Communications

Palladium-Catalyzed Amination of Allylic Alcohols Using Anilines

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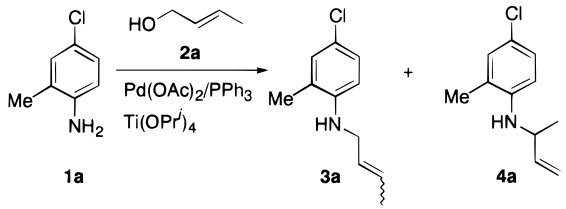
Palladium-catalyzed allylation is an established, efficient, and highly stereoselective method for C−C, C−N, and C−O bond formation, which has been widely applied to organic chemistry.[1] The processes have been shown to proceed by attack of nucleophiles on intermediate η^3-allylpalladium(II) complexes generated by oxidative addition of allylic compounds including allylic halides,[2] acetates,[3] and carbonates[4] to a Pd(0) complex. However, there have been only limited and sporadic reports dealing with the direct cleavage of the C−O bond in allylic alcohols on interaction with a transition metal complex.[5] Successful applications using allylic alcohols directly in catalytic processes are even more limited. This apparently stems from the poor capability of a nonactivated hydroxyl to serve as a leaving group.[6] Itoh has reported that palladium-catalyzed nucleophilic substitution of allylic alcohols using zinc enolates can proceed efficiently in the presence of titanium(IV) alkoxides and LiCl.[7] This result prompted us to study the reaction between anilines and allylic alcohols in order to understand the regio- and stereocontrol of the reaction; this is important for practical synthetic applications and also for gaining more insight into the mechanism. This is, to our knowledge, the first example of palladium-catalyzed allylation of anilines by the direct use of allylic alcohols in the presence of $Ti(OPr^i)_4$.

When a mixture of 4-chloro-2-methylaniline (**1a**, 1 mmol) and 2-buten-1-ol (**2a**, 1.2 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 (MS4A) (200 mg) in benzene (5 mL) under nitrogen at 50 °C for 3 h, the mixtures of regio- and stereoisomeric anilines **3a** and **4a** were formed in 22% and 29%, respectively (entry 1 in Table 1). The 87/13 *E*/*Z* ratio of **3a** was determined by GC and ^{1}H NMR spectroscopy: the CH_2 signal appeared at δ 3.71 ppm for the *E*-isomer and at δ 3.80 ppm for the *Z*-isomer. This stereochemistry was confirmed by the coupling constant of the vinylic protons for this major isomer (J = 15.2 Hz) being characteristic of *E*-stereochemistry. The reaction should be

Table 1. Reaction of 4-Chloro-2-methylaniline (1a) with 2-Buten-1-ol (2a)[a]

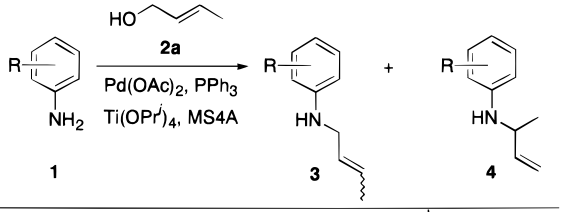


1a **3a** **4a**

entry	$Pd(OAc)_2$:PPh_3:$Ti(OPr^i)_4$ (in mmol)	solvent	yield (%)[b] (**3a**:**4a**)	*E*/*Z* ratio of **3a**[c]
1	0.01:0.04:0.25	benzene	51 (43:57)	87:13
2[d]	0.01:0.04:0.25	benzene	10 (53:47)	88:12
3	0.025:0.1:0	benzene	0	
4	0.025:0:0.25	benzene	0	
5	0.025:0.1:0.25	benzene	80 (55:45)	86:14
6[e]	0.01:0.04:0.25	benzene	94 (42:58)	87:13
7	0.01:0.04:0.25	MeCN	10 (15:85)	100:0
8	0.01:0.04:0.25	THF	12 (39:61)	100:0
9	0.01:0.04:0.25	HMPA	18 (34:66)	95:5
10	0.01:0.04:0.25	DMF	10 (26:74)	100:0
11	0.01:0.04:0.25	toluene	32 (33:67)	100:0

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), and MS4A (200 mg) in a solvent (5 mL) at 50 °C for 3 h. [b] Isolated yield. [c] The *E*/*Z* ratio of **3a** was determined by GC. [d] Without MS4A. [e] Reflux for 3 h.

