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Palladium-Catalyzed Difunctionalization of Enol Ethers to Amino Acetals with Aminals and Alcohols

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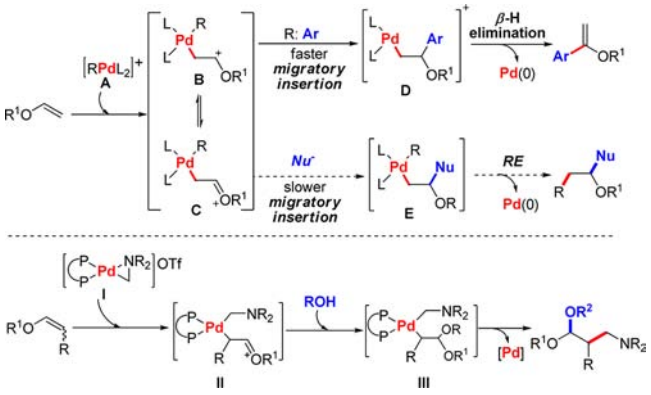
Supporting Information

ABSTRACT: A new strategy was developed for intercepting the palladium−alkyl species generated in Heck reaction via nucleophilic addition prior to the step of migratory insertion, which leads to a new palladium-catalyzed difunctionalization of enol ethers with aminals and alcohols to afford amino acetals. Mechanistic studies suggested that the cationic cyclometalated Pd(II) complex generated by the oxidative addition of aminal to a Pd(0) species was crucial for this unusual transformation.

Palladium-catalyzed Heck reaction has proved to be one of the most powerful strategies for constructing C−C bonds and has been widely used for synthesis of organic materials, natural products, and bioactive compounds.[1] In these transformations, the Pd−alkyl species is known to be formed as a versatile reactive species that could be intercepted with different substrates, other than β-hydride elimination, for establishing diverse new transformations.[2] In this context, the discovery and development of new and efficient strategies for intercepting the active Pd−alkyl species is a key for establishing some new transformations by using a Heck reaction as a starting point. As such, various methods, such as trapping by alkenes, alkynes, or CO insertion[3] and oxidative intercepting with strong oxidants, have already been developed to initiate subsequent more complex reactions.[4] However, most reactions suffer from some disadvantages, such as the use of a stoichiometric amount of metallic oxidants, toxic reagents, and harsh reaction conditions. Herein, we described an alternative approach to intercept the palladium−alkyl species, which led to a new three-component reaction to afford amino acetals in the absence of oxidants. Such a reaction would be particularly valuable for synthesis of amino aldehydes, which are synthetically versatile compounds for the construction of important pharmaceuticals, natural products, and modified proteins.[5]

Our inspiration for this new transformation stems from the fact that an electron-rich enol ether, when subjected to a Heck-type reaction to react with an electrophilic cationic $RPdL_2$ species (**A**), would give rise to a Pd−alkyl species (**B** or **C**) with a carbocation character (Scheme 1).[6] Previous studies suggest that the polarized cationic species is crucial to give the α-arylated product with high selectivity. We thought that the cationic Pd(II) intermediate **C** might be intercepted by a nucleophile via an out-sphere style mechanism to form the intermediate **E**, which will furnish the difunctionalization product via further reductive elimination. One of the potential

Scheme 1. New Strategy for Difunctionalization of Alkenes



problems facing the development of this transformation is the competition between the inner nucleophilic attack by the aryl moiety (migratory insertion) and the proposed nucleophilic addition by an outer nucleophile. Because the olefin insertion into metal−alkyl bonds of complexes containing more electrophilic metal centers are faster than those with more electron-rich metal centers,[7] it would be expected that the Pd−alkyl species **C** generated from an cationic alkylpalladium **A** containing a more electron-donating moiety would favor the desired reaction.

