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Direct palladium-catalyzed selective monoallylation of anilines using allylic alcohols

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Abstract

N-Allylation of anilines using allylic alcohols directly to give monoallylic anilines selectively in high yields has been realized by employing palladium acetate–triphenylphosphine as the catalyst. Palladium-catalyzed one-pot cyclization of 2-aminophenols with 2-butene-1,4-diol leads to 3,4-dihydro-2-vinyl-2*H*-1,4-benzoxazines. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: palladium-catalyzed; selective monoallylation; cyclization; 1,4-benzoxazines.

The palladium-catalyzed allylation of nucleophiles is an established, efficient, and highly stereo- and chemoselective method, which has been widely applied to organic chemistry.[1] The catalytic cycle requires the formation of the cationic η^3-allylpalladium(II) complex, an intermediate which is generated by oxidative addition of allylic compounds including allylic halides,[2] acetates,[3] and carbonates[4] to a Pd(0) complex and which can be attacked by nucleophiles at both termini of the allylic system. However, there have been only limited and sporadic reports dealing with the direct cleavage of the C–O bond of allylic alcohols on interaction with a transition metal complex.[5] Although secondary amines are often excellent nucleophiles for palladium-catalyzed allylic amination, the use of primary anilines has found limited success, with diallylation often a problem.[6] We recently reported some successful applications of a process involving C–O bond cleavage with direct use of allylic alcohols catalyzed by palladium complexes.[7] This result prompted us to study in some detail the reaction between anilines and allylic alcohols in order to prepare monoallylic anilines, which are useful compounds in organic synthesis.[1]

When a mixture of 4-chloro-2-methylaniline (**1a**, 1 mmol) and allyl alcohol (**2**, 0.8 mmol) was heated in the presence of $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.04 mmol), $Ti(OPr^i)_4$ (0.25 mmol) and molecular sieves (MS 4 Å) (200 mg) in benzene (5 mL) under nitrogen at 50°C for 3 h, the selective monoallylation product *N*-allylaniline (**3a**) was formed in 74% yield (entry 1 in Table 1). The reaction did not occur in the absence of the palladium species (entry 2). Note that the product

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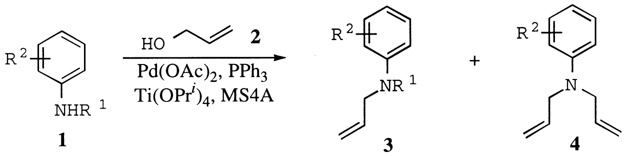
Table 1
Allylation of anilines **1a**–**n** with allyl alcohol (**2**)[a]



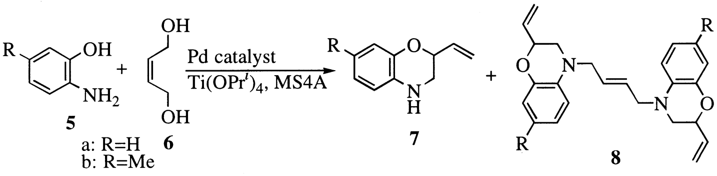
Entry	Aniline	R^1	R^2	Method[b]	T (°C)	Products		Yield(%)[c] (**3**: **4**)
1	**1a**	H	2-Me, 4-Cl	A	50	**3a**		74
2[d]	**1a**			A	50			0
3	**1a**			A	80	**3a**		98
4[e]	**1a**			A	50	**3a**		90
5	**1a**			B	50	**3a**	**4a**	86 (91:9)
6	**1a**			B	80	**3d**	**4a**	97 (97:3)
7	**1a**			C	80		**4a**	99
8	**1b**	H	4-Me	A	80	**3b**		91
9	**1b**			B	80	**3b**	**4b**	99 (27:73)
10	**1b**			C	80		**4b**	99
11	**1c**	H	4-Cl	A	80	**3c**		99
12	**1c**			B	80	**3c**	**4c**	100 (55:45)
13	**1d**	H	4-OMe	A	80	**3d**		94
14	**1d**			B	80	**3d**	**4d**	99 (56:44)
15	**1e**	H	4-CO_2Et	A	80	**3e**		83
16	**1f**	H	4-CN	A	80	**3f**		99
17	**1g**	H	4-NO_2	A	80	**3g**		98
18	**1h**	H	H	A	80	**3h**		95
19	**1i**	H	3,5-OMe	A	80	**3i**		98
20	**1j**	H	2,4-Me	A	80	**3j**		100
21	**1k**	H	2-Cl, 4-Me	A	80	**3k**		99
22	**1l**	H	A	A	80	**3l**		82
23	**1m**	Me	H	A	80	**3n**		99
24	**1n**	Et	H	A	80	**3o**		98

[a] Reaction conditions: **1** (1 mmol), **2** (n 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) were reacted for 3 h. [b] Method A, **2** (0.8 mmol); Method B, **2** (1.2 mmol); Method C, **2** (4 mmol). [c] Isolated yield. [d] Without $Pd(OAc)_2$. [e] 0.025 Mmol of $Pd(OAc)_2$ and 0.1 mmol of PPh_3 were used.

