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Pd-catalyzed C-H activation in water: synthesis of bis(indolyl)methanes from indoles and benzyl alcohols[†]

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A method for the synthesis of bis(indolyl)methanes via palladiumcatalyzed domino reactions of indoles with benzyl alcohols was developed. This protocol involves C3-benzylation of indoles and benzylic C-H functionalization in water.

The development of methods for the direct conversion of C-H bonds into C-C and C-N bonds has received significant attention in organic chemistry.¹ Palladium complexes are particularly attractive catalysts for such transformations.

We are interested in unique strategies for the activation of C-H bonds by palladium catalysts and benzyl alcohol in water. In our previous work, palladium-catalyzed N-benzylation of anthranilic acid with benzyl alcohol and benzylic C-H benzylation occurred simultaneously to give dibenzylated product A.^{2a} By replacing anthranilic acid with o-aminobenzamide as the starting material, the N-benzylated product undergoes benzylic C-H amidation to give 2-phenylquinazolin-4(3H)-one \mathbf{B}^{2b} (Scheme 1: previous work). Herein, we report a synthesis of bis(indolyl)methanes 3 via the palladium-catalyzed domino reaction of indoles 1 with benzyl alcohols 2 in water (Scheme 1: present work). This domino process includes C-H activation/benzylation at the C3-position of the indole and benzylic C-H functionalization. Recently, the synthesis of C3-benzylated indoles from indoles 1 and benzyl alcohols 2 has been reported.3 For example, Grigg and co-workers reported iridium(III)-catalyzed cascade reactions using borrowing hydrogen methodology.^{3f} Additionally, Kobayashi and Shirakawa reported dehydrative nucleophilic substitution using dodecylbenzenesulfonic acid (DBSA) as a surfactant-type Brønsted acid catalyst in water.3e However, to the best of our knowledge, the palladiumcatalyzed C-H activation/benzylation of indoles with benzyl alcohol has not been described before. Benzylic C-H functionalization of 3-benzylindole is also extremely rare.⁴ For example,

Gong and co-workers reported the C-H-activation-based oxidative coupling reaction of 3-arylmethylindoles with dibenzyl malonate.4a

Bis(indolyl)methanes 3 are key units in a wide range of relevant pharmacophores with a broad spectrum of activities.5 While condensation of aldehydes with indoles in the presence of acid is the most practical method of synthesizing bis(indolyl)methanes 3^{6} , there are no examples of the synthesis of 3 from benzyl alcohols 2.

First, we heated a mixture of 5-methoxyindole 1a and benzyl alcohol 2a (3 equiv.) in the presence of Pd(OAc)₂ (5 mol%) and sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, mol%) in water at 60 °C for 16 h under air in a sealed tube. To our surprise, indolyl product 3a was obtained in 81% yield in spite of the possibility of forming the C3-benzylated 4a (Table 1, entry 1). Importantly, the reaction was completely C3-selective, with no N-benzylated product formed. The reaction did not proceed in the absence of both the palladium catalyst and the phosphine ligand (entry 2), and the use of only Pd(OAc)₂ resulted in a low yield (entry 3, 38%). With regard to the palladium catalyst, the use of $PdCl_2$ or Pd₂(dba)₃ also gave product **3a** in good yields (entry 4, 82%; entry 5, 90%). Since the reaction did not occur when using $PdCl_2(PPh_3)_2$



Scheme 1 Our concept of Pd-catalyzed benzylation/C-H functionalization.

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^{*a*} Reaction conditions: **1a** (0.5 mmol), Pd catalyst (5 mol%), ligand (10 mol%), benzyl alcohol **2a** (3 equiv.), solvent (2 mL), 60 $^{\circ}$ C, 16 h under air in a sealed tube. ^{*b*} Yield of isolated product.

instead of a water-soluble ligand (entry 6) or when using DMF, EtOH or THF (entry 7) as the solvent, water must play an important role in our catalytic system. In addition, the reaction in DMF-H₂O (1 : 1) did not proceed (entry 8). Thus, the hydrophobic effect in water was also observed in our catalytic system.

Results for the reaction of 5-methoxyindole **1a** with a number of benzyl alcohols **2** or several indoles **1** with benzyl alcohol **2a** using Pd(OAc)₂ and TPPMS are summarized in Table 2. Benzyl alcohols with electron-donating methyl, ethyl and methoxy groups resulted in moderate to good yields (**3b**, 60%; **3c**, 97%; **3d**, 65%; **3e**, 94%). The use of 4-fluorobenzyl alcohol also resulted in a good yield (**3f**, 73%). A sterically demanding *ortho*-methyl-substituted benzyl alcohol was also tolerated in the reaction (**3g**, 87%). 2-Thiophenemethanol resulted in a moderate yield (**3h**, 56%). Indole resulted in a moderate yield (**3i**, 58%). Indoles with 5-methyl, 5-fluoro and 5-cyano groups resulted in moderate to good yields (**3j**, 74%; **3k**, 56%; **3l**, 90%). Methyl ester substituents were also tolerated in the reaction (**3m**, 84%). Sterically demanding 2-methylindole resulted in an excellent yield (**3n**, 98%). 1-Methylindole also afforded the desired **3o** in good yield (73%).

