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Article

Mechanistic Studies for Synthesis of Bis(indolyl)methanes: Pd-Catalyzed C–H Activation of Indole–Carboxylic Acids with Benzyl Alcohols in Water

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Abstract: A method for synthesis without protecting groups of bis(indolyl)methanes by the (η^3-benzyl)palladium system generated from a palladium catalyst and benzyl alcohol in water is developed. This domino protocol involves C3–H bond activation/benzylation of indole–carboxylic acids and benzylic C–H functionalization. Mechanistic studies indicate that the (η^3-benzyl)palladium(II) complex, which is formed via oxidative addition of benzyl alcohol **2** to a Pd(0) species, activates the C–H bond at the C3-position of indole **1**. Notably, water plays an important role in our catalytic system for sp^3 C–O bond activation and stabilization of OH^- by hydration for the smooth generation of the activated Pd(II) cation species, as well as for nucleophilic attack of indoles to hydrated benzyl alcohols.

Keywords: palladium; C–H activation; water; indole; benzyl alcohol

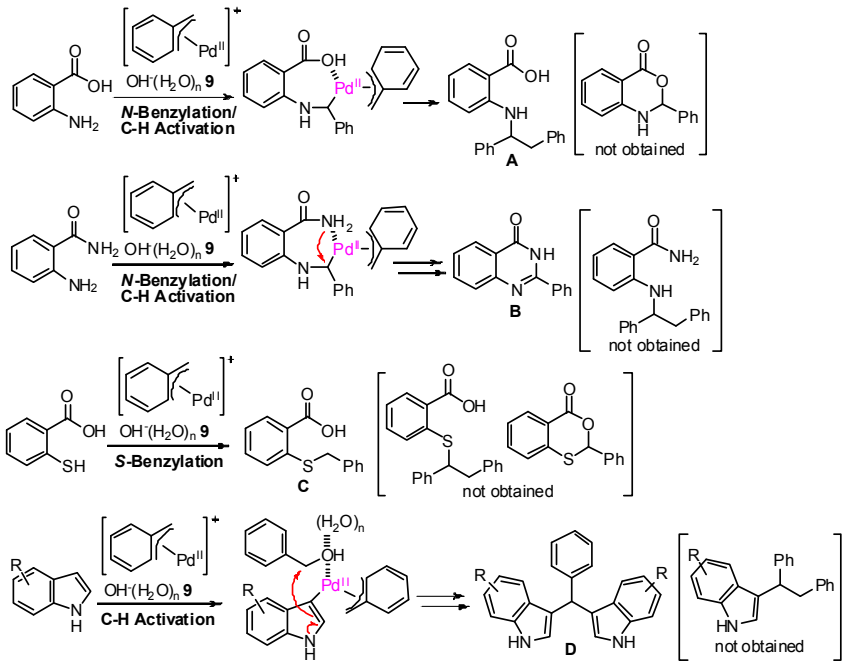
1. Introduction

The (η^3-benzyl)palladium catalysts are gaining increasing interest. The powerfulness of these complexes is still far from other well-established Tsuji–Trost reactions, merely due to a more recent development [1–9]. Palladium-catalyzed benzylations with benzylic alcohols via the (η^3-benzyl)palladium intermediate are especially challenging, because the reactivity of benzylic alcohols towards Pd(0) is poor compared to benzylic halides, esters, carbonates and phosphates.

Therefore, the development of a direct catalytic substitution of benzylic alcohols, which produces the desired products along with water as the sole co-product, is highly desired in organic chemistry. Recently, direct application of benzyl alcohols as electrophiles in various reactions was achieved via Brønsted/Lewis acid [10–12], transition metal [13,14] or water–promoted [15–17] sp^3 C–O bond activation.

We have developed a unique strategy for benzylation and C–H activation [18–24] by the (η^3-benzyl)palladium system from a palladium catalyst and benzyl alcohol in water [25–28]. Water activates the benzyl alcohol via hydration of the hydroxyl group for generation of the (η^3-benzyl)palladium species, which can then undergo innovative direct transformation reactions. We became interested in further expanding the substrate scope of the (η^3-benzyl)palladium system to water-soluble unprotected indole carboxylic acids **1**, since we have been studying the development of synthesis without protecting groups and selective reactions towards various reactive functional groups [29–32]. In general, synthesis without protecting groups represents a distinct challenge and has been fraught with a number of difficulties such as chemoselectivity [33]. One of the most effective ways for achieving synthesis without protecting groups is the development of selective reactions towards various reactive functional groups. Although the possibility of generating by the different coupling reactions the undesired products shown in parentheses exists, in our catalytic system, only the desired products were obtained selectively in excellent to good yields (Scheme 1). Oxygen nucleophilicity of the carboxyl group may be weak due to hydration under aqueous conditions.

