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Palladium-Catalyzed Vinylation of Aminals with Simple Alkenes: A New Strategy To Construct Allylamines

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Supporting Information

ABSTRACT: A novel, highly selective palladium-catalyzed vinylation reaction for the direct synthesis of allylic amines from styrenes and aminals has been established. The utility of this method was also demonstrated by the rapid synthesis of cinnarizine from aldehydes, amines, and simple alkenes in one-pot manner. Mechanistic studies suggested that the reaction proceeds through a valuable cyclometalated Pd(II) complex generated by the oxidative addition of aminal to a Pd(0) species.

Allylic amines represent an important structural motif frequently found in natural products, pharmaceuticals, and other synthetics (Figure 1).[1b] Among the myriad methods

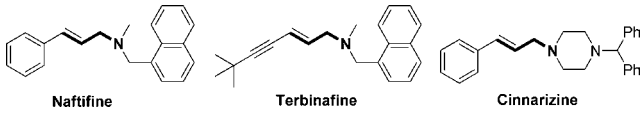
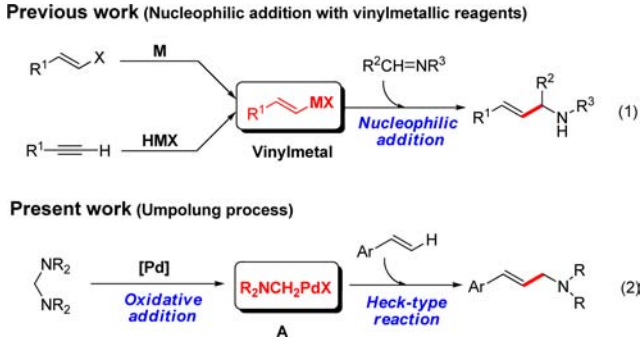


Figure 1. Examples of Significant Allylamine-Containing Pharmaceuticals.

available for constructing the allylamine scaffold,[1] metal-catalyzed vinylation of imines is one of the most commonly used approaches, but the incorporation of reactive functionality into the alkene moiety prior to nucleophilic addition (such as halogenation and subsequent metalation) is required for such elegant methods (eq 1 in Scheme 1).[2] In this context, direct vinylation of imines or their surrogates via C−H functionalization of alkenes,[3] which would avoid the use of a vinylmetallic intermediate, would be an attractive alternative to the aforementioned traditional methods. However, such a reaction is a synthetic challenge exacerbated by the intrinsic poor nucleophilicity of simple alkenes.[4] One way to circumvent this problem would be to develop an umpolung process, in which the electrophilic imine or its surrogate is converted into a nucleophilic species and the nucleophilic alkene is switched to an electrophilic one. In this respect, we envisioned that the palladium-catalyzed Heck-type reaction could be desirable for realizing such a transformation, since simple alkenes exhibit umpolung reactivity in Heck-type reactions.[5]

Scheme 1. Strategies for the Formation of Allylamines via Vinylation



To this end, the main challenge is to identify an imine surrogate that can act as an electrophile to undergo the Heck-type reaction. Aminals are recognized as surrogates of imines and are widely used as electrophiles in metal-catalyzed nucleophilic addition reactions.[6] The C−N bond in these molecules is easily cleaved under mild conditions to generate an iminium ion because of the better leaving ability of the amino group, and therefore, aminals have good electrophilicity toward organometallic reagents. Intrigued by this unique feature and the fact that oxidative addition of anilines,[7] ammonium salts,[8] arylhydrazines,[9] and allylamines[10] to low-valent transition metals can be realized via cleavage of unactivated C−N bonds, we envisaged that oxidative addition of aminals to low-valent metals via C−N bond cleavage might also be possible. Herein we report a novel palladium-catalyzed vinylation of aminals with simple alkenes that provides access to allylic amines in stereodefined fashion. The proposed process is initiated by the formation of a Pd(II) complex, **A**, via oxidative addition of the aminal to a Pd(0) complex. **A** then undergoes a Heck-type reaction, affording the desired allylamine (eq 2 in Scheme 1).

