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Palladium-Catalyzed Dehydrogenative Difunctionalization of Aminoalkenes with Aminals as Oxidants and Electrophiles

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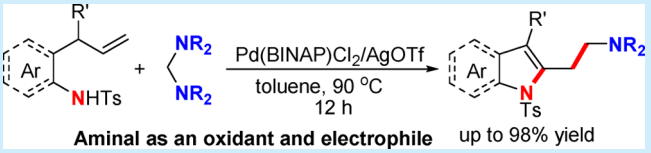
Supporting Information

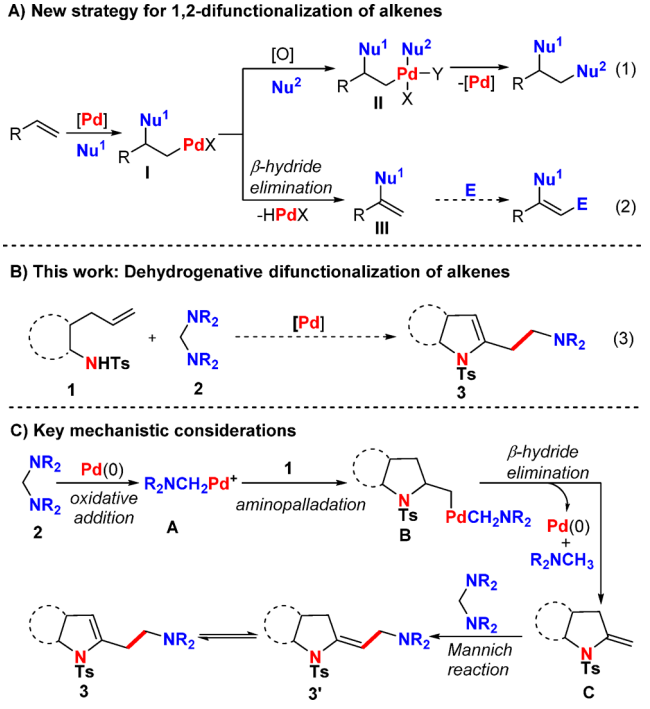
ABSTRACT: A novel palladium-catalyzed aminomethylamination of aminoalkenes with an aminal, functioning not only as an aminomethylation reagent but also as an oxidant, was developed. This direct and operationally simple protocol provides a fundamentally novel and unique approach toward the synthesis of 2-(2-aminoethyl)indoles and 2-(2-aminoethyl)pyrrolidines, which are important building blocks in synthetic organic chemistry. The unity of this method was highlighted by the rapid synthesis of Alosetron, a drug used for the treatment of irritable bowel syndrome.



Palladium-catalyzed alkene difunctionalization reactions provide a powerful means to assemble carbon−carbon and carbon−heteroatom bonds, which have been widely used for the synthesis of organic materials, natural products, and bioactive compounds.[1] Classically, these reactions are thought to proceed by initial Pd(II)-promoted addition of a nucleophile to alkenes, yielding an alkyl-Pd(II) species **I**, which is then intercepted with another nucleophile to construct the second C−X bond (Scheme 1A).[1c] However, such a reaction has proved challenging. This is not only because of the reluctance of the alkyl-Pd(II) intermediate toward reductive elimination but also due to the inherent rapid β-hydride elimination. As a result, great effort has been invested to find efficient strategies to suppress the β-hydride elimination prior to achieving the second bond construction.[2,3] In this context, since the pioneering work of Sanford, the oxidative intercepting method with strong oxidants has become a fundamental method in Pd-catalyzed simple alkene difunctionalization reactions (Scheme 1A-1).[3] One drawback of this strategy is that it usually requires super stoichiometric amounts of strong oxidants, and the oxidants must be able to oxidize Pd(II) to Pd(IV), thereby limiting the potential scope of these useful transformations. Moreover these oxidants often produce a large amount of byproducts. Thus, the discovery of efficient difunctionalization processes that do not need to suppress the β-hydride elimination will also be of great importance because such procedures obviate the need for strong oxidants.