Scheme 1. Our previous work.



In our previous paper [25], we reported a method for the synthesis of bis(indolyl)methanes via palladium-catalyzed domino reactions of indoles with benzyl alcohols in water and suggested a plausible mechanism for the formation of bis(indolyl)methanes. In the present study, we explore the synthesis without protecting groups of bis(indolyl)methanes **3** from indole-carboxylic acids **1** and propose a more detailed mechanism based on various control experiments. Herein, we report the

development of synthesis without protecting groups of bis(indolyl)methanes **3** via palladium-catalyzed domino reactions of indole–carboxylic acids **1** with benzyl alcohols **2** in water. Based on observations made in this investigation, we can now provide strong support for the Pd-catalyzed C3–H activation and benzylation pathway. This paper describes mechanistic investigations aimed at providing a rational explanation for the formation of bis(indolyl)methanes **3**.

2. Results and Discussion

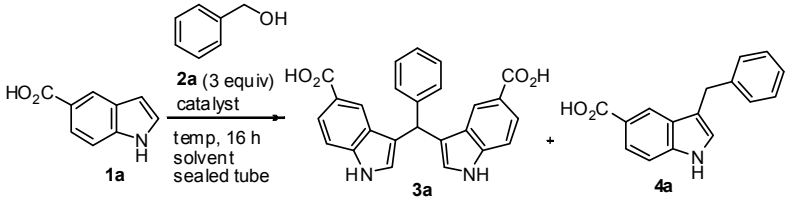
First, we heated a mixture of indole-5-carboxylic acid **1a** and benzyl alcohol **2a** (3 equiv) in the presence of $Pd(OAc)_2$ (5 mol%) and sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 10 mol%) in water at 120 °C for 16 h in a sealed tube. Bis(indolyl) product **3a** was obtained in 84% yield along with C3-benzylated **4a** in 15% yield (Table 1, entry 1). Importantly, the reaction was completely C3-selective, with no C2- or *N*-benzylated product formed. When **1a** was consumed completely at 60 °C in 16 h, the reaction afforded only desired **3a** in excellent yield (entry 2, 91%). In contrast, the reaction at room temperature did not occur (entry 3). The reaction also did not proceed in the absence of the palladium catalyst and phosphine ligand (entry 4). With regard to the palladium catalyst, the use of $PdCl_2$ or $Pd_2(dba)_3$ also gave the product **3a** in excellent yields (entry 5, 91%; entry 6, 93%). Since the reaction did not occur when using $PdCl_2(PPh_3)_2$ instead of a water-soluble ligand (entry 7) or when using DMSO, EtOH or THF (entry 8) as a solvent, water must play an important role in our catalytic system. AcOH also resulted in excellent yield (entry 9, 93%). To our surprise, the reaction proceeded when 1 M NaOH aq. was used as a solvent at 60 °C (entry 10). In our previous work, benzylation of anthranilic acid did not occur at 120 °C in 1 M NaOH aq [28]. Thus, the (η^3-benzyl)palladium intermediate might be unstable under high temperature and strong basic conditions [34].

Results for the reaction of indole-5-carboxylic acid **1a** with a number of benzyl alcohols **2** or several indole carboxylic acids **1** with benzyl alcohol **2a** using $Pd(OAc)_2$ and TPPMS are summarized in Figure 1. The benzyl alcohols with electron-donating methyl, ethyl and methoxy groups resulted in moderate to good yields (**3b**, 83%; **3c**, 92%; **3d**, 54%; **3e**, 54%). The reaction of 4-fluorobenzyl alcohol also proceeded (**3f**, 52%). The benzyl alcohol with a chloro group produced desired **3g** in good yield with the carbon–halogen moiety left intact, which could be employed for further manipulation (**3g**, 67%). A heteroaryl methyl alcohol, thienyl methanol, also resulted in a moderate yield (**3h**, 52%). To our surprise, aliphatic benzyl alcohol, 2-naphthalenemethanol, which is not very soluble in water, gave desired product **3i** in 96% yield. The indoles with 4-, 6- and 7-carboxyl groups resulted in moderate to good yields (**3j**, 52%; **3k**, 60%; **3l**, 76%). Interestingly, the indole with 2-carboxyl groups was also tolerated in the reaction (**3m**, 45%), despite the weak nucleophilicity at the C3 position of indole due to the electron-withdrawing 2-carboxyl acid group. Therefore, synthesis without protecting groups is possible to prepare **3m** with our catalytic system.

