

Palladium-Catalyzed Allylation of Acidic and Less Nucleophilic Anilines Using Allylic Alcohols Directly

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The direct activation of C–O bonds in allylic alcohols by palladium complexes has been accelerated by carrying out the reactions in the presence of titanium(IV) isopropoxide and 4 Å molecular sieves. The acidic and less nucleophilic anilines such as diphenylamine, phenothiazine, 4-cyanoaniline, and nitroanilines are efficiently allylated under palladium catalysis using allylic alcohols as allylating reagents.

Key words palladium-catalyzed; allylation; acidic anilines; C–N bond formation

A principal goal of organometallic chemistry is the catalytic synthesis of organic compounds by using the chemistry of organic ligands covalently bound to transition metals. Most organometallic chemistry has focused on complexes with covalent metal-carbon or metal-hydrogen bonds. Transition metals have been workhorse elements in many commercialized catalytic processes that include hydrogenations, hydroformylations, acetic acid production, and other C–C and C–H bond forming processes.^{1–5} Although carbon–oxygen, carbon–nitrogen, or carbon–sulfur bonds are found in the majority of important organic molecules, catalytic organometallic reaction chemistry that leads to the formation of carbon–heteroatom bonds is less common than that forming carbon–carbon and carbon–hydrogen bonds. Transition metal η^3 -allyl complexes, as well as transition metal σ -alkyl complexes, play important roles as active species and key intermediates in many reactions catalyzed by transition metal complexes.⁶ The palladium-catalyzed allylation is an established, efficient, and highly stereo- and chemoselective method for C–C, C–N, and C–O bond formation, which has been widely applied to organic chemistry.^{7–10} 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 halides,^{11–13} esters,^{14–26} carbonates,^{27–36} carbamates,^{37–39} phosphates,^{40–42} and related derivatives^{43–49} to a Pd(0) complex. Because these substrates are synthesized from the corresponding allylic alcohols, palladium-catalyzed conversion of allylic alcohols directly into allylation products are highly desirable, especially from the viewpoint of the atom economy.^{50,51} For achieving the palladium-catalyzed C–O bond cleavage of allylic alcohols, various other processes to facilitate the bond cleavage have been reported.⁵² These processes include conversion of allylic alcohols into the esters of inorganic acids (e.g., As₂O₃,⁵³ B₂O₃,⁵⁴ CO₂⁸) or employment of a Lewis acid (e.g., BEt₃,^{55–57} BF₃,⁵⁸ BPh₃,^{59,60} SnCl₂^{61–64}). 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.^{65–72} 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.^{59,60} We have recently reported our attempts and some successful applications of a process involving the C–O bond cleavage with direct use of

allylic alcohols catalyzed by palladium complexes.^{73–76} Herein, we report the application of this methodology to the palladium-catalyzed allylation of acidic and less nucleophilic anilines^{77–80} using allylic alcohols directly.

The allylation process is straightforward. We studied the reactions of acidic and less nucleophilic anilines⁸¹ with allyl alcohol (**2a**). When a mixture of diphenylamine (**1a**, 1 mmol) and allyl alcohol (**2a**, 1.2 mmol) was refluxed in the presence of catalytic amounts of Pd(OAc)₂ (0.01 mmol), PPh₃ (0.04 mmol), Ti(OPr)₄ (0.25 mmol), and molecular sieves (MS 4 Å) (200 mg) in benzene (5 ml) under nitrogen for 3 h, the product *N*-allyldiphenylamine (**3a**) was formed 68% yield (entry 1 in Table 1). Phenothiazine (**1b**) behaved the same (entry 4). 2-Nitroaniline (**1c**) gave only monoallylation product under similar experimental conditions, but its *meta* isomer **1d**, free of steric constraints, gave diallylated products **4d** (entries 7, 10). 4-Cyanoaniline (**1f**) also gave mono- and diallylated products in high yields (entry 15). Using cinnamyl alcohol (**2b**) as allylating agent worked well with acidic and less nucleophilic anilines (entries, 2, 5, 8, 11, 13, 15). The sterically more demanding 2-cyclohexenol (**2c**), was an inefficient allylation reagent for **1a** and for the more acidic anilines, although at reflux temperature (entries 3, 6, 9, 12, 14, 16). Reaction of **2c** with steric constraints amines **1a–c** gave the worst yields.

