

Palladium-Catalyzed Benzylolation of Unprotected Anthranilic Acids with Benzyl Alcohols in Water

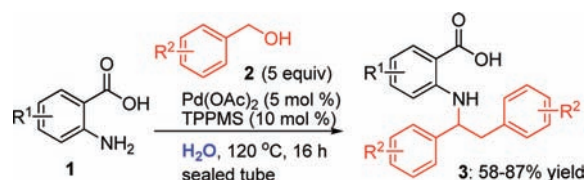
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ABSTRACT



Palladium-catalyzed benzylolation of unprotected anthranilic acids with benzyl alcohols in the presence of Pd(OAc)₂ (5 mol %) and sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 10 mol %) in water at 120 °C for 16 h gave only dibenzylated anthranilic acids in good yields. Water may play important roles for the smooth generation of the (η^3 -benzyl)palladium species by activation of the hydroxyl group of the benzyl alcohol.

Palladium-catalyzed benzylolation via a (η^3 -benzyl)palladium intermediate is one of the most powerful and useful methodologies for the formation of carbon–carbon and carbon–nitrogen bonds. Because of the poor reactivity of benzylic alcohols toward Pd⁰, the reaction typically employs activated benzylic alcohols such as benzylic halides,¹

esters,² carbonates,³ and phosphates.⁴ Therefore, the development of a direct catalytic substitution of benzylic alcohols, which produces the desired products along with water as the sole coproduct, is highly desired. To the best of our knowledge, the palladium-catalyzed *N*-benzylolation with benzyl alcohols has not been described before.⁵ On the other hand, palladium-catalyzed *N*-allylation with allylic alcohols proceeds smoothly in water, which plays an important role in the activation of the allylic alcohol to form the π -allyl complex.⁶ We applied this finding to the *N*-allylation of water-soluble free amino acids⁷ and anthranilic acids⁸ to give the mono-*N*-allylated products

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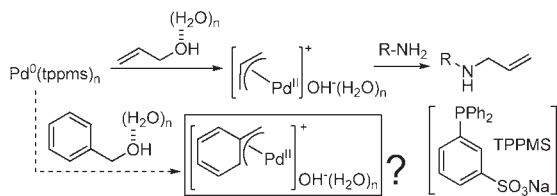
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Scheme 1. Hydration of the Hydroxyl Group



selectively in good yields. Thus, we expected an analogous reaction for the palladium-catalyzed benzylation of benzyl alcohols because of their structural similarity to allylic alcohols. Water may activate the benzyl alcohol via hydration of the hydroxyl group for the generation of the (η^3 -benzyl)palladium (Scheme 1). We are interested in the development of unprotected syntheses and selective reactions toward various reactive functional groups in aqueous media.^{7–9} Thus, we began our studies of the benzylation with benzyl alcohol **2a** in water by choosing water-soluble unprotected anthranilic acid **1a** as the substrate. First, we heated a mixture of anthranilic acid **1a** and benzyl alcohol **2a** (5 equiv) in the presence of Pd(OAc)₂ (5 mol %) and sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 10 mol %) in water at 120 °C for 16 h in a sealed tube. To our surprise, dibenzylated product **3a** was obtained in good yield despite the possibility of forming the mono-*N*-benzylated product **4a** (Table 1, entry 1). In general, benzylation of imines,¹⁰ hydroamination of alkynes/reduction,¹¹ and reductive amination of ketones¹² are used for formation of *N*-(1,2-diphenylethyl)amines, which are structural constituents of pharmacologically interesting compounds.¹³ After 1 h, the reaction afforded **3a** in 64% yield along with **4a** in 24% yield (entry 2). When **1a** was consumed completely at 80 °C in 16 h, the reaction afforded a mixture of **3a** and **4a** (entry 3).

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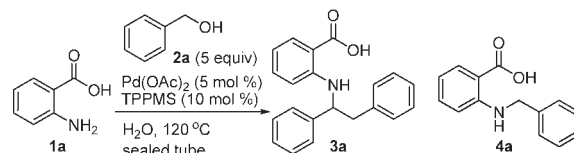
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Thus, *N*-benzylation of anthranilic acid **1a** may proceed to give the mono-*N*-benzylated product **4a** first, which is then *C*-benzylated at the benzylic position to give dibenzylated **3a**. To the best of our knowledge, the palladium-catalyzed benzylation of sp³ C–H bonds adjacent to a nitrogen atom has not been described before.¹⁴ Herein we describe palladium-catalyzed benzylation of anthranilic acids via (η^3 -benzyl)palladium from benzyl alcohol in water and syntheses of 2-(1,2-diphenylethylamino)benzoic acids using benzylation of the sp³-carbon attached to the nitrogen atom.