We monitored the C3–H activation reaction by ^{1}H NMR spectroscopy (Table 2). In general, a C–H bond activation mechanism is used to describe the substitution of indoles by electrophilic metals such as Pd(II) [35–38]. Thus, indole **1a** reacted with (η^3-benzyl)palladium(II) to form intermediate **A**, followed by formation of intermediate **B**, which reacted with D_2O to give C3-D indole **1a'** (Scheme 2, path A). Indeed, treatment of indole-5-carboxylic acid **1a** with $Pd_2(dba)_3$, TPPMS and benzyl alcohol

2a in D_2O at 60 °C for 3 h showed 65% deuterium incorporation at the C3-position of indole (entry 1). In contrast, in the absence of benzyl alcohol **2a**, or when using toluene instead of **2a**, only a trace amount of deuterium was incorporated (entry 2; 12%, entry 3; 14%). Use of 4-methylbenzyl alcohol **2b** or 4-chlorobenzyl alcohol **2c** instead of **2a** resulted in good yields (entry 4; 80%, entry 5; 70%). These results suggested that the palladium(II) complex which was formed via oxidative addition of benzyl alcohol **2** to a Pd(0) species activated the C–H bond at the C3-position of **1a**. While the indole with 2-carboxylic acid ethyl ester **1b** resulted in no reaction (entry 6; 3%), the indole with 2-carboxylic acid **1c** showed 81% deuterium incorporation (entry 7). This observation suggested that the 2-carboxylic acid moiety plays an important role as a directing group in C3–H palladation to afford the desired product **3m** (Figure 2). In addition, 1,2-migration of intermediate **A** did not occur to give C2-palladated **C** (Scheme 2, path B).

Table 1. Effect of catalysts and solvents [a].



Entry	Catalyst	Solvent	Temp (°C)	product (%) [b] 3a	4a
1	$Pd(OAc)_2$/TPPMS	H_2O	120	84	15
2	$Pd(OAc)_2$/TPPMS	H_2O	60	91 (92) [c]	trace
3	$Pd(OAc)_2$/TPPMS	H_2O	rt	trace	0
4	none	H_2O	60	0	0
5	$PdCl_2$/TPPMS	H_2O	60	91	trace
6	$Pd_2(dba)_3$ [d]/TPPMS	H_2O	60	93	trace
7	$PdCl_2(PPh_3)_2$	H_2O	60	trace	trace
8	$Pd(OAc)_2$/TPPMS	DMSO, EtOH or THF	60	0	0
9	$Pd(OAc)_2$/TPPMS	AcOH	60	93	trace
10	$Pd(OAc)_2$/TPPMS	1M NaOHaq. [e]	60	63	trace

[a] Reaction conditions: **1a** (0.5–1 mmol), Pd catalyst (5 mol%), ligand (10 mol%), benzyl alcohol **2a** (3 equiv), solvent (1–2 mL), rt-120 °C, 16 h in a sealed tube. [b] Yield of isolated product. [c]The yield was determined by ^{1}H NMR analysis of the crude product using *p*-nitroanisole as an internal standard. [d] 2.5 mol%. [e] 4 equiv were used.

Figure 1. Scope of alcohols **2** and indole carboxylic acids **1** [a]. [a] Reaction conditions: **1a** (0.5–1 mmol), $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), benzyl alcohols **2** (3 equiv), H_2O (2–4 mL), 60 °C, 16 h in a sealed tube. Yield of isolated product. [b] benzyl alcohols **2** (5 equiv), 80 °C.

