, through sequential C–N coupling and hydrogenation. Furthermore, 1,2-dihydroquinoline **8**, which resulted from the C–N coupling reaction, could be isolated and selectively oxidized by $[\{RuCl_2(benzene)\}_2]$/TBHP to give the corresponding 2-quinolinone derivative **9** in good yield.[11] Both **7** and **9** are valuable precursors for the synthesis of some bioactive compounds.[12]

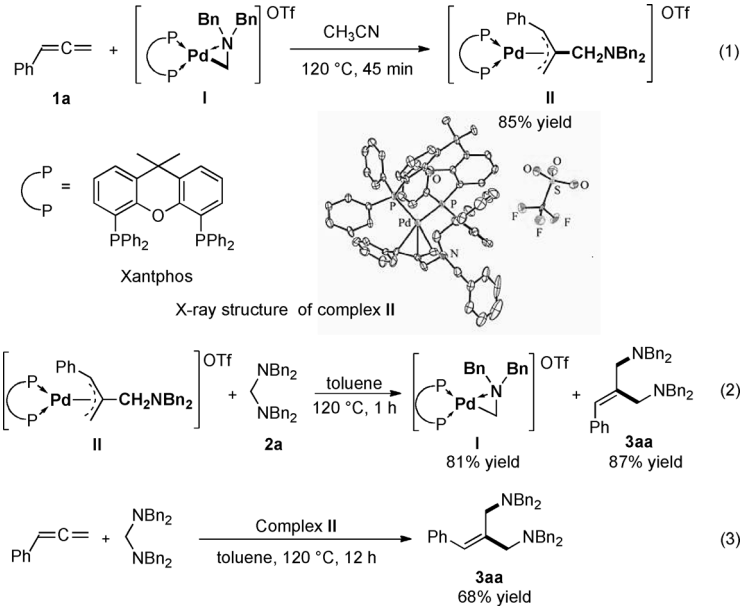


Scheme 2. Synthetic utility of the 1,3-diamines. a) [Pd(Xantphos)-(CH_2NBn_2)]OTf (2.5 mol%), toluene, 120°C, 12 h, 76%. b) Na/NH_3, THF, −78°C, 1.5 h, 74%. c) CAN (4.2 equiv), $MeOH/H_2O$ (4:1), RT, 12 h, 58%. d) $[Pd(PPh_3)_4]$ (5 mol%), *t*BuONa, K_2CO_3, toluene, 100°C, 5 h; then Pd/C, H_2 (50 atm), EtOAc, RT, 20 h, 65% over two steps. e) $[Pd(PPh_3)_4]$ (5 mol%), *t*BuONa, K_2CO_3, toluene, 100°C, 5 h; then $(Boc)_2O$, DMAP, THF, RT, 12 h, 73% over two steps. f) $[\{RuCl_2(benzene)\}_2]$ (5 mol%), TBHP (2.5 equiv), benzene, RT, 2 h, 64%. Boc = *tert*-butyloxycarbonyl, CAN = cerium ammonium nitrate, DMAP = 4-dimethylaminopyridine, TBHP = *tert*-butyl hydroperoxide.

Several experiments were conducted to gain insight into the possible mechanism of this process. As shown in Scheme 3, treatment of the cyclometalated Pd^{II} complex **I** with allene **1a** (1.5 equiv) in CH_3CN at 120°C resulted in rapid C=C double bond insertion to afford the expected π-allylpalladium species **II** in an 85% yield [Scheme 3, Eq. (1)]. The π-allylpalladium complex was fully characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy as well as high-resolution mass spectrometry (see the Supporting Information). Furthermore, an X-ray crystal structure of **II** was obtained,[9] which revealed that an unsymmetric allyl ligand with an aminomethyl moiety $(CH_2NBn_2)$is coordinated to the Pd center in an η^3 mode, and that the Ph group is oriented *anti* to the attached CH_2NBn_2 group. This solid-state structure correlated well with the ^1H and ^{31}P NMR data; in the ^{31}P NMR spectrum, two doublets could be seen, which is consistent with the unsymmetric nature of the structure shown in Scheme 2. Furthermore, the magnitude of the *J*(PH) coupling constant (5.6 Hz) for C*H*Ph at 5.46 ppm suggested that the CH_2NBn_2 group and the phenyl group were arranged in a *trans* fashion.[13]