In summary, we have shown that palladium-catalyzed allylation of anilines using allylic alcohols directly is a simple and efficient route for C–N bond formation. The effect of addition of Ti(OPr)₄ to promote the palladium-catalyzed allyl-OH bond cleavage remarkably enhanced both the reaction rate and yield. The amination of allylic alcohol worked well with acidic and less nucleophilic anilines, giving generally high yields of the corresponding allylic anilines. Anilines with steric constraints gave lower chemical yields. The sterically more demanding 2-cyclohexenol (**2c**) was an inefficient allylation reagent.

Experimental

General Considerations All reactions were carried out under a nitrogen atmosphere. Solvents were dried and distilled by known methods. Column chromatography was performed on silica gel. All melting points were uncorrected. IR absorption spectra were recorded on a Perkin-Elmer System 2000 FT-IR spectrophotometer. Proton and carbon-13 NMR were measured with a Unity-400 spectrometer. Carbon multiplicities were obtained from DEPT experiments. Chemical shifts (δ) and coupling constants (Hz) were measured with respect to TMS or chloroform-*d*₁. MS and high-resolution mass spectra (HR-MS) were taken on a Hewlett-Packard 5989A or JEOL

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Table 1. Palladium-Catalyzed Allylation of Acidic Anilines **1** with Allylic Alcohols **2**^{a)}

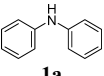

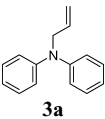

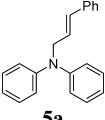

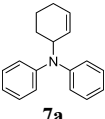
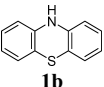
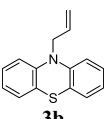
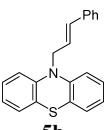
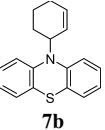

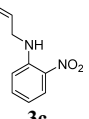
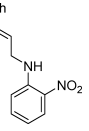
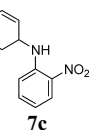

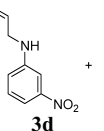
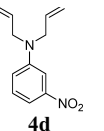
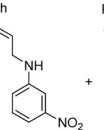
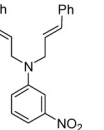
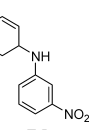
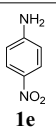
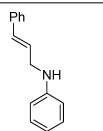
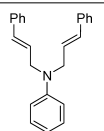
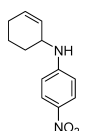
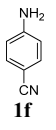
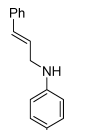
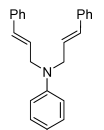
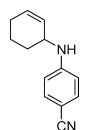
Entry	1	2	Products	Yield (%) ^{b)}
1				68
2	1a			83
3	1a			trace
4		2a		76
5	1b	2b		70
6	1b	2c		5
7		2a		84
8	1c	2b		78
9	1c	2c		5
10		2a	 + 	67+29
11	1d	2b	 + 	69+30
12	1d	2c		34

Table 1. (Continued)

Entry	1	2	Products	Yield (%) ^{b)}
13		2b	 + 	77+19
14	1e	2c		34
15		2b	 + 	73+26
16	1f	2c		27

a) Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), Pd(OAc)₂ (0.01 mmol), PPh₃ (0.04 mmol), Ti(OPr)₄ (0.25 mmol), and MS 4 Å (200 mg) in benzene (5 ml) were refluxed for 3 h. b) Isolated yield.

JMS D-100 instrument, with a direct inlet system.

General Procedure for the Palladium-Catalyzed Allylation of Anilines. Reaction with Diphenylamine (1a) A mixture of diphenylamine (**1a**) (169 mg, 1 mmol), allyl alcohol (**2a**) (70 mg, 1.2 mmol), Pd(OAc)₂ (2.3 mg, 0.01 mmol), PPh₃ (10.5 mg, 0.04 mmol), Ti(OPr)₄ (0.075 ml, 0.25 mmol), and MS 4 Å (200 mg) in benzene (5 ml) was refluxed under nitrogen for 3 h. After cooling, the reaction mixture was filtered through Celite and the solvent was distilled under reduced pressure. Column chromatography (*n*-hexane/EtOAc 5 : 1) of the residue afforded **3a** in 68% yields.

