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Palladium Nanoparticle-Catalyzed C−N Bond Formation. A Highly Regio- and Stereoselective Allylic Amination by Allyl Acetates

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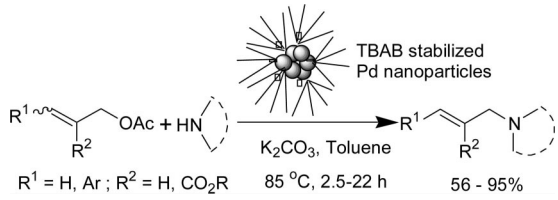
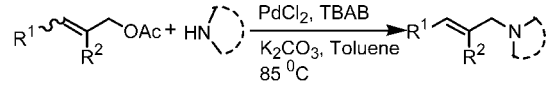
Received February 11, 2009



Palladium nanoparticles, generated in situ from the reaction of palladium(II) chloride, have been demonstrated to be an efficient catalyst for C−N bond formation. A variety of aliphatic and aromatic amines have been allylated by substituted and unsubstituted allyl acetates in high yields by using palladium nanoparticles in the presence of a base without any ligand. The allylations are highly regio- and stereoselective.

The allylamines are of great importance in organic synthesis. They are found in a wide variety of bioactive natural products,[1] and are useful intermediates to a range of products such as alkaloids,[2] α- and β-amino acids, etc.[3] Thus, their synthesis is of high interest. The transition metal-catalyzed allylic amination of allyl alcohols or their derivatives is one of the most effective protocols for C−N bond formation.[4] Although several metals such as Rh,[5] Ir,[6] Fe,[7] Ru,[8] Ni,[9] and Pd[10] have been used, Pd catalysts are found to be the most powerful. Usually, palladium complexes in combination with ligands are employed for allylic amination reactions.[10] Recently, metal nanoparticles have attracted considerable interest in the catalysis of organic reactions.[11] As a part of our continued activities to explore the potential of Pd nanoparticles as catalysts for organic transformations,[12] we discovered that allylic amination was very efficiently catalyzed by Pd nanoparticles in the presence of a base (Scheme 1). Our literature survey found only one example of allylic amination using Pd nanoparticles supported on mesoporous silica in the presence of a ligand.[13]

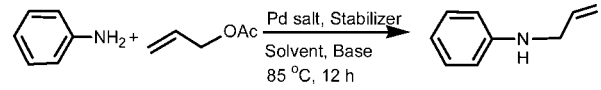
SCHEME 1. Palladium Nanoparticle-Catalyzed Allylic Amination with Allyl Acetates



To standardize the reaction conditions a series of experiments were performed in different solvents with various palladium salts, bases, and stabilizers for a representative reaction of aniline and allyl acetate. The results are summarized in Table 1. It was found that the reaction proceeds best in toluene by using $PdCl_2$ and tetrabutylammonium bromide (TBAB) as a stabilizer[11d] in the presence of K_2CO_3 (Table 1, entry 6). The amount of $PdCl_2$ was also optimized to 4.5 mol %. The reaction also proceeds well in the presence of Cs_2CO_3; however, Cs_2CO_3 being more expensive K_2CO_3 was used in all these reactions.

In a typical experimental procedure, a mixture of amine, allyl acetate, palladium(II) chloride, TBAB, and K_2CO_3 in toluene was heated at 85 °C for a period of time as required for completion (TLC). The usual workup and purification by column chromatography provided the product.

TABLE 1. Standardization of Reaction Conditions[a]