Having confirmed that the cyclometalated palladium complex **I** could be facilely converted into complex **II**, we proceeded to conduct a set of experiments to elucidate the catalytic cycle of the present reaction (Scheme 3). Complex **I**, together with the desired product **3aa**, was obtained in high yield when π-allylpalladium complex **II** was treated with one equivalent of aminal **2a** in toluene at 120°C for one hour [Scheme 3, Eq. (2)].[14] Moreover, when the isolated π-allylpalladium complex **II** replaced cyclometalated Pd complex **I** as the catalyst, the reaction proceeded well under the standard conditions, thus indicating the plausible intermediacy of complex **II** in the catalytic cycle [Scheme 3, Eq. (3)].

Taking the results described above into consideration, we propose the following catalytic cycle for the novel palladium-catalyzed aminomethylamination of allenes (Figure 1). Initially, the terminal double bond of allene **1a** coordinates to the palladium center to form intermediate **III**. Subsequently, migratory insertion of the more electron-deficient C=C bond of the allene into the C–Pd bond of complex **I** takes place. The selective C–C bond formation proceeds at the sp-hybridized carbon atom of the allene to give π-allylpalladium complex **II**, which contains an aminomethyl moiety that is located *trans* to the phenyl group because of steric hindrance. Nucleophilic addition of a nitrogen nucleophile to the π-allylpalladium species at the less substituted carbon atom affords the desired 1,3-diamine and regenerates the cationic Pd–alkyl complex **I** for the next catalytic cycle.



Scheme 3. Preliminary mechanistic studies.

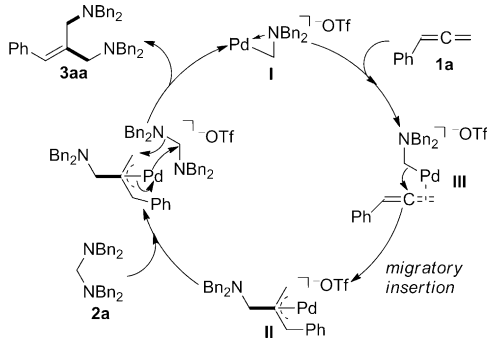


Figure 1. Plausible reaction mechanism. Ligand omitted for clarity.

In summary, we have developed the first direct insertion of an allene into an aminal C–N bond to provide 1,3-diamines through a palladium-catalyzed C–N bond activation. A unique cyclometalated Pd^{II} complex has been identified as an efficient catalyst for this reaction. This new transformation may be used for the coupling of a broad range of substrates and thus represents a concise, operationally simple, and useful method for the preparation of 1,3-diamines that are of interest in synthetic organic chemistry. Mechanistic studies suggest that the reaction proceeds via a π-allylpalladium complex, which has promise as a valuable intermediate in many other reactions.

Experimental Section

N,*N*,*N*′,*N*′-Tetrabenzylmethanediamine **2a** (162.4 mg, 0.4 mmol), propa-1,2-dienylbenzene **1a** (58 mg, 0.5 mmol), [Pd(Xantphos)-(CH_2NBn_2)](OTf) (20.8 mg, 0.02 mmol), and toluene (1.5 mL) were added to a 25 mL flame-dried Young-type tube. The mixture was degassed by a freeze–thaw method and stirred at 120 °C for 12 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel with diethyl ether/petroleum ether (1:200–1:50) as the eluent, affording the desired product **3aa** as a white solid.

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