To test our initial proposal, the model reaction of styrene (**1a**) and *N*,*N*,*N*′,*N*′-tetrabenzylmethanediamine (**2a**) was used to optimize the reaction conditions (Table 1). Our initial attempts demonstrated that no desired reaction occurred when commonly used $PdCl_2$, $Pd(CH_3CN)_2Cl_2$, or $Pd(OAc)_2$ was utilized as the catalyst (entries 1−3). Furthermore, other typical Lewis acids such as $Zn(OTf)_2$, $Cu(OTf)_2$, $Fe(OTs)_3$, and $AlCl_3$ were ineffective catalysts for this reaction [see the Supporting Information (SI)], which indicated that the reaction is most likely not Lewis acid-catalyzed. Next, we investigated the effect of the ligand. When Pd(dppf)Cl_2 [dppf = 1,1′-bis-(diphenylphosphino)ferrocene] was used as the catalyst, the

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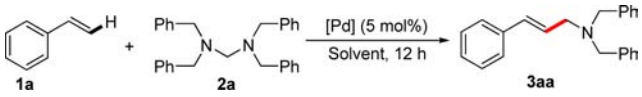
Table 1. Screening of Reaction Conditions[a]



entry	[Pd]	solvent	T (°C)	yield (%)
1	$PdCl_2$	MeOH	120	<5
2	$Pd(CH_3CN)_2Cl_2$	MeOH	120	<5
3	$Pd(OAc)_2$	MeOH	120	<5
4	$Pd(dppf)Cl_2$	MeOH	120	17
5	$Pd(BINAP)Cl_2$	MeOH	120	30
6	$Pd(Xantphos)Cl_2$	MeOH	120	85
7	Cat **A**	MeOH	120	89
8	Cat **B**	MeOH	120	82
9	Cat **C**	MeOH	120	79
10	Cat **A**	EtOH	120	75
11	Cat **A**	*n*-PrOH	120	64
12	Cat **A**	2-PrOH	120	92
13	Cat **A**	*n*-BuOH	120	74
14	Cat **A**	CH_3CN	120	74
15	Cat **A**	THF	120	75
16	Cat **A**	2-PrOH	110	93
17	Cat **A**	2-PrOH	100	88
18	Cat **A**	2-PrOH	80	75
19	Cat **A**	2-PrOH	60	54

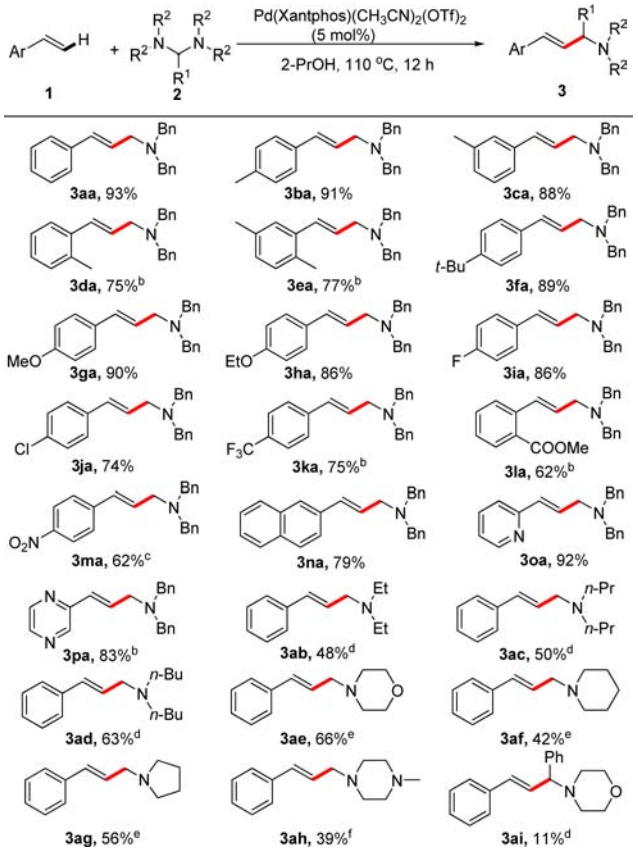
[a]Reaction conditions: **1a** (0.8 mmol), **2a** (0.4 mmol), [Pd] (0.02 mmol), solvent (1.5 mL), 12 h. only the (*E*)-allylamine was obtained in all cases. Cat **A**, $Pd(Xantphos)(CH_3CN)_2(OTf)_2$; Cat **B**, $Pd(Xantphos)(CH_3CN)_2(SbF_6)_2$; Cat **C**, $Pd(Xantphos)(CH_3CN)_2(BF_4)_2$.