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 Pd−alkyl species **I** (confirmed by X-ray crystallographic analysis).[8] The metal center in the isolated Pd−alkyl complex **I** is thought to be comparably more electron-rich due to the attached electron-donating CH_2NR_2 moiety. Fascinated and inspired by this unique feature, we envisioned that the complex **I** could slow down the corresponding migratory insertion of enol ether and form intermediate **II**, which enabled the subsequent nucleophilic addition by an outer nucleophile to form **III**, and then reductive elimination yielded the desired product of difunctionalization. To test the viability of the envisioned strategy, we started the investigation by exploring the reaction of butyl vinyl ether (**1a**) with *N*,*N*,*N*′,*N*′-tetrabenzylmethanediamine (**2a**) and 2-PrOH. Because palladium in combination with Xantphos has shown to be highly effective for the generation of Pd−alkyl complex **I**, we initially focused on exploring conditions using

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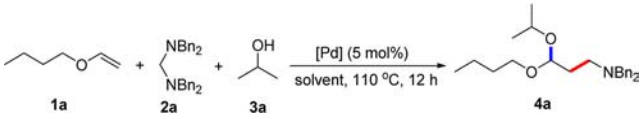
this readily available catalyst. The results are summarized in Table 1. As can be seen, when the reaction was conducted in

Table 1. Screening of Reaction Conditions[a]



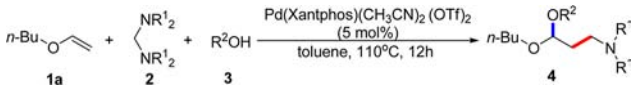
entry	[Pd]	solvent	yield (%)[b]
1	$Pd(Xantphos)Cl_2$	CH_3CN	71
2	$Pd(Xantphos)Cl_2$	THF	74
3	$Pd(Xantphos)Cl_2$	toluene	75
4	$Pd(Xantphos)Cl_2$	dioxane	66
5	$Pd(Xantphos)Cl_2$	DCM	trace
6	$Pd(Xantphos)Cl_2$	DMA	65
7	$PdCl_2$	toluene	trace
8	$Pd(OAc)_2$	toluene	trace
9[c]	$Pd_2(dba)_3$/Xantphos	toluene	72
10	$Pd(PPh_3)Cl_2$	toluene	trace
11	Pd(DPPHex)Cl_2	toluene	31
12	Pd(BINAP)Cl_2	toluene	58
13	Pd(DPPE)Cl_2	toluene	50
14	Pd(DPEPhos)Cl_2	toluene	65
15	Pd(DPPF)Cl_2	toluene	66
16	$Pd(Xantphos)(CH_3CN)_2(OTf)_2$	toluene	85
17	–	toluene	trace

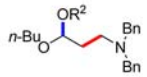
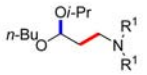
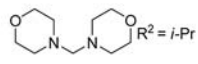
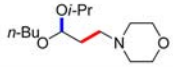
[a]Reaction conditions: **1a** (0.8 mmol), **2a** (0.4 mmol), **3a** (4.0 mmol), [Pd] (0.02 mmol), solvent (1.5 mL), 110 °C, 12 h. [b]Isolated yield. [c]Reaction conditions: $Pd_2(dba)_3$ (0.01 mmol), Xantphos (0.02 mmol), HOTf (0.04 mmol).

the presence of a catalytic amount of $Pd(Xantphos)Cl_2$ in CH_3CN, the desired difuctionalized product **4a** was obtained in good yield (Table 1, entry 1). Screening of some representative solvents revealed that the most efficient catalysis was furnished in toluene, in which the desired product **4a** was obtained in 75% yield (Table 1, entry 3). Variation of the phosphine ligands revealed it to be a key factor. Almost no reaction occurred when $Pd(OAc)_2$ or $PdCl_2$ served as catalyst. The reaction performed well with $Pd_2(dba)_3$ as the palladium source in the presence of Xantphos, suggesting that Pd(0) was involved in the present reaction (Table 1, entries 7–9). When PPh_3 was used in place of Xantphos, the reaction virtually stopped. Among the phosphine ligands examined here, bidentate phosphine ligands are effective for this reaction, and Xantphos gave the best result in affording **4a**. As expected, a higher yield of **4a** was gained when the cationic $Pd(Xantphos)(CH_3CN)_2(OTf)_2$ was utilized as catalyst (Table 1, entry 16). In the absence of Pd catalyst, only a trace amount of desired product was observed under otherwise identical conditions (Table 1, entry 17).