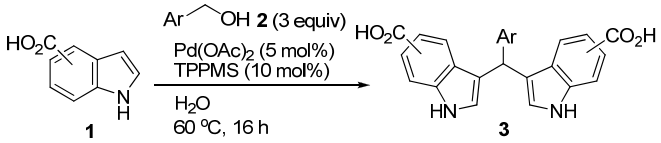
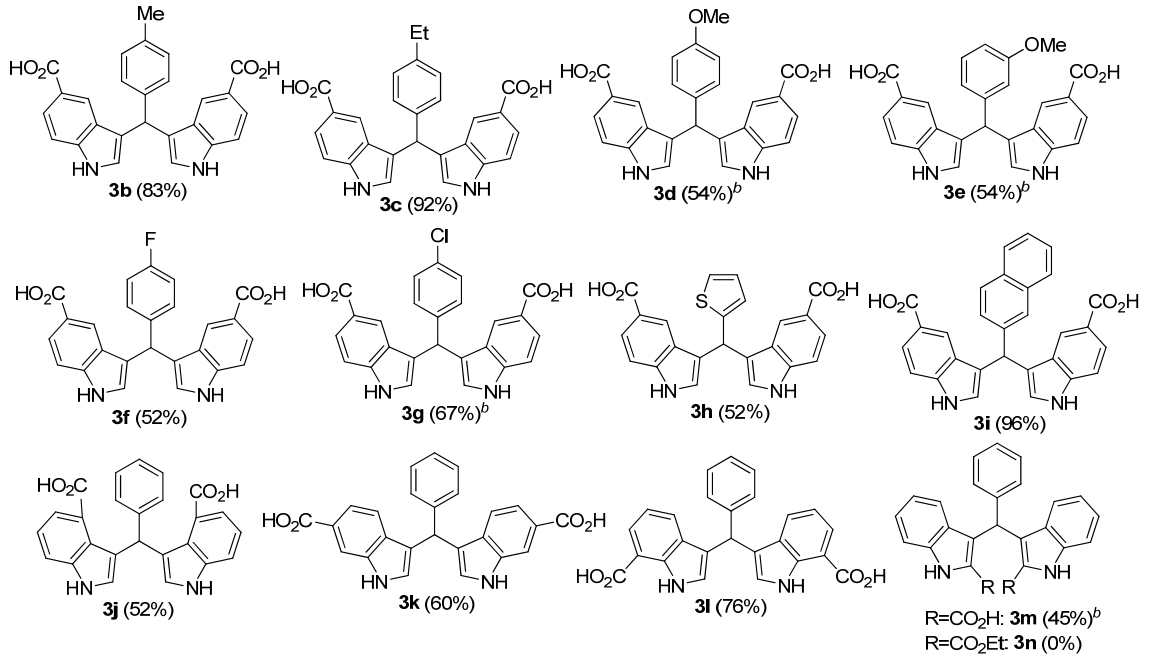


Figure 1. *Cont.*



Scheme 2. Possible mechanism of C–H bond activation.

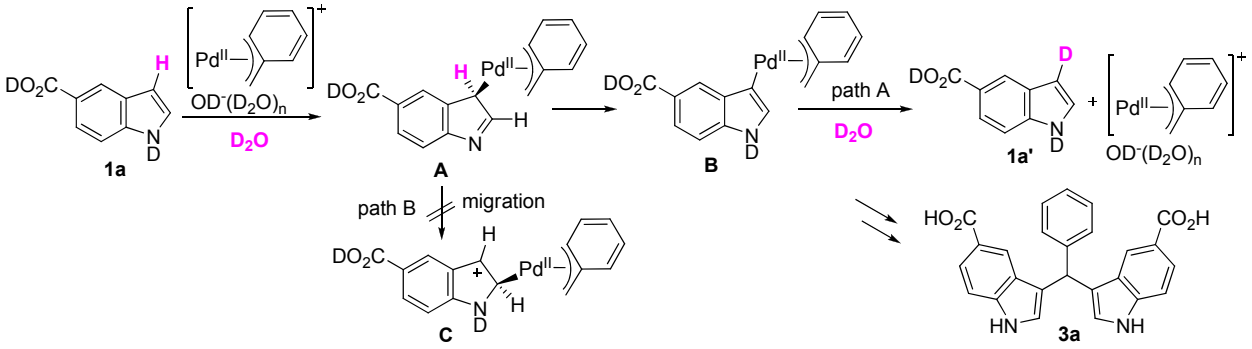
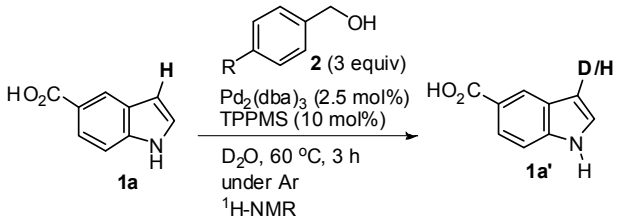


Table 2. C–H bond activation at the C3-position of indole-5-carboxylic acid **1a** [a].



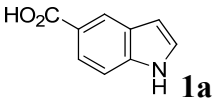
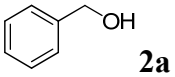
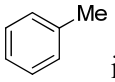
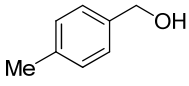
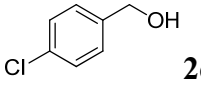
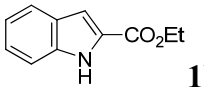