entry	solvent	Pd salt	stabilizer	base	yield (%)
1	dioxan	$PdCl_2$	TBAB	K_2CO_3	0
2	DMF	$PdCl_2$	TBAB	K_2CO_3	0
3	CH_3CN	$PdCl_2$	TBAB	K_2CO_3	0
4	H_2O	$PdCl_2$	TBAB	K_2CO_3	15
5	THF	$PdCl_2$	TBAB	K_2CO_3	35
6	toluene	$PdCl_2$	TBAB	K_2CO_3	80
7	toluene	$PdCl_2$		K_2CO_3	0
8	toluene	$PdCl_2$	SDS	K_2CO_3	0
9	toluene	$PdCl_2$	PEG-6000	K_2CO_3	20
10	toluene	$PdCl_2$	TBAI	K_2CO_3	55
11	toluene	Na_2PdCl_4	TBAB	K_2CO_3	0
12	toluene	$Pd(OAc)_2$	TBAB	K_2CO_3	0
13	toluene	PdNPs[b]	TBAB	K_2CO_3	38
14	toluene	$PdCl_2$	TBAB	DBU	0
15	toluene	$PdCl_2$	TBAB	KF	10
16	toluene	$PdCl_2$	TBAB	K_3PO_4	15
17	toluene	$PdCl_2$	TBAB	Na_2CO_3	60
18	toluene	$PdCl_2$	TBAB	Et_3N	65
19	toluene	$PdCl_2$	TBAB	Cs_2CO_3	82

[a] Reaction conditions: aniline (1 mmol), allyl acetate (3 mmol), Pd salt (4.5 mol %), stabilizer (1 mmol), solvent (3 mL), and base (2 mmol) were heated at 85 °C. [b] Pd nanoparticles were prepared separately.

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(4) Trost, B. M.; Vanvranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422.
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(6) (a) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem.—Eur. J.* **2006**, *12*, 3596–3609. (b) Welter, C.; Koch, O.; Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 896–897.
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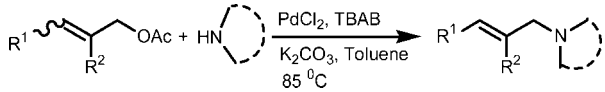
10.1021/jo9003037 CCC: $40.75 © 2009 American Chemical Society
Published on Web 04/21/2009

TABLE 2. Pd Nanoparticle-Catalyzed Allylation of Amines in the Presence of K_2CO_3



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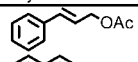
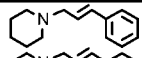
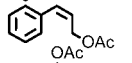
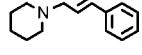
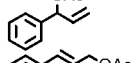
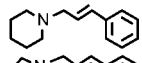
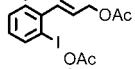
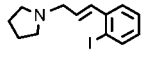
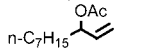
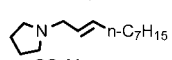
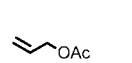
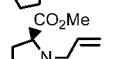
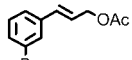
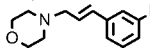
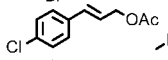
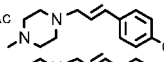
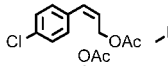
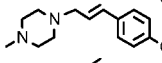
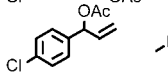
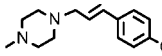
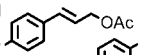
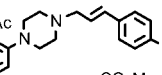
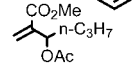
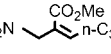
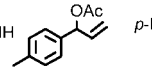
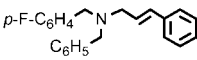
1				5.0	95	10i
2				5.5	90	10i
3				5.0	88	10i
4				3.0	92	
5				5.0	90	18
6				2.5	86	19
7				3.5	87	
8				4.0	93	
9				5.0	86	
10				4.5	88	
11				3.5	90	
12	$(^i Pr)_2NH$		$(^i Pr)_2N$ 	4.0	92	
13				16	78	
14				10	80	
15				12	72	10h
16				15	62	10g
17				22	55	20

[a] Yields refer to those of purified isolated products characterized by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR).