Table 1. Pd-Catalyzed Benzylation of Anthranilic Acid **1a**^a



entry	temp (°C)	time (h)	yield (%) ^b	
			3a	4a
1	120	16	81	0
2	120	1	64	24
3	80	16	41	39

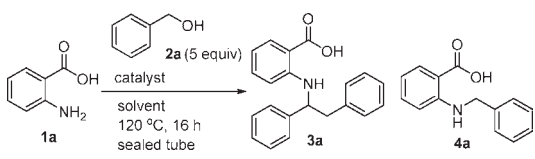
^a Pd(OAc)₂ (5 mol %), TPPMS (10 mol %), benzyl alcohol **2a** (5 equiv), and H₂O (0.25 M) in sealed tube. ^b Yield of isolated product.

We next examined the effects of catalysts and solvent on the benzylation of **1a**. Since the reaction did not proceed in the absence of the palladium catalyst and phosphine ligand (Table 2, entry 1) or in the presence of only Pd(OAc)₂ (entry 2), a S_N2-type reaction mechanism was excluded in the formation of the benzylated product. With regard to the palladium catalyst, the use of zero- or divalent palladium, Pd₂(dba)₃ or PdCl₂, gave the product in good yields (entry 3, 86%; entry 4, 79%). The use of a water-soluble ligand, 4-(diphenylphosphino)benzoic acid **L1**, resulted in a good yield of **3a** (entry 5, 79%). In contrast, using 4-(dimethylamino)phenyldiphenylphosphine **L2**, dibenzylated **3a** was obtained in 27% yield along with mono-*N*-benzylated **4a** in 38% yield (entry 6). Since the reaction did not occur using Pd(PPh₃)₄ instead of a water-soluble ligand (entry 7) or when using DMSO (entry 8) as a

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solvent, water must play an important role in the benzylation with benzyl alcohol. With regard to the additive, NaOH suppressed the benzylation (entry 9). In contrast, the reaction proceeded in AcOH(aq) in good yield (entry 10). Basset and co-workers reported that the π -allyl palladium intermediate is unstable under strong basic conditions.¹⁵ In contrast, Manabe¹⁶ and Yang^{6b} reported that carboxylic acids enhanced the formation of the π -allyl complex in aqueous media. Since our results are consistent with a previous report on the palladium-catalyzed allylation with allylic alcohols, (η^3 -benzyl)palladium may be an intermediate in analogy to the allylic substitution.

Table 2. Effects of Catalysts and Solvents on Benzylation of **1a**^a



entry	catalyst	solvent	yield [%] ^b	
			3a	4a
1	none	H ₂ O	no reaction	
2	Pd(OAc) ₂	H ₂ O	no reaction	
3	Pd ₂ (dba) ₃ ^c /TPPMS	H ₂ O	86	0
4	PdCl ₂ /TPPMS	H ₂ O	79	0
5	Pd(OAc) ₂ / L1 ^d	H ₂ O	79	0
6	Pd(OAc) ₂ / L2 ^e	H ₂ O	27	38
7	Pd(PPh ₃) ₄	H ₂ O	no reaction	
8	Pd(OAc) ₂ /TPPMS	DMSO	no reaction	
9	Pd(OAc) ₂ /TPPMS	1 N NaOH(aq) ^f	no reaction	
10	Pd(OAc) ₂ /TPPMS	H ₂ O/AcOH ^f	87	0

^aPd catalyst (5 mol %), ligand (10 mol %), benzyl alcohol **2a** (5 equiv), and solvent (0.25 M), 120 °C, 16 h in sealed tube. ^bYield of isolated product. ^c2.5 mol %. ^d**L1**: 4-(diphenylphosphino)benzoic acid. ^e**L2**: 4-(dimethylamino)phenyldiphenylphosphine. ^f4 equiv was used.