desired product **3aa** was isolated in 17% yield (entry 4). Moreover, with BINAP as the ligand, the yield was improved to 30% (entry 5). Encouraged by these results, we investigated a series of phosphine ligands with different bite angles and electronic natures and found that the reactivity was significantly affected by the nature of phosphine ligand (see the SI). Xantphos turned out to be far superior, affording **3aa** in 85% yield (entry 6). Further investigation of the palladium catalyst demonstrated that the reactivity was affected by the nature of the counterion (entries 6–9). For example, with $Pd(Xantphos)(CH_3CN)_2(SbF_6)_2$ as the catalyst, **3aa** was obtained in 82% yield (entry 8), while $Pd(Xantphos)(CH_3CN)_2(BF_4)_2$ delivered the desired product in 79% yield (entry 9). Among those tested, $Pd(Xantphos)(CH_3CN)_2(OTf)_2$ led to the best result (89% yield; entry 7). Finally, control reactions demonstrated that the vinylation product **3aa** was not formed in the absence of a palladium catalyst.

After $Pd(Xantphos)(CH_3CN)_2(OTf)_2$ was identified as the best catalyst, the other reaction parameters were optimized using it. The effects of solvent and temperature in this reaction were also investigated. The reaction could be conducted perfectly in alcohol solvents, and the green solvent 2-PrOH was the best for this reaction (Table 1, entry 12). Other nonprotic polar solvents, such as CH_3CN and THF (entries 14 and 15), were also suitable for the vinylation reaction but gave only moderate yields. The best yield of **3aa** (93%; entry 16) was obtained at 110 °C, whereas at higher temperatures no appreciable increase in yield was obtained (see the SI). On the contrary, the use of temperatures below 110 °C reduced the reactivity and conversion (entries 17–19). It is worth mentioning that the reaction is highly selective: only the linear *E* isomer **3aa** was observed in all cases.

With the optimized conditions in hand, a wide variety of substituted styrenes **1** were submitted to the Pd-catalyzed vinylation reaction to investigate its substrate scope and generality. As shown in Table 2, the reaction proceeded in

Table 2. Substrate Scope of Pd-Catalyzed Vinylation[a]



[a]Reaction conditions: **1** (0.8 mmol), **2** (0.4 mmol), $Pd(Xantphos)(CH_3CN)_2(OTf)_2$ (0.02 mmol), 2-PrOH (1.5 mL), 110 °C, 12 h, unless otherwise noted. Isolated yields are shown. Only the *E* isomer was observed in all cases. [b]24 h. [c]$Pd(Xantphos)(CH_3CN)_2(OTf)_2$ (0.04 mmol), CH_3CN (1.5 mL). [d]$Pd(Xantphos)Cl_2$ (0.02 mmol), MeOH (1.5 mL). [e]**1a** (2.0 mmol), $Pd(Xantphos)Cl_2$ (0.02 mmol), MeOH (1.5 mL), 120 °C, 12 h. [f]$Pd(Xantphos)Cl_2$ (0.04 mmol), MeOH (1.5 mL), 110 °C, 12 h.