could also be obtained in high yield if the reaction was heated under reflux (entry 3) or if the amount of palladium catalyst was increased (2.5 mol%) (entry 4). Depending on the ratio of **1a**:**2** used, either the monoallylated product **3a** or the diallylated product **4a** was produced selectively (entries 5–7). Allylation of anilines containing both electron-withdrawing and electron-donating groups **1b**–**n** worked well with allyl alcohol (**2**) under reflux giving the corresponding *N*-allylanilines in overall yields ranging from 82–100%. Increasing the amount of **2** also afforded *N*,*N*-diallylanilines **4** (entries 9, 10, 12, and 14).

One synthetic application of this allylation procedure involves the preparation of 3,4-dihydro-2*H*-1,4-benzoxazine derivatives starting from 2-aminophenols. The reaction of 2-aminophenol (**5a**) with 2-butene-1,4-diol (**6**) in the presence of $Pd(OAc)_2$–PPh_3 as the catalyst gave the cyclic compound 3,4-dihydro-2-vinyl-2*H*-1,4-benzoxazine (**7a**) together with **8a** in 51 and 13% yields, respectively (entry 1 in Table 2). Changing the palladium catalyst to $PdCl_2(MeCN)_2$ gave higher yields of **7a**, up to 58% (entry 4). In the presence of $Pd(acac)_2$, the products **7a** and **8a** were obtained in 36 and 29% yields, respectively (entry 5). Compound **5b** also reacted with **6** to give the products **7b** and **8b** in 24 and 50% yields, respectively (entry 6). As expected, increasing the relative amount of the 2-aminophenol favored the formation of the cyclic compound **7a** (entries 1–3).

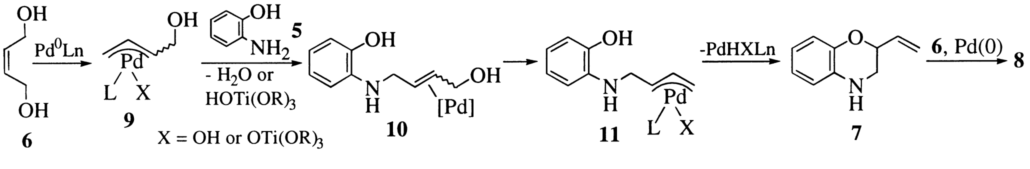
Table 2
Palladium-catalyzed reaction of **5** with 2-butene-1,4-diol (**6**)[a]



Entry	5	Palladium Catalyst	[**5**]/[**6**]	Products		Yield (%)[b] (**7**:**8**)
1	**5a**	$Pd(OAc)_2$	1/0.5	**7a**	**8a**	64 (78:22)
2	**5a**	$Pd(OAc)_2$	1/0.8	**7a**	**8a**	86 (25:75)
3	**5a**	$Pd(OAc)_2$	1/1.2	**7a**	**8a**	73 (20:80)
4	**5a**	$PdCl_2(MeCN)_2$	1/0.5	**7a**	**8a**	71 (82:18)
5	**5a**	$Pd(acac)_2$	1/0.5	**7a**	**8a**	65 (55:45)
6	**5b**	$Pd(OAc)_2$	1/0.5	**7b**	**8b**	74 (33:67)

[a] Reaction conditions: **5** (1 mmol), **6** (n mmol), Pd (0.01 mmol), PPh_3 (0.04 mmol), $Ti(OPr^i)_4$ (0.5 mmol) and MS4A (200 mg) in benzene (5 mL) were refluxed for 3 h. [b] Isolated yield.

A plausible reaction pathway for this reaction is shown in Scheme 1. Diol **6** or an allyl titanate, formed by an alcohol exchange reaction between **6** and isopropoxide in $Ti(OPr^i)_4$, reacts with Pd(0) species generated in situ[8] to afford the π-allylpalladium intermediate **9**. Intermolecular nucleophilic substitution of the amino group of **5** takes place at the less hindered terminus of the π-allyl system to give the allylic amine **10**. Intramolecular nucleophilic attack on the second π-allylpalladium intermediate **11** at the more substituted internal allylic carbon atom produces **7**. This regiospecificity is in agreement with the fact that nitrogen nucleophiles are generally more reactive than the oxygen nucleophiles towards π-allylpalladium complexes.[9] Compound **8** may be obtained by two nucleophilic substitutions via intermediate **7** on the diol **6** in the presence of palladium.



Scheme 1.

In summary, we have prepared monoallylic anilines selectively in high yields in the presence of a palladium catalyst. This method was applied to the cyclization of 2-aminophenols with 2-butene-1,4-diol. This cyclization proceeds through tandem allylic substitutions via π-allylpalladium intermediates leading to 3,4-dihydro-2-vinyl-2*H*-1,4-benzoxazines.

Acknowledgements

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