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Palladium-Catalyzed *N*-Allylation of Anilines by Direct Use of Allyl Alcohols in the Presence of Titanium(IV) Isopropoxide

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Abstract: The direct activation of C-O bonds in allyl alcohols by palladium complexes has been accelerated by carrying out the reactions in the presence of titanium(IV) isopropoxide and 4Å molecular sieves. *N*-Allylation of anilines to give mono- and diallylanilines using allyl alcohols directly has been realized by employing palladium catalysts.

Allyl amines are an important class of compounds, due not only to their utility as intermediates in organic synthesis[1] but also because of their physiological properties[2] and their presence in several natural products.[3] A number of synthetic methods for the preparation of allyl amines from alkene derivatives have been developed, but these require severe reaction conditions or several sequential reactions.[4] Allylation of carbon-, nitrogen-, and oxygen-nucleophiles catalyzed by palladium complexes has been widely applied to organic synthesis.[5] The processes have been shown to proceed by attack of nucleophiles on intermediate η^3-allylpalladium(II) complexes generated by oxidative addition of allylic compounds including allylic halides, acetates, and carbonates to a Pd(0) complex.[6] However, there have been only limited and sporadic reports dealing with the direct cleavage of the C-O bond in allyl alcohols on interaction with a transition metal complex.[7] Successful applications using allyl alcohols directly in catalytic processes are even more limited. Itoh has reported that palladium-catalyzed nucleophilic substitution of allyl alcohols using zinc enolates can proceed efficiently in the presence of titanium(IV) alkoxides and LiCl;[8] the alkoxides appear to enhance the reactivity of allyl alcohols toward palladium(0) species. We considered that, when anilines are employed as nucleophiles for the reaction, a convenient method to prepare *N*-allylanilines could be realized; the anilines are useful compounds in organic synthesis.[5] We have examined the reaction of allyl alcohols with anilines in the presence of a palladium catalyst and titanium(IV) isopropoxide. This is, to our knowledge, the first example of palladium-catalyzed allylation of anilines by the direct use of allyl alcohols.

When a mixture of aniline (**1a**, 1 mmol) and allyl alcohol (**2a**, 1.2 mmol) was heated in the presence of $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.04 mmol) and $Ti(OPr^i)_4$ (0.25 mmol) in benzene (5 ml) under nitrogen at 50°C for 3 h., *N*-allylaniline (**3a**) was formed in 22% yield (entry 1 in Table 1).[9] The reaction should be accompanied by formation of water. Addition of molecular sieves (MS4A) for its removal, increased the yields of products **3a** and *N,N*-diallylaniline (**4a**) to 66% and 10%, respectively (entry 2). Addition of MS4A was needed to prevent catalyst deactivation which is probably due to water formed during the reaction. The reaction of allyl alcohols

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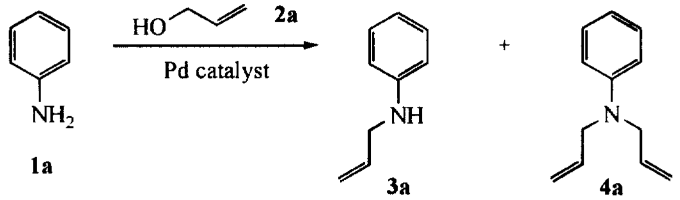
with zinc enolates, mentioned above, required addition of a chloride source such as LiCl together with $Ti(OR)_4$ to proceed efficiently.[8] However, this was not necessary for the present reaction (entry 3). Without $Ti(OPr^i)_4$ (entry 4) or when it was substituted by Et_3N (entry 5) or K_2CO_3 (entry 6), allylation products were not obtained. Six useful solvents are benzene, MeCN, THF, HMPA, DMF or toluene; benzene gave the best results (entries 2 and 12-19). The bidentate ligand dppe (entry 12), dppp (entry 13) or dppb (entries 14 and 16) did not increase the yield of products significantly. Among the palladium catalysts including $Pd(OCOCF_3)_2$ (entries 15 and 16), $Pd(PPh_3)_4$ (entry 17) and $PdCl_2$ (entries 18 and 19), $Pd(OAc)_2$ was found to be superior (entry 2).

Table 1 Allylation of aniline (**1a**) with allyl alcohol (**2a**)[a]