After establishing these optimized conditions, we next investigated the generality of this novel difunctionalization reaction. First, a series of alcohols were used as nucleophiles in the present reaction. As shown in Table 2, alcohols including MeOH, EtOH, and *n*-BuOH reacted successfully with butyl vinyl ether **1a** and aminal **2a**, affording the corresponding products in good to excellent yields (Table 2, entries 1–4).[9] Intriguingly, when the sterically hindered *t*-BuOH was used as a substrate, not only the corresponding product **4e** but also the product **4d** was detected (Table 2, entry 5). Furthermore, aminals derived from simple alkylamines were also compatible

Table 2. Scope of Aminals and Alcohols[a]



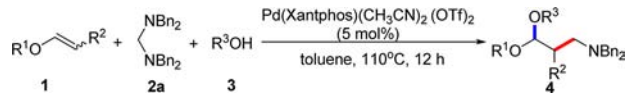
Entry	Substrate	Product		Yield(%)
1	R^1 = Bn, R^2 = *i*-Pr		**4a**	85
2	R^1 = Bn, R^2 = Me		**4b**	82
3	R^1 = Bn, R^2 = Et		**4c**	81
4	R^1 = Bn, R^2 = *n*-Bu		**4d**	78
5[b]	R^1 = Bn, R^2 = *t*-Bu	**4e** (R^2 = *t*-Bu) / **4d** = **85/15**		70
6	R^1= Et, R^2 = *i*-Pr		**4f**	54
7	R^1= *n*-Pr , R^2 = *i*-Pr		**4g**	55
8	R^1= *n*-Bu, R^2 = *i*-Pr		**4h**	66
9	 R^2 = *i*-Pr		**4i**	31

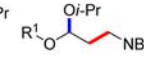
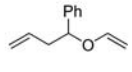
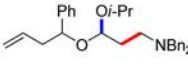
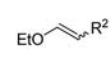
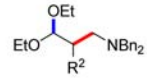
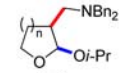
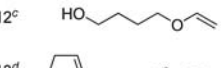
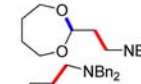
[a]Reaction conditions: **1a** (0.8 mmol), **2** (0.4 mmol), **3** (4.0 mmol), [Pd] (0.02 mmol), toluene (1.5 mL), 110 °C, 12 h, isolated yield unless otherwise noted. [b]The ratio of **4e** to **4d** was determined by ^{1}H NMR.

with this process to afford the desired products in moderate to good yields (Table 2, entries 6–8). However, relatively lower yield was obtained for aminal derived from cyclic amine (Table 2, entry 9).

Subsequently, the substrate scope of enol ethers was explored by employing a variety of different substituted enol ethers (Table 3). Alkyl vinyl ethers can be smoothly transformed into the desired products in good to excellent yields (Table 3, entries 1–6). Particularly, when the long-chain dodecyl vinyl

Table 3. Scope of Enol Ethers[a]



Entry	Substrate	Product		Yield(%)
1	 R^1 = Et, R^3 = *i*-Pr		**4j**	74
2			**4k**	91
3			**4l**	84
4			**4m**	87
5			**4n** (R^1= *t*-Bu) / **4l**= **58/42**	73
6	 R^3 = *i*-Pr		**4o** dr (1:1)[e]	79
7	 R^2 = Me, R^3 = Et		**4p**	68
8	R^2 = Et, R^3 = Et		**4q**	79
9	R^2= Bn, R^3 =Et		**4r**	56
10	 n= 1, R^3 = *i*-Pr		**4s** dr (4:1)[e]	87
11[b]	n= 2, R^3 = *i*-Pr		**4t** dr (1:1)[e]	81
12[c]			**4u**	61
13[d]	 R^3 = *i*-Pr		**4v** dr (2.5:1)[e]	72