good to excellent yields in the presence of both electron-deficient and electron-rich aromatic systems. In general, styrenes bearing electron-donating groups provided higher yields than those containing electron-withdrawing groups. For instance, the reactions of substrates with electron-donating substituents, such as Me and MeO at the 4-position of the benzene ring, proceeded smoothly to provide the coupling products in >90% yield (**3ba** and **3ga**). Typical functional groups such as alkyl, alkyoxyl, fluoro, chloro, trifluoromethyl, ester, and nitro were also tolerated under the reaction conditions. Importantly, the successful preparation of **3ja** with an intact chlorine provides a good opportunity for further formation of C–C or C–heteroatom bonds by transition-metal-catalyzed coupling and other reactions. In addition to substituted styrenes, naphthyl-substituted alkenes and heteroaryl-substituted alkenes such as 2-vinylpyridine and 2-vinylpyrazine were also compatible with this new reaction, generating the corresponding allylic amines (**3na**, **3oa**, and **3pa**) in good to excellent yields under slightly modified

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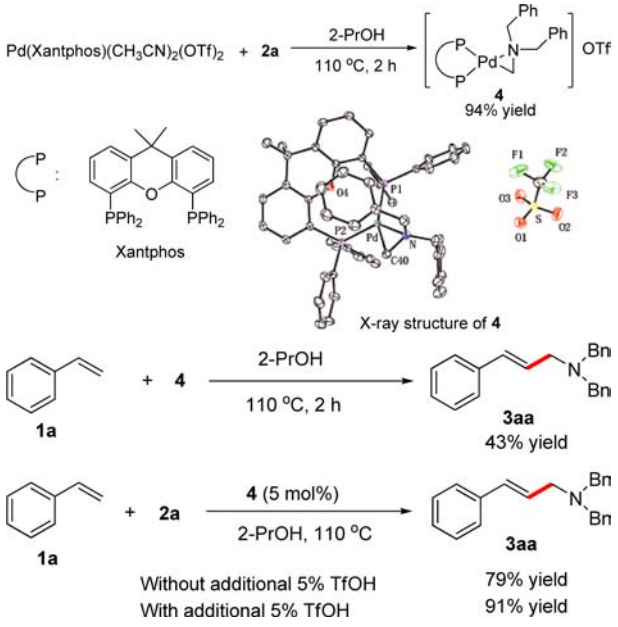
conditions. The structure of the allylic amines was confirmed by X-ray crystallographic analysis of derivative **3na** (see the SI).[11] In addition, the scope of the aminal was also explored. Aminals derived from alkylamines afforded the desired products in moderate to good yields (**3ab**–**ad**). Moreover, aminals derived from cyclic amines could also be used as coupling partners, giving the corresponding products (**3ae**–**ah**) in good yields. However, under the present reaction conditions, only an 11% yield of **3ai** was observed when a benzaldehyde-derived aminal was employed as the coupling partner. The observed lower reactivity for this type of substrate may stem from difficulty in the oxidative addition step.

To gain some preliminary understanding of the mechanism, several experiments were carried out under the optimized conditions (Scheme 2).[12] A stoichiometric reaction of **2a** with

Scheme 2. Preliminary Mechanistic Studies



$Pd(Xantphos)(CH_3CN)_2(OTf)_2$ was conducted under the standard conditions. After 2 h, cyclometalated Pd(II) complex **4** containing a three-membered-ring was obtained in 94% yield, and its structure was unambiguously characterized by X-ray crystallography and high-resolution mass spectrometry (see the SI). The corresponding Pd–C σ bond was undoubtedly formed [Pd–C bond, 2.031(2) Å; Pd–N bond, 2.185(3) Å],[13] suggesting that the oxidative addition process indeed occurred. This result represents the first observation of oxidative addition of aminals to a Pd(0) species. Here the Pd(0) species was generated by the reduction of Pd(II) with 2-propanol.[14] The stoichiometric reaction of complex **4** with styrene at 110 °C successfully provided the desired Heck coupling product **3aa** in 43% yield. Moreover, complex **4** catalyzed the vinylation of **2a** with styrene to give **3aa** in high yield, suggesting the plausible intermediacy of **4** in the catalytic cycle.