TABLE 3. Allylation of Anilines in the Presence of K_2CO_3

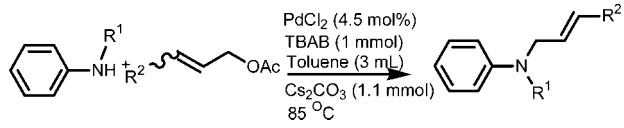
entry	amine	allyl acetate	product	time (h)	yield (%)[a]	ref.
18				10	80	10g
19				5.0	88	
20				8.5	78	21
21				6.5	84	
22				13	65	22
23				36	0	
24				36	0	
25				36	20	

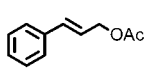
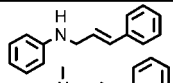
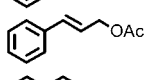
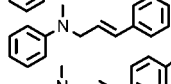
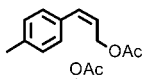
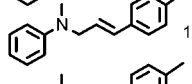
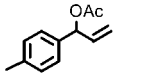
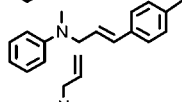
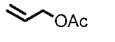
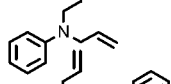
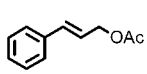
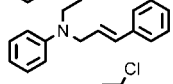
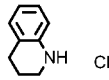
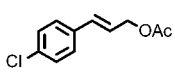
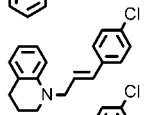
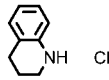
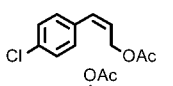
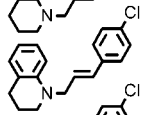
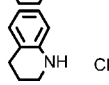
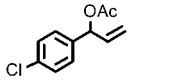
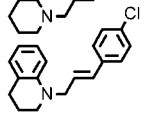
[a] Yields refer to those of purified isolated products characterized by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR).

To check the formation of Pd nanoparticles in situ in the reaction mixture, an extract of aniline and allyl acetate taken after 4 h from the start of the reaction showed the formation of 3−5 nm nanoparticles by a TEM (Transmission Electron Microscope) image. The identity of these particles as palladium was confirmed by EDS (Energy Dispersive Spectroscopy). The residual powder left after extraction of product also showed the presence of Pd metal by XRD (X-ray Diffraction).

A wide variety of substituted cyclic and open chain amines, aniline, and ring-substituted anilines underwent allylations by allyl acetates with varied substituents to produce the corresponding allylated amines by this procedure catalyzed by Pd nanoparticles. The results of allylations of amines are summarized in Table 2 and those of anilines are reported in Table 3. The cyclic amines such as piperidine, pyrrolidine, morpholine, and piperazine participated in this reaction. Very interestingly, both *trans*- and *cis*-cinnamyl acetates on reaction with piperidine (Table 2, entries 1 and 2) or piperazine (Table 2, entries 8 and 9) provided the trans-allylated amines as sole products. No cis-isomer was detected in the crude. The branched cinnamyl acetates (Table 2, entries 3, 10, 13, and 14) provided the same linear trans-products. The branched allyl acetates (Table 2, entries 5 and 12) also provided the corresponding products without any hydride elimination.[14] The F, Cl, Br, and I functionalities (Table 2, entries 4, 7−11, and 14) in the aromatic ring remained inert during this allylic amination reaction without undergoing Buchwald−Hartwig amination.[15] The open chain amines (Table 2, entries 12−14) produced the corresponding trans-products without any difficulty. The aliphatic primary amines (Table 2, entries 15−17) led to bis-allylated products in all three reactions. No monoallylation was detected at any stage of the reaction. The anilines (Table 3, entries 18−22) underwent allylations by allyl acetate and 2-carboxyallyl acetates giving the corresponding allylated anilines with a terminal double bond. However, aniline and *N*-substituted anilines failed to react with cinnamyl acetate under this condition. We rationalized that possibly $-NH_2$ of aniline binds strongly to Pd nanoparticles[16a] thus reducing its nucleophilicity. Hence, we investigated this reaction in the presence of a stronger base than K_2CO_3. After a series of experiments with different bases, we found Cs_2CO_3 as the only one to perform this reaction efficiently. Although the reaction of aniline itself was not good, several *N*-substituted anilines underwent allylations by a variety of cinnamyl acetates efficiently. The results are reported in Table 4. The tetrahydroquinolines (Table 4, entries 7−9) and brached cinnamyl acetates (Table 4, entries 4 and 9) also participated in this reaction. In this allylation too, *cis*- and *trans*-cinnamyl acetates led to the same trans products (Table 4, entries 2, 3, 7, and 8). The monoallylated anilines which failed to undergo a second allylation in the presence of K_2CO_3 were allylated without any difficulty under this condition (Table 4, entries 5