Results for the benzylation of various anthranilic acids, 3-aminobenzoic acids, and 4-aminobenzoic acid using Pd(OAc)₂ and TPPMS in water are summarized in Figure 1. All of the anthranilic acids smoothly underwent benzylation with benzyl alcohol **2a** to give only the corresponding dibenzylated anthranilic acids **3b–i** in overall yields ranging from 70% to 87%. The use of methyl-substituted benzyl alcohols also resulted in good yields of **3j–q**. To our surprise, 2-naphthalenemethanol, which is not very soluble in water, gave desired product **3r** in 66% yield. Legros and co-workers reported that palladium-catalyzed nucleophilic substitution of naphthylmethyl esters and the loss of resonance energy for the formation of the (η^3 -naphthalenemethyl)palladium intermediate is

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less important than for the (η^3 -benzyl)palladium intermediate.¹⁷

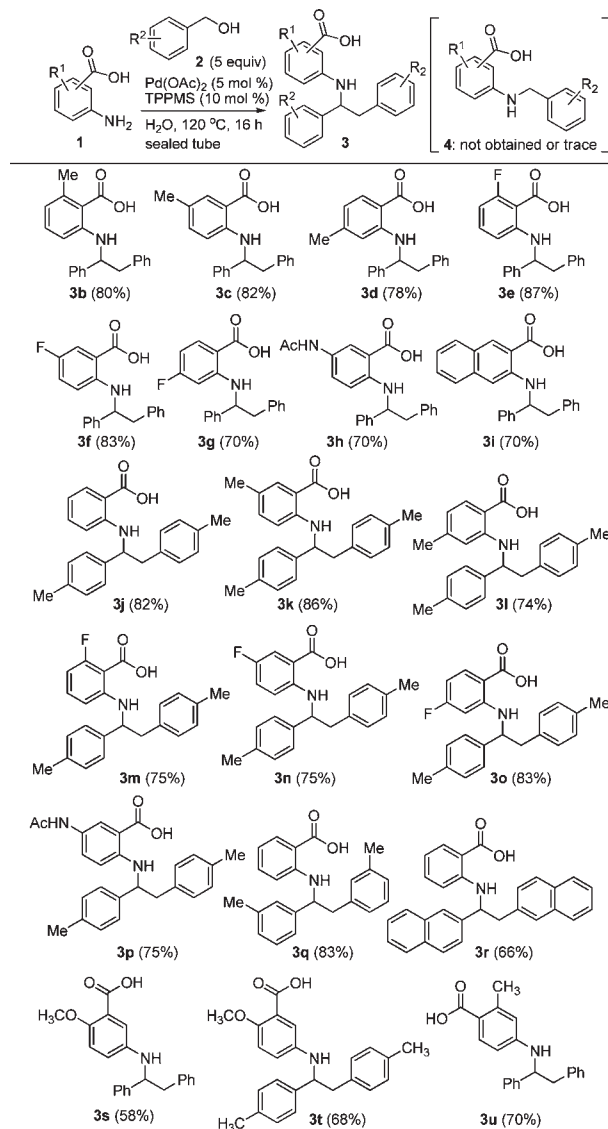


Figure 1. Scope of benzylation of anthranilic acids and amino-benzoic acids. Reaction conditions: **1** (1 mmol), Pd(OAc)₂ (5 mol %), TPPMS (10 mol %), benzyl alcohols **2** (5 equiv), and H₂O (4 mL) at 120 °C to 16 h in a sealed tube. Yield of isolated product.

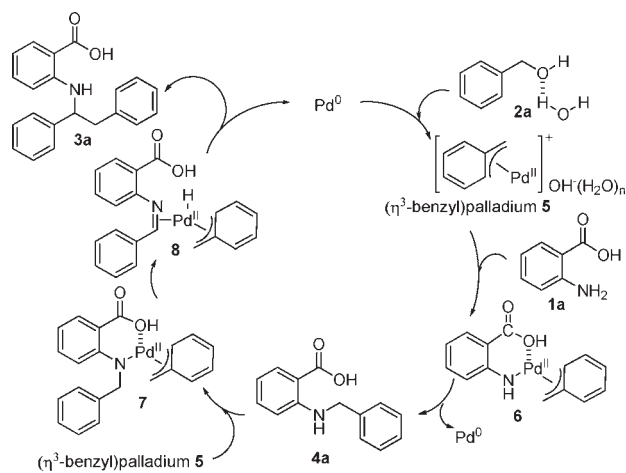
Thus, benzylation with 2-naphthalenemethanol can proceed smoothly in our catalytic system. In addition to anthranilic acids, 3- and 4-aminobenzoic acids afforded the corresponding dibenzylated **3s–u** selectively in good yields.