Aminopalladation of alkenes is a fundamental process for the generation of alkyl-Pd(II) species **I**, which is prone to undergoing β-hydride elimination to give rise to the enamine product **III**.[4] Due to its high nucleophilicity, enamine **III** would be potentially captured by an appropriate electrophile to furnish a new type of difunctionalization products with the double bond remaining (Scheme 1A-2) and avoiding the use of large amounts of strong oxidants. However, the successful realization of such a reaction needs to identify an appropriate oxidant to recycle the oxidative

Scheme 1. Pd-Catalyzed Dehydrogenative Difunctionalization of Alkenes



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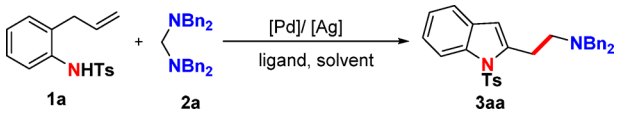
amination process and an effective electrophile to quickly capture the enamine species **III**, furnishing the difunctionalization products. Aminals are electrophilic in nature and have long been recognized as surrogates of iminium ions and are widely used as electrophiles in nucleophilic addition reactions.[5] Moreover, our recent studies demonstrated that aminals are capable of oxidizing Pd(0) to Pd(II), generating a unique electrophilic cationic alkyl-Pd(II) species **A** via oxidative addition.[6] These results suggest that an aminal can play a dual role by acting first as the oxidant to promote the oxidative amination reaction and then as the electrophile to capture an enamine. Inspired by this unique feature, we reasoned that the Pd-alkyl species **A**, generated from the oxidative addition with Pd(0) and an aminal, would promote the intramolecular aminopalladation of the aminoalkenes **1** to form the intermediate **B**, which undergoes β-hydride elimination to produce the intermediate **C** together with R_2NCH_2PdH. Reductive elimination of R_2NCH_2PdH regenerates Pd(0) to finish the oxidative amination catalytic cycle. Subsequently, the intermediate **C** would be captured by another molecular of aminal to give the desired product **3** or **3′**, furnishing the dehydrogenative difunctionalization reaction (Scheme 1C). It should be noted that the exocyclic double bond of enamide **C** would be migrated to form the endocyclic double bond. As a consequence, the desired tapping reaction might be stopped or other regioisomers can be observed. Nevertheless, the reaction is likely facilitated by the higher reactivities of aminals, and the regioselectivity is biased by higher reactivity of the enamide with an exocyclic double bond. In this paper, we describe our success in promoting this pathway and thus achieving a practical synthetic method toward 2-(2-aminoethyl)indoles, which are important common intermediates for the synthesis of indole-containing natural products and drugs.[7]

We started our study with the model reaction between *N*-(2-allylphenyl)-4-methylbenzenesulfonamide (**1a**) and *N*,*N*,*N*′,*N*′-tetrabenzylmethanediamine (**2a**). On the basis of our previous studies,[6] the initial experiments were conducted in toluene at 110 °C with $Pd(CH_3CN)_2Cl_2$ as a catalyst precursor. Catalytic amount of AgOTf was added in situ to generate the cationic palladium species. After an extensive screening of the phosphine ligands (Table 1, entries 1−6), BINAP stood out as the best ligand to deliver the desired product **3aa** in 69% yield. The structure of **3aa** was unambiguously confirmed by NMR spectroscopy and further validated by a single-crystal X-ray diffraction analysis.[8] To improve the reaction yield, a solvent screening was conducted (Table 1, entries 6−10). As a result, toluene was found to be the best choice. The yield increased to 73% when the reaction was carried out at 90 °C in toluene (Table 1, entry 7). Further decreasing the reaction temperature led to lower yield (Table 1, entry 11 vs entry 12). Variation of the counterion of the palladium complexes indicated that the counterion was a key factor, and the best result was obtained when OTf^- was served as counterion. Almost no desired reaction occurred when $CF_3CO_2^-$ or Cl^- served as a counterion (see Supporting Information), suggesting that the cationic palladium complexes have an advantage in this reaction. Several other palladium complexes with BINAP were examined; most of them could furnish the desired products in good yields (Table 1, entries 13−15). To our delight, the highest yield up to 81% was obtained when $Pd(BINAP)Cl_2$/AgOTf was utilized as the catalyst (Table 1, entries 16). Control experiments confirmed that the reaction with AgOTf in the absence of palladium did not afford indole **3aa** at all. It was also proven that typical Lewis acids, such as $Zn(OTf)_2$, $Sc(OTf)_2$, or $AlCl_3$, and Brönsted acids were ineffective catalysts for this reaction (see Supporting Information), which suggested that the reaction was most likely not acid-catalyzed.