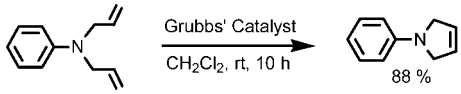
TABLE 4. Pd Nanoparticle-Catalyzed Allylation of Anilines by Allyl Acetates in the Presence of Cs_2CO_3



entry	amine	allyl acetate	product	time (h)	yield (%)[a]	ref.
1				24	25	23
2				15	75	21
3				18	64	
4				17	70	
5				14	82	10g
6				15	56	24
7				16	68	
8				18	60	
9				17	65	

[a] Yields refer to those of purified isolated products characterized by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR).

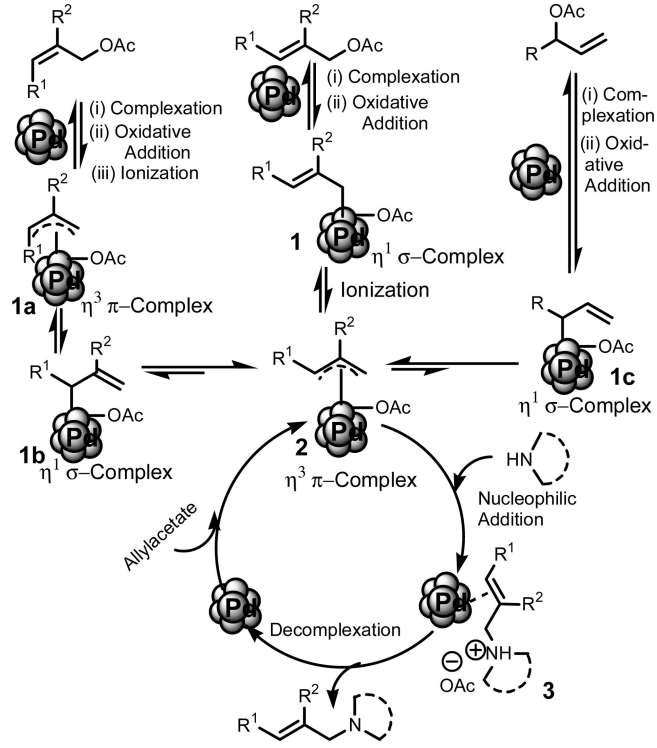
SCHEME 2



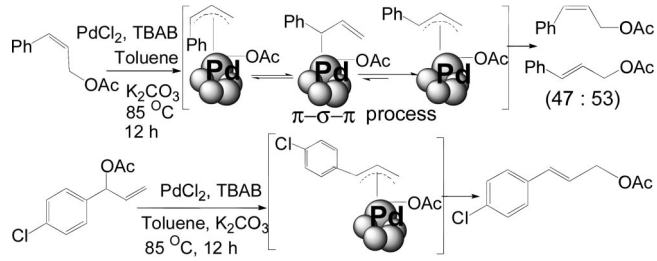
and 6). These bis-allylated products are useful precursors to *N*-aryl dihydropyrroles (Scheme 2).

In view of these observations that both cis and trans and branched substituted allyl acetates led to the same trans-products, we proposed the reaction pathway outlined in Scheme 3. An allyl acetate undergoes complexation and oxidative addition with Pd nanoparticles to form the corresponding η^1-σ-allyl palladium acetate complex **1**, which then leads to a common η^3-π-complex **2**. This undergoes nucleophilic addition of an amine at the less hindered terminal position to provide an intermediate **3**, which on decomplexation with a base produces the trans-allylated amine and gives back Pd nanoparticles which take part in the next cycle. This process is applicable straightway in case of *trans*-allyl acetates. In the case of *cis*-allyl acetates η^3-π-complex **1a** was formed after initial complexation, oxidative addition, and ionization, which then changes its heptacity with the loss of its stereochemistry to give rise to **1b**.[12d,16b] This intermediate then isomerizes to the more stable intermediate **2**. Similarly, the branched allyl acetate also proceeds to lead to the same intermediate **2** via **1c**. To check the feasibility of isomerization of η^3-π-complex **1a** and η^1-σ-complex **1c** to **2**, we carried out two blank experiments with cis and branched acetates in the absence of amine and we observed 53% isomerization in *cis*-