We monitored the reaction using ¹H NMR experiments. First, treatment of 5-methoxyindole **1a** with Pd(OAc)₂, TPPMS and benzyl alcohol **2a** in D₂O at 60 °C for 30 min showed 97% deuterium incorporation at the C3-position of indole (Scheme 2). The reaction did not proceed in the absence of Pd(OAc)₂, TPPMS and benzyl alcohol **2a**. The use of zero valent palladium, Pd₂(dba)₃, instead of Pd(OAc)₂ for 3 h resulted in 34% deuterium incorporation. Hence, palladium-catalyzed activation of the C-H bond at the C3-position of indole **1a** is possible in our catalytic system. C-H activation is usually conducted in organic solvents and extrusion of moisture is essential. To the best of our knowledge, palladium-catalyzed C-H functionalization of indoles in water has not been described before.⁷ After the reaction, toluene should be formed from the (η³-benzyl)palladium complex and indoles **1** in our catalytic system. We were delighted to observe

Table 2 Scope of indoles 1 and alcohols 2^a



^{*a*} Reaction conditions: **1** (0.5 mmol), Pd(OAc)₂ (5 mol%), TPPMS (10 mol%), benzyl alcohols **2** (3 equiv.), H_2O (2 mL), 60 °C, 16 h in sealed tube. Yield of isolated product. ^{*b*} 48 h.

that indeed toluene **5** was obtained in the reaction mixture (Scheme 3, A). In addition, the desired **3a**, 3-benzylated indole **4a** and benzaldehyde **6** were detected (**3a** : **4a** : **5** : **6** : **2a** = 1 : 0.1 : 0.7 : 0.5 : 3). To confirm that 3-benzylindole **4b** was the intermediate in our catalytic system, we tested the reaction of **4b** (Scheme 3, B). To our surprise, the reaction afforded desired **3b** (78% from **1b**), recovery of 3-benzylindole **4b** (96%) and indole **1b**



Without $Pd(OAc)_2$, TPPMS and **2a**: **1a**' was not obtained. The use of $Pd_2(dba_3)$ instead of $Pd(OAc)_2$ for 3 h: 34% D incorporation.

Scheme 2 C–H bond acitvation at the C3-position of indole 1a.⁹



Scheme 3 ¹H NMR experiments to monitor the reaction.⁹

(trace). This result suggested that 3-benzylindole **4b** might not be the intermediate in our catalytic system.

These results suggest the following mechanism of the formation of bis(indolyl)methanes **3** from indole **1** and benzyl alcohol **2** in water (Scheme 4). First, oxidative addition of benzyl alcohol **2** to a Pd⁰ species affords (η^3 -benzyl)palladium complex **7**. Water may play an important role in the smooth generation of the (η^3 -benzyl)palladium species **7** by hydration of the hydroxyl group and stabilization of hydroxide ion by hydration, followed by formation of an active Pd^{II} cation species, since the reaction does not occur without water.⁸

Next, activation of the C–H bond at the C3-position of indole **1a** with (η^3 -benzyl)palladium **7** occurs to generate intermediate **8**, which does not form 3-benzylated **4** through reductive elimination (see Scheme 3, B). Instead, intermediate **8** reacts with benzyl alcohol **2a** to give C3-benzylated **9**. Rawal and Zhu reported the Pd-catalyzed C3-benzylation of 3-substituted indoles using benzyl carbonates, and the reaction between indole and excess benzyl-carbonate afforded 3,3-dibenzylindole in high yield.^{3g} Thus, the

(H₂O),

ЮH

(H₂O),

Pd^{II}

(n3-benzyl)palladium 7

OH⁻(H₂O)_n

Scheme 4 Possible mechanism.

same intermediate **9** might possibly form in our catalytic system. Next, β -hydride elimination of C3-benzylated **9** occurs to generate intermediate **10**, followed by addition of indole **1** to give the desired product **3** along with toluene **5**, with regeneration of Pd⁰ through reductive elimination.

Notably, the (η^3 -benzyl)palladium system plays an important role for benzyl transfer and C–H activation. In previous work, after *N*-benzylation occurred, dibenzylated **A** was obtained by C–H activation/C-benzylation (Scheme 1). In contrast, quinazolinone **B** was formed by C–H activation/amidation. To our surprise, the role of (η^3 -benzyl)palladium system was quite different in the present work, and activated intermediate **8** might form C3-benzylated **9**, followed by intermediate **10**. We are attracted to the versatile (η^3 benzyl)palladium system.

In summary, we have developed a method for achieving a palladium-catalyzed domino reaction for the synthesis of bis(indolyl)methanes **3**. The domino reactions achieved C–H activation of the C3-position of indole followed by benzylic C–H functionalization. Our method provides a unique strategy for the activation of C–H bonds by palladium catalyst and benzyl alcohol in water. We are developing new C–H activation/functionalization reactions using (η^3 -benzyl)palladium from benzyl alcohols in aqueous media, which will be reported in due course.

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Communication

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- 9 Yield was determined by ¹H NMR analysis (see ESI† for experimental details).