The mechanism of the formation of dibenzylated anthranilic acid **3a** from anthranilic acid **1a** and benzyl alcohol **2a** in water has not been investigated in detail at this stage. However, on the basis of our results

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and literature reports, the following mechanism can be suggested (Scheme 2). First, oxidative addition of benzyl alcohol **2a** to a Pd⁰ species affords the (η^3 -benzyl)-palladium complex **5**. Water may play an important role for the smooth generation of the (η^3 -benzyl)palladium species **5** by hydration of the hydroxyl group, since the reaction did not occur without water. Next, ligand exchange of the (η^3 -benzyl)palladium system with the amino group of **1a** takes place to generate intermediate **6**, followed by reductive elimination to give the mono-*N*-benzylated product **4a** exclusively. Ligand exchange of the (η^3 -benzyl)palladium system with the amino group of **4a** takes place to generate intermediate **7**, followed by β -hydride elimination. Wang and co-workers reported that *N*-phenyl benzylamines could be oxidized to the corresponding imines using a PdCl₂/PPh₃ catalyst.¹⁸ Benzylation to imine **8** occurs to give the dibenzylated **3a** and regenerates Pd⁰ through reductive elimination. Yamamoto and co-workers reported palladium-catalyzed allylation of aldimines with allylstannanes. The π -allylpalladium intermediate reacted with imines to give the corresponding homoallylic amines.¹⁹ Fields and co-workers reported palladium-catalyzed benzylation of benzyl diphenylglycinate imines to the corresponding homobenzylic imines.^{2b}

Scheme 2. Possible Mechanism



To confirm that *N*-benzylanthranilic acid **4a** is the intermediate in our catalytic system, we tested benzylation of **4a** instead of anthranilic acid **1a**. As expected, *C*-benzylation of **4a** proceeded smoothly to give dibenzylated

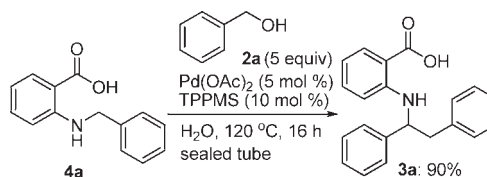
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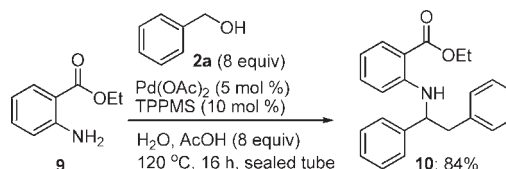
3a in 90% yield (Scheme 3). In contrast, the reaction did not proceed without Pd(OAc)₂/TPPMS or with only Pd(OAc)₂. No reaction occurred in DMSO instead of water as a solvent. These results indicated that water plays an important role for the *C*-benzylation of **4a** with benzyl alcohol in our catalytic system.

Finally, this method was applied to the benzylation of aliphatic substrates such as anthranilic acid ethyl ester **9**. The reaction proceeded smoothly to give dibenzylated **10** in 84% yield (Scheme 4). Thus, this reaction is applicable to the benzylation of various aliphatic substrates.

Scheme 3. Pd-Catalyzed Benzylation of **4a**



Scheme 4. Pd-Catalyzed Benzylation of Ethyl Ester **9**.



In conclusion, we have developed a new methodology for achieving the palladium-catalyzed benzylation of unprotected anthranilic acids **1** with benzyl alcohols **2** in water. Palladium-catalyzed reactions with both allylic and benzylic alcohols proceeded smoothly in aqueous media. Water played an important role in the activation of the allylic and benzylic alcohols to form the corresponding palladium complexes. In addition, this methodology performs the unique benzylation of sp³ C–H bonds adjacent to a nitrogen atom. We are currently investigating the scope of various amines on the benzylation and are developing new reactions using (η^3 -benzyl)palladium from benzyl alcohol in aqueous media.

Supporting Information Available. Experimental procedures and characterization data; copies of ¹H and ¹³C NMR spectra of the new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.