Table 2. Reaction of Anilines (1b−h) with 2-Buten-1-ol (2a)[a]



1 **3** **4**

1	R	products		yield (%)[b] (**3**:**4**)	*E*/*Z* ratio of **3**[c]
1b	H	**3b**	**4b**	97 (83:17)	80:20
1c	4-Me	**3c**	**4c**	91 (83:17)	80:20
1d	4-Cl	**3d**	**4d**	97 (44:56)	84:16
1e	4-CO_2Et	**3e**	**4e**	86 (58:42)	87:13
1f	3,5-OMe	**3f**	**4f**	98 (67:33)	84:16
1g	2,4-Me	**3g**	**4g**	99 (59:41)	92:8
1h	2-Cl, 4-Me	**3h**	**4h**	83 (42:58)	89:11

[a] Reaction conditions: **1** (1 mmol), **2a** (0.8 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 refluxed for 3 h. [b] Isolated yield. [c] Determined by GC.

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Table 3. Reaction of 4-Chloro-2-methylanilines (1a) with Allyl Alcohols (2b−f)[a]

2	yields[b]
HO 2b	**3a** 45% (*E*/*Z*=84/16)[c] **4a** 53%
HO 2c	Cl, Me, N, H **5** 70%
	Cl, Me, N, H **6** 28%
HO 2d	Cl, Me, N, H **7** 94%
HO Ph 2e	Cl, Me, N, H, Ph **8** 99%
HO 2f	Cl, Me, N, H **9** 75%

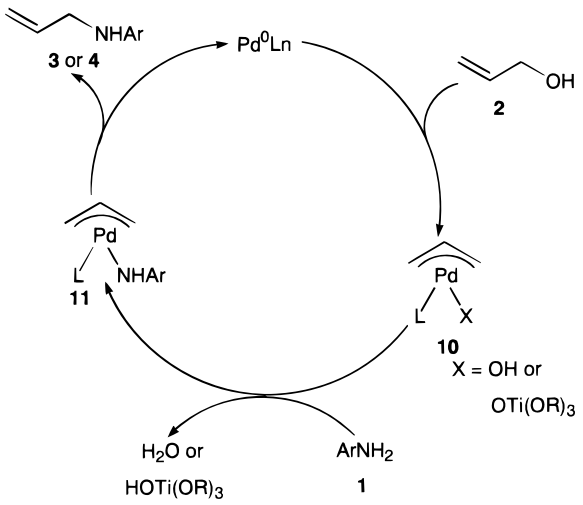
[a] Reaction conditions: **1a** (1 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.04 mmol), $Ti(OPr^i)_4$ (0.25 mmol), and MS4A (200 mg) in benzene (5 mL) were refluxed for 3 h. [b] Isolated yield. [c] Determined by GC.

accompanied by formation of water. Addition of molecular sieves (MS4A) for its removal showed a positive effect (entry 2). It was confirmed that the reaction did not occur in the absence of $Ti(OPr^i)_4$ (entry 3) or phosphine species (entry 4). Note that the products could also be afforded in good yield in the reaction under reflux (entry 6) or an increase in the amount of palladium catalyst (2.5 mol %) (entry 5). Six solvents were investigated: MeCN, THF, HMPA, DMF, and toluene, with benzene giving the best results (entries 1 and 6−10). Use of MeCN, THF, DMF, or toluene medium led to **4a** and a single stereoisomer *E*-**3a**.

The results collected in Table 2 show the amination of 2-buten-1-ol (**2a**) worked well with anilines containing both electron-withdrawing and electron-donating groups, giving generally high yields of the corresponding allylic anilines.

Results for amination of a number of allylic alcohols **2b**−**f** with 4-chloro-2-methylaniline (**1a**) using $Pd(OAc)_2$, PPh_3, $Ti(OPr^i)_4$, and MS4A are summarized in Table 3. All of the allylic alcohols examined underwent amination smoothly to give the corresponding *N*-allylanilines in overall yields ranging from 75 to 99%. Since both regioisomeric alcohols **2a** and **2b** gave identical mixtures of the anilines **3a** and **4a** in similar ratios, the reaction is considered to proceed via π-allylpalladium intermediates.

Scheme 1



A possible mechanism for the formation of *N*-allylanilines from **1** and **2** is illustrated in Scheme 1, in which the substituent on allyl alcohol is omitted. Alcohol **2** or an allyl titanate, formed by an alcohol exchange reaction between **2** and isopropoxide in $Ti(OPr^i)_4$,[7] reacts with Pd(0) species generated in situ[8] to afford a π-allylpalladium intermediate **10**. Subsequently, the reaction of **11** with aniline **1** followed by reductive elimination gives *N*-allylaniline. It is possible that **11** could be formed by ligand exchange between **10** and the $Ti(HNAr)_n(OR)_{4-n}$ species generated in the reaction medium.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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