N-Allyldiphenylamine (3a)⁸²⁾ ¹H-NMR (CDCl₃) δ 4.33 (2H, ddt, *J*=1.6, 1.6, 4.0 Hz), 5.14 (1H, ddt, *J*=1.2, 1.6, 8.4 Hz), 5.25 (1H, ddt, *J*=1.2, 1.6, 13.6 Hz), 5.91 (1H, ddt, *J*=4.0, 8.4, 13.6 Hz), 6.91 (2H, t, *J*=6.0 Hz), 7.01 (4H, d, *J*=6.8 Hz), 7.23 (4H, dd, *J*=6.0, 6.8 Hz); ¹³C-NMR (CDCl₃) δ 54.7 (t), 116.3 (t), 120.7 (d), 121.2 (d), 129.2 (d), 134.3 (d), 147.8 (s); EI-MS *m/z*: 209 (M⁺), 194, 182, 167, 117, 104, 91, 77; HR-MS *m/z*: 209.1201 (Calcd for C₁₅H₁₅N: 209.1204).

N-Cinnamoyldiphenylamine (5a)⁸²⁾ ¹H-NMR (CDCl₃) δ 4.47 (2H, dd, *J*=1.6, 5.2 Hz), 6.29 (1H, dt, *J*=5.2, 16.0 Hz), 6.55 (1H, dt, *J*=1.6, 16.0 Hz), 6.90–6.94 (2H, m), 7.03–7.06 (4H, m), 7.14–7.18 (1H, m), 7.21–7.30 (8H, m); ¹³C-NMR (CDCl₃) δ 54.3 (t), 120.8 (d), 121.3 (d), 126.1 (d), 126.3 (d), 127.4 (d), 128.5 (d), 129.3 (d), 131.3 (d), 136.9 (s), 147.8 (s); EI-MS *m/z*: 285 (M⁺), 194, 193, 167, 117, 115, 91, 77; HR-MS *m/z*: 285.1517 (Calcd for C₂₁H₁₉N: 285.1517).

N-Allylphenothiazine (3b) ¹H-NMR (CDCl₃) δ 4.34 (2H, ddd, *J*=2.0, 2.4, 4.4 Hz), 5.18 (1H, ddt, *J*=2.0, 2.4, 17.6 Hz), 5.22 (1H, ddt, *J*=2.0, 2.0, 10.4 Hz), 5.88 (1H, ddt, *J*=4.4, 10.4, 17.6 Hz), 6.74 (2H, dd, *J*=1.2, 8.4 Hz), 6.79 (2H, ddd, *J*=1.2, 7.6, 8.4 Hz), 6.97–7.01 (4H, m); ¹³C-NMR (CDCl₃) δ 50.9 (t), 115.1 (d), 117.3 (t), 122.2 (d), 122.8 (s), 126.6 (d), 127.0 (d), 132.9 (d), 144.2 (s); EI-MS *m/z*: 239 (M⁺), 199, 198, 171, 167, 154, 127, 69; HR-MS *m/z*: 239.0768 (Calcd for C₁₅H₁₃NS: 239.0769).

N-Cinnamylphenothiazine (5b)⁸²⁾ ¹H-NMR (CDCl₃) δ 4.57 (2H, dd, *J*=1.6, 4.4 Hz), 6.31 (1H, dt, *J*=4.4, 16.4 Hz), 6.53 (1H, dt, *J*=1.6, 16.4 Hz), 6.82–6.86 (4H, m), 7.00–7.06 (4H, m), 7.17–7.32 (5H, m); ¹³C-NMR (CDCl₃) δ 50.9 (t), 115.3 (d), 122.4 (d), 123.0 (s), 124.8 (d), 126.3 (d), 126.8 (d), 127.3 (d), 127.6 (d), 128.6 (d), 132.0 (d), 136.4 (s), 144.4 (s); EI-MS *m/z*: 315 (M⁺), 198, 171, 166, 154, 140, 127, 115, 91, 77; HR-MS *m/z*: 315.1080 (Calcd for C₂₁H₁₇NS: 315.1082).

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1e, 20.9, 4-cyanoaniline, **1f**, 25.26 as compared with aniline (30.6).
 pK_a values in H₂O of amines according to the ref. 80: diphenylamine,
1a, 0.9, 2-nitroaniline, **1c**, -0.28, 3-nitroaniline, **1d**, 2.46, 4-nitroani-
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