Table 1. Screening of Reaction Conditions[a]



entry	[Pd]	ligand	solvent	t (°C)	yield (%)[b]
1	$Pd(CH_3CN)_2Cl_2$	DPPE	toluene	110	<5
2	$Pd(CH_3CN)_2Cl_2$	DPPP	toluene	110	52
3	$Pd(CH_3CN)_2Cl_2$	DPPB	toluene	110	53
4	$Pd(CH_3CN)_2Cl_2$	DPPF	toluene	110	30
5	$Pd(CH_3CN)_2Cl_2$	Xantphos	toluene	110	<5
6	$Pd(CH_3CN)_2Cl_2$	BINAP	toluene	110	69
7	$Pd(CH_3CN)_2Cl_2$	BINAP	2-PrOH	110	56
8	$Pd(CH_3CN)_2Cl_2$	BINAP	dioxane	110	57
9	$Pd(CH_3CN)_2Cl_2$	BINAP	THF	110	48
10	$Pd(CH_3CN)_2Cl_2$	BINAP	CH_3CN	110	54
11	$Pd(CH_3CN)_2Cl_2$	BINAP	toluene	90	73
12	$Pd(CH_3CN)_2Cl_2$	BINAP	toluene	70	49
13	$[Pd(ally)Cl]_2$	BINAP	toluene	90	72
14	$[Pd(COD)Cl]_2$	BINAP	toluene	90	73
15	PdI_2	BINAP	toluene	90	<5
16	$Pd(BINAP)Cl_2$		toluene	90	81
17[c]		BINAP	toluene	90	0

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), [Pd] (5.0 mol %), ligand (5.5 mol %), AgOTf (10 mol %), solvent (1.0 mL), 12 h. [b]Isolated yield. [c]AgOTf (10 mol %), BINAP (10 mol %).

With the optimized reaction conditions in hand, the substrate scope with respect to the aminoalkene was investigated. As shown Scheme 2, the reaction is compatible with a wide range of *N*-sulfonyl-2-allylanilines to afford different 2-(2-aminoethyl)-indoles **3aa**−**3qa** in good to excellent yields. Alkyl, methoxyl, chloro, fluoro, and cyan substituents on the phenyl ring of the *N*-sulfonyl-2-allylanilines are well-tolerated. Moreover, for substrates with disubstituents on the aryl ring, including the dimethyl and dichloro-substituted *N*-sulfonyl-2-allylanilines, the reactions proceeded smoothly to provide the desired products **3ga** and **3ha** in excellent yields. It is notable that the reactions of **1i**, **1j**, and **1k**, which bear a methyl group on the allylic position, yield the corresponding 2,3-disubstituted indoles **3ia**−**3ka** in 81−87% yields. Furthermore, various functional groups at the allylic position, such as hydroxymethyl and esters, could be tolerated to provide the corresponding products **3la**−**3na** in good yields, which provide vast opportunities for further transformations. Subsequently, an investigation into different N-protecting groups showed that sulfonyl groups provided the corresponding products in good yields (**3oa**−**3qa**); however, no desired product was observed when free amine or Boc-protected amine was subjected to the given reaction conditions. Similarly, the reaction was also amenable to the linear *N*-alkenylsulfonamides to give the corresponding cyclization products (**3sa**−**3ua**) with pyrrolidine framework, albeit in moderate yields.

Next, we explored the scope and limitations of this cascade process for various substituted aminals with *N*-sulfonyl-2-allylanilines **1i**. As shown in Table 2, the benzyl aminals with substituents on the *para*-position of the phenyl ring furnished the corresponding products in high yields (Table 2, entries 2 and 3). However, relative lower yields were achieved when the