[a]Reaction conditions: **1** (0.8 mmol), **2a** (0.4 mmol), **3** (4.0 mmol), [Pd] (0.02 mmol), toluene (1.5 mL), 110 °C, 12 h, isolated yield unless otherwise noted. [b]Reaction conditions: [Pd] (0.04 mmol), 24 h. [c]Reaction conditions: **1a** (0.8 mmol), **2a** (0.4 mmol), [Pd] (0.02 mmol), toluene (1.5 mL), 110 °C, 24 h. [d]Reaction conditions: 6 h. [e]The dr ratio was determined by ^{1}H NMR.

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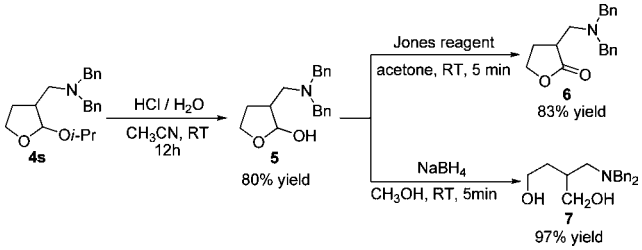
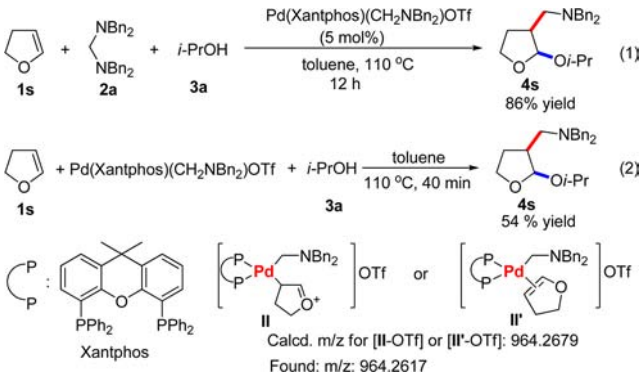
ether was subjected to this reaction, a higher yield (91%) could be obtained (Table 3, entry 2). In addition, nonterminal alkenyl ethers were also suitable for this process, furnishing the corresponding products in good results (Table 3, entries 7−9). Cyclic vinyl ethers such as 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran were also compatible, giving the products **4s** and **4t** with 4:1 and 1:1 dr ratios as well as 87% and 81% yields, respectively (Table 3, entries 10 and 11). The product **4s** could also be obtained in gram scale with identically high yield (see Supporting Information). Impressively, 4-(vinyloxy)butan-1-ol gave rise to the corresponding adduct **4u** in good yield (Table 3, entry 12). Finally, the reaction can also be conducted with another electron-rich olefin, *N*-Boc-2,3-pyrroline,[10] giving the desired product **4v** in 72% yield (Table 3, entry 13).

The resulting amino acetals can be readily converted into useful building blocks via simple functional group transformations. For example, the product **4s** could be converted into hemiacetal **5** by hydrolysis under mild conditions in high yield. Oxidation of **5** with Jones reagent afforded lactone **6** in 83% yield, which is an important building block for synthesis of bioactive compounds.[11] In addition, reduction of the hemiacetal moiety in **5** with $NaBH_4$ produced amino alcohol **7** in a 97% yield.