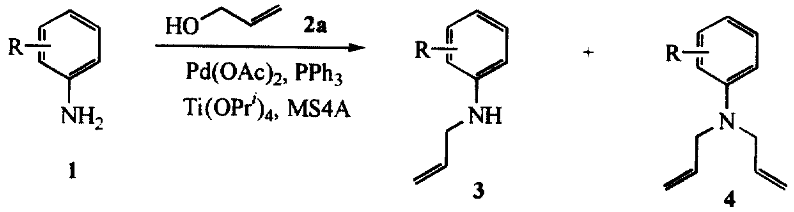


Entry	Catalyst	Base	Solvent	Yield (%)[d] (**3a**: **4a**)
1[b]	$Pd(OAc)_2$-PPh_3	$Ti(OPr^i)_4$	benzene	22 (100: 0)
2	$Pd(OAc)_2$-PPh_3	$Ti(OPr^i)_4$	benzene	76 (87: 13)
3[c]	$Pd(OAc)_2$-PPh_3	$Ti(OPr^i)_4$	benzene	24 (62: 38)
4	$Pd(OAc)_2$-PPh_3	——	benzene	0
5	$Pd(OAc)_2$-PPh_3	Et_3N	benzene	0
6	$Pd(OAc)_2$-PPh_3	K_2CO_3	benzene	0
7	$Pd(OAc)_2$-PPh_3	$Ti(OPr^i)_4$	MeCN	34 (82: 18)
8	$Pd(OAc)_2$-PPh_3	$Ti(OPr^i)_4$	THF	36 (81: 19)
9	$Pd(OAc)_2$-PPh_3	$Ti(OPr^i)_4$	HMPA	52 (83: 17)
10	$Pd(OAc)_2$-PPh_3	$Ti(OPr^i)_4$	DMF	24 (100: 0)
11	$Pd(OAc)_2$-PPh_3	$Ti(OPr^i)_4$	toluene	61 (85: 15)
12	$Pd(OAc)_2$-dppe	$Ti(OPr^i)_4$	benzene	64 (88: 12)
13	$Pd(OAc)_2$-dppp	$Ti(OPr^i)_4$	benzene	67 (88: 12)
14	$Pd(OAc)_2$-dppb	$Ti(OPr^i)_4$	benzene	69 (91: 9)
15	$Pd(OCOCF_3)_2$-PPh_3	$Ti(OPr^i)_4$	benzene	57 (68: 32)
16	$Pd(OCOCF_3)_2$-dppb	$Ti(OPr^i)_4$	benzene	68 (81: 19)
17	$Pd(PPh_3)_4$	$Ti(OPr^i)_4$	benzene	51 (90: 10)
18	$PdCl_2$-PPh_3	$Ti(OPr^i)_4$	benzene	19 (79: 21)
19	$PdCl_2$-dppb	$Ti(OPr^i)_4$	benzene	18 (100: 0)

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), Pd (0.01 mmol), ligand (0.04 mmol), base (0.25 mmol) and MS4A (200 mg) in a solvent (5 ml) at 50 °C for 3 h. [b] Without MS4A. [c] Reaction was carried out using LiCl (1 mmol). [d] Isolated yield.

Results for allylation of a number of anilines substituted by both electron-withdrawing and electron-donating groups (**1b-h**) with allyl alcohol (**2a**) using $Pd(OAc)_2$, PPh_3, $Ti(OPr^i)_4$ and MS4A are summarized in Table 2. All of the anilines examined underwent *N*-allylation smoothly to give the corresponding *N*-allylanilines in overall yields ranging from 48-86%.

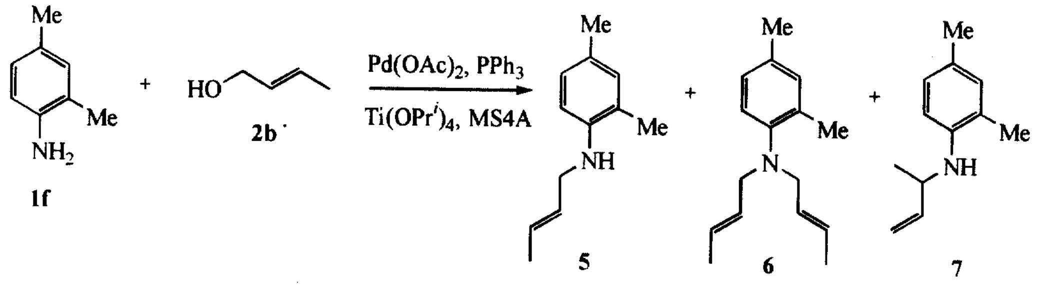
Table 2 Allylation of anilines (**1b-g**) with allyl alcohol (**2a**)[a]



1	R	Products		Yield(%)[c] (3: 4)
1b	4-Me	**3b**	**4b**	76 (87: 13)
1c	4-Cl	**3c**	**4c**	70 (87: 13)
1d	4-OMe	**3d**	**4d**	56 (91: 9)
1e	3,5-OMe	**3e**	**4e**	67 (87: 13)
1f	2,4-Me	**3f**	**4f**	82 (90: 10)
1g	2-Me, 4-Cl	**3g**	**4g**	86 (91: 9)
1h[b]	2-Cl, 4-Br	**3h**		48

[a] Reaction conditions: **1** (1 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.04 mmol), $Ti(OPr^i)_4$ (0.25 mmol) and MS4A (200 mg) in benzene (5 ml) at 50 °C for 3h. [b] Reaction for 24h. [c] Isolated yield.

Treatment of 2,4-dimethylaniline (**1f**) with crotyl alcohol (**2b**) using $Pd(OAc)_2$, PPh_3, $Ti(OPr^i)_4$ and MS4A gave the corresponding products of **5** and **6** in 5% and 12% yield, respectively, while a regioisomeric aniline 7 was formed in 52% yield. (Scheme 1)



Scheme 1

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9. A typical example for the *N*-allylation of anilines: A mixture of **1a** (1 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), PPh_3 (10 mg, 0.04 mmol), $Ti(OPr^i)_4$ (0.075 ml, 0.25 mmol), MS4A (200 mg) and benzene (5 ml) was stirred under nitrogen at 50℃ for 3 h. After cooling, the reaction mixture was poured into aq. 10% HCl and extracted with ether. The aqueous layer was mixed with aq. 10% NaOH and extracted with ether. The ether layers were combined, dried over Na_2SO_4 and concentrated. Column chromatography (hexane:EtOAc=5:1) of the residue afforded products.
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