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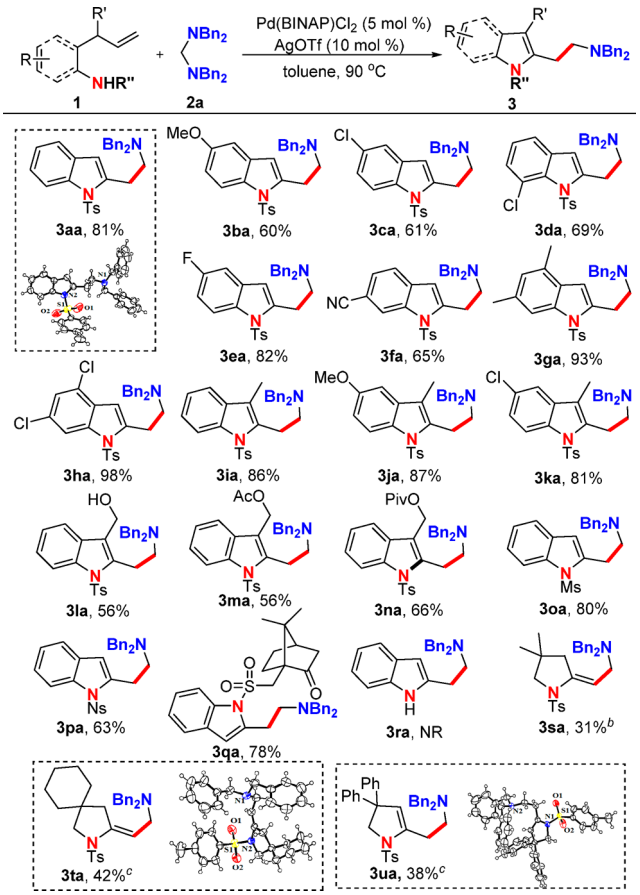
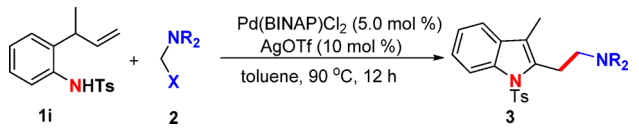
Scheme 2. Substrate Scope of Aminoalkene[a]



[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.5 mmol), $Pd(BINAP)Cl_2$ (5 mol %), Ag(OTf) (10 mol %), toluene (1 mL), 90 °C, 12 h; unless otherwise noted, isolated yields are shown. [b]$PdCl_2$ (10 mol %), BINAP (10 mol %), AgOTf (20 mol %), toluene (1 mL), 90 °C, 24 h. [c]**1** (0.25 mmol), **2a** (0.25 mmol), $PdCl_2$ (10 mol %), BINAP (10 mol %), AgOTf (20 mol %), toluene (1 mL), 100 °C, 24 h, yield based on **2a**.

Table 2. Substrate Scope of Aminals[a]



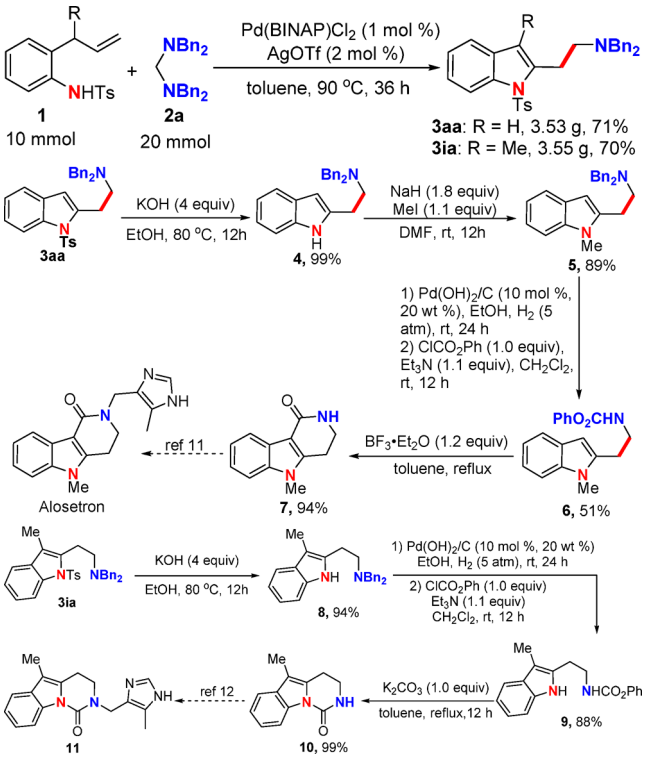
entry	R	X	3	yield (%)[b]
1	$C_6H_5CH_2$	$(C_6H_5CH_2)_2N$	**3ia**	86
2	4-$CF_3C_6H_4CH_2$	$(4\text{-}CF_3C_6H_4CH_2)_2N$	**3ib**	82
3	4-$ClC_6H_4CH_2$	$(4\text{-}ClC_6H_4CH_2)_2N$	**3ic**	97
4	2-$BrC_6H_4CH_2$	$(2\text{-}BrC_6H_4CH_2)_2N$	**3id**	50
5	2-$ClC_6H_4CH_2$	$(2\text{-}ClC_6H_4CH_2)_2N$	**3ie**	57
6	$CH_3(CH_2)_3$	$(CH_3(CH_2)_3)_2N$	**3if**	28
7	$CH_3CH_2CH_2CH_2$	OCH_3	**3if**	60
8	$CH_3CH_2CH_2$	OCH_3	**3ig**	54
9	$-(CH_2)_2O(CH_2)_2-$	OCH_3	**3ih**	70