Studies were conducted to gain insight into a possible mechanism for this unusual process (Scheme 2). When

Scheme 2. Preliminary Mechanistic Studies



$Pd(Xantphos)(CH_3CN)_2(OTf)_2$ was replaced with HOTf as the catalyst, the reaction did not occur at all, which indicated that the Pd catalyst was essential for this process (see Supporting Information). On the other hand, the reaction proceeded well when the isolated $Pd(Xantphos)(CH_2NBn_2)(OTf)$ complex **I** was used as catalyst under the standard conditions. Moreover, the stoichiometric reaction of complex **I** with 2,3-dihydrofuran **1s** and 2-PrOH at 110 °C successfully afforded the desired product **4s** in a 54% yield, thus indicating the plausible intermediacy of complex **I** in the catalytic cycle of the present reaction. To get further insights into the catalytic cycle of the present reaction, ^{31}P NMR and ESI-MS experiments were conducted to monitor the standard reaction catalyzed by complex **I** in toluene-d_8 (see Supporting Information). At the beginning, complex **I** showed up as two resonances at 3.59 and 14.05 ppm in the ^{31}P NMR spectra. After heating up to 110 °C for 10 min, two new signals at 6.87 and 9.15 ppm grew up simultaneously. At the same time, the HRMS (ESI) analysis of the reaction mixture showed a peak at m/z 894.2297, which corresponded to the mass of $[\mathbf{I}\text{-OTf}]^+$. Another peak at m/z 964.2617 was also detected, corresponding to the mass of $[\mathbf{II}\text{-OTf}]^+$. After 1 h, the ^{31}P NMR became messy and the above four signals almost disappeared with the formation of the desired product **4s**, which was detected by GC and ^1H NMR (76% yield). The above results support that the intermediates **I** and **II** (or **II′**) might be involved in the catalytic cycle of this transformation.

On the basis of the results described above and our previous report,[8] a possible reaction mechanism of the three components reaction is exemplified in Figure 1. Initially,

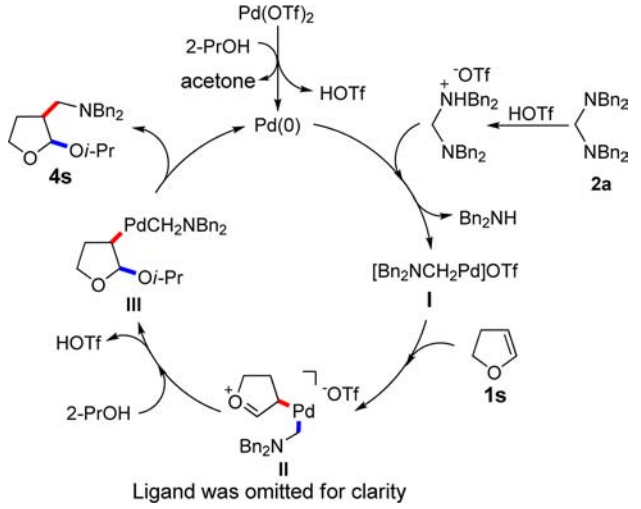


Figure 1. Plausible reaction mechanism.

reduction of Pd(II) precatalyst by 2-PrOH gives a catalytically active Pd(0) species together with a catalytic amount of acid. Subsequent oxidative addition of aminal **2** to the Pd(0) species quickly takes place via acid-assisted C−N bond cleavage, generating the key intermediate **I**. This electrophilic cationic Pd−complex **I** reacts with electron-rich enol ether **1**, forming a new Pd−alkyl intermediate **II**, which is further attacked by a nucleophile to give intermediate **III**. Reductive elimination from **III** releases the desired product **4** and regenerates the active Pd(0) species to complete the catalytic cycle.

In summary, we have developed a novel strategy for intercepting the Pd−alkyl species generated in the Heck reaction. As a result, a novel palladium-catalyzed difunctionlization of enol ethers with alcohols and aminals has been established. One C−C and one C−O bond are formed in this transformation, which provides a facile access to amino acetals. Mechanistic experiments suggest that our present work not only offers a simple and general method for difunctionalization of simple enol ethers but also provides fundamentally important insight into intercepting Heck-type Pd−alkyl species via nucleophilic addition prior to migratory insertion of alkenes.

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■ 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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