On the basis of the results described above, a tentative reaction mechanism for the palladium-catalyzed vinylation reaction is presented in Figure 2. Initial reduction of the Pd(II) precatalyst by 2-PrOH should furnish a catalytically active Pd(0) species together with a catalytic amount of acid.[14] Subsequent oxidative addition of aminal **2** to the Pd(0) species would then take place via cleavage of the C–N bond facilitated

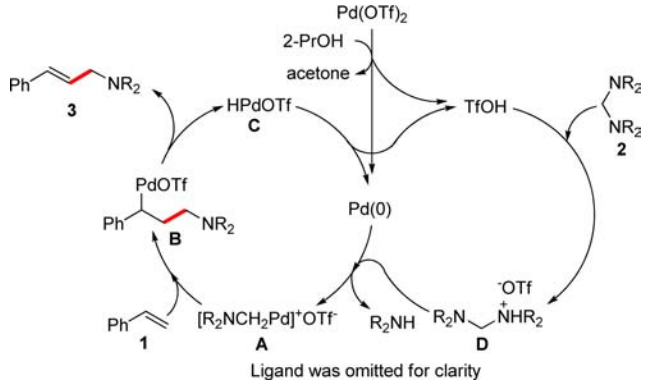
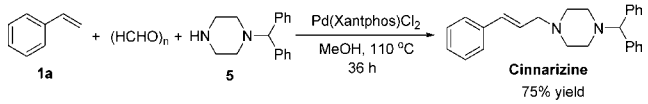


Figure 2. Proposed reaction mechanism.

by the acid, generating the key intermediate **A**, an analogue of the fully characterized complex **4**. Alternatively, **A** might be formed via direct oxidative addition of an iminium species (generated in situ from aminal **2**) to Pd(0). This key active species **A** would then react with styrene **1** via carbopalladation to give intermediate **B**, which would undergo *syn*-β-hydride elimination to deliver the cross-coupling product **3** as well as intermediate **C**. Reductive elimination of **C** to regenerate the active catalyst species would complete the catalytic cycle.

The usefulness of this new protocol was demonstrated via a one-pot, three-component cascade cross-coupling starting from aldehyde, styrene, and amine without separation of the aminal. As shown in Scheme 3, we successfully applied our present

Scheme 3. Synthesis of Cinnarizine via a One-Pot Procedure



method in a one-pot manner with simple starting materials to achieve the rapid synthesis of cinnarizine, a commercially available antihistamine pharmaceutical used to treat cerebral apoplexy, post-traumatic cerebral symptoms, cerebral arteriosclerosis, and seasickness.[15] This approach represents a highly atom-economical protocol for the synthesis of allylamines, since only water is formed as a coproduct.

In summary, we have developed a novel palladium-catalyzed vinylation reaction that enables the catalytic functionalization of alkenes with aminals. The reaction proceeds with complete regioselectivity and stereoselectivity, delivering exclusively the linear *E* isomer of the allylic amine product. Importantly, this reaction can also be employed in a one-pot, three-component cascade with high efficiency. Evidence suggests that the reaction proceeds through a cyclometalated Pd(II) complex generated by oxidative addition of the aminal to a Pd(0) species, which has promise as a valuable catalytic intermediate in a variety of C–C bond-forming manifolds. Further investigations to gain a detailed mechanistic understanding of this reaction and apply this strategy in other C–C bond-forming reactions are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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(11) Allylbenzene and α-methylstyrene were also suitable for this reaction, affording the homoallylamines in good yields with migration of the double bond. Simple aliphatic alkenes and acrylates did not react to give allylamines. See the SI for details.

(12) When a nucleophilic scavenger such as anisole or thioanisole was introduced into the reaction system under the standard conditions, a high yield was still obtained, suggesting that traditional nucleophilic addition may not be involved in this reaction. See the SI for details.

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