[a]Reaction conditions: **1i** (0.25 mmol), **2** (0.5 mmol), $Pd(BINAP)Cl_2$ (5.0 mol %), AgOTf (10.0 mol %), toluene (1.0 mL), 90 °C, 12 h. [b]Isolated yield.

substituent was attached on the *ortho*-position (Table 2, entries 4 and 5). Aminals derived from simple alkylamines were also compatible with this process, but only lower yield was afforded. The observed lower reactivity for this type of aminal may stem from the difficulty in the oxidative addition step. To improve the reaction yield, *N,O*-aminals derived from simple alkylamines and CH_3OH, which are much easier to form iminium ions due to the facile C−O bond cleavage,[9] were used as coupling partners for the current reaction. As expected, the target molecules **3if**−**3ih** were obtained in moderate to good yields (Table 2, entries 7−9).

The synthetic versatility of the present catalytic protocol was demonstrated through large-scale reactions and the formal synthesis of drug Alosetron and another 5-HT3 receptor antagonist. The reaction of **1a** with **2a** on a 10 mmol scale completed in the presence of 1 mol % of catalyst, yielding 3.53 g of the corresponding product **3aa** in 71% yield. Remarkably, **3aa** could be obtained in 46% yield even in the presence of 0.1 mol % of catalyst. As an application to bioactive molecule synthesis, the drug Alosetron (a 5-HT3 antagonist originated by GlaxoSmithKline Plc; a drug molecule used for the treatment of irritable bowel syndrome)[10] was prepared from **3aa** via indole C3-cyclization (Scheme 3). The *N*-tosyl group on the indole ring of **3aa** was

Scheme 3. Synthetic Utility of 2-(2-Aminoethyl)indoles



rapidly removed to give **4** by treatment with KOH in EtOH, and then the methyl group was introduced with MeI under basic conditions to give **5** in good yield. Compound **5** could then be successfully transformed into **6** through $Pd(OH)_2$/C-catalyzed hydrogenolysis with H_2 and amidation with phenyl chloroformate. Under the catalysis of Lewis acid ($BF_3{\cdot}Et_2O$), Alosetron intermediate **7** was obtained in 94% yield. It could be easily converted into Alosetron via simple nucleophilic substitution according to the reported method.[11] Similarly, **3ia** was also prepared in 3.55 g scale using our Pd-catalyzed protocol in the presence of 1 mol % of catalyst. Indole-annulated compound **10** was prepared in good yield by the following deprotection−cyclization process, which could be used for the synthesis of a variety of 5-HT3 receptor antagonist molecules.[12]

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In summary, we have developed a new strategy for dehydrogenative difunctionalization of alkenes, which does not need to suppress β-hydride elimination, thus obviating the use of strong oxidants.[13] After identifying that aminal can play a dual role acting as a nucleophile and a mild oxidant, a palladium-catalyzed aminomethylamination of aminoalkenes was established using this strategy, providing a novel synthetic method to 2-(2-aminoethyl)indoles and 2-(2-aminoethyl)pyrrolidines. As demonstrated by the given synthetic applications, the method provides an efficient means to access indole-annulated heterocycles, with relevance to both natural product and bioactive molecule synthesis. Ongoing studies are focused on exploring the scope of this reactivity and probing the catalytic mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02203.

Experimental details and full spectroscopic data for all new compounds (PDF)
X-ray structure of **3aa** (CIF)
X-ray structure of **3ta** (CIF)
X-ray structure of **3ua** (CIF)

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Author Contributions

L.L. and X.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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(8) CCDC 1558678 (**3aa**), 1558689 (**3ta**), and 1558679 (**3ua**) contain 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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(13) The enamide intermediate was isolated and could be directly converted into the desired product with aminal, suggesting that the enamide intermediate like C was most likely involved in our catalytic system (see Supporting Information for details).

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