SCHEME 3. Proposed Reaction Pathway



SCHEME 4



cinnamyl acetate, probably via a π-σ-π process,[16b] and 100% in the case of a branched cinnamyl acetate. This supports our proposed pathway (Scheme 4).

In general, the reactions are very clean and high yielding. No additional step is required for the preparation of palladium nanoparticles in our procedure in contrast to the tedious preparation of mesoporous silica-supported Pd nanoparticles used for allylic amination reported earlier.[13] Several functionalities such as F, Cl, Br, I, OMe, and NO_2 are compatible with this procedure. The remaining Pd nanoparticles, after extraction of product, were recycled for three runs with gradual loss of efficiency possibly due to agglomerization of Pd nanoparticles on each exposure. It may be mentioned that the TEM image of the Pd catalyst, left after the first cycle, showed particle sizes in the range of 10−12 nm compared to 3−5 nm before the first cycle. Usually, the reactivity and efficiency of nanoparticles decrease with an increase of size.[17]

In conclusion, we have developed an efficient procedure for C−N bond formation leading to allylic amination by allyl acetates using in situ generated Pd nanoparticles in the absence of any ligand. Most significantly, a wide range of amines (cyclic, open chain, aromatic) and allyl acetates have been addressed making it a general methodology and to the best of our knowledge no other existing procedure demonstrated such a

wide scope. The allylations are highly regio- and stereoselective providing only one product in each reaction. Nevertheless, this demonstrates the potential of Pd nanoparticles for C−N bond formation.

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Experimental Section

Representative Experimental Procedure for Allylation of Amine (Table 3, Entry 18). A mixture of aniline (93 mg, 1 mmol), allyl acetate (300 mg, 3 mmol), $PdCl_2$ (8 mg, 0.045 mmol), tetrabutylammonium bromide (323 mg, 1 mmol), and K_2CO_3 (276 mg, 2 mmol) in toluene (3 mL) was heated with stirring at 85 °C for 10 h (TLC). The reaction mixture was extracted with Et_2O (3 × 10 mL). The extract was washed with water and brine then dried (Na_2SO_4). Evaporation of solvent left the crude product, which was purified by column chromatography over neutral alumina (hexane/ether 95:5) to provide allylphenylamine as a colorless oil (106 mg, 80%). The spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR) of this compound are in good agreement with those reported.[10g] The remaining black Pd nanoparticles, after extraction with ether, were further washed with ether, dried, and reused for subsequent runs.

Several of these products are known compounds (see the references in Tables 2 and 3) and were easily characterized by comparison of their spectroscopic data with those reported. The unknown compounds were properly characterized by their IR, ^{1}H NMR, ^{13}C NMR, and HRMS data (see the SI).

This procedure was followed for all the reactions listed in Tables 2−4. Although the representative procedure is based on a 1 mmol scale reaction, it has been scaled up to 10 mmol with reproducible results.

Acknowledgment. We are pleased to acknowledge financial support from DST, New Delhi under a J.C. Bose National Fellowship (Grant No. SR/S2/JCB-11/2008). L.A. and K.C. are thankful to CSIR for their fellowships.

Supporting Information Available: TEM (Figure 1), EDS (Figure 2), XRD (Figure 3), and recyclability chart (Figure 4); characterization data (IR, ^{1}H and ^{13}C NMR spectroscopic data, HRMS, or elemental analysis report) of the products in entries 4 and 7−14 in Table 2 and entries 19, 21, 23−25 in Table 3 and entries 3, 4, and 7−9 in Table 4; copies of ^{1}H and ^{13}C NMR spectra of all products listed in Tables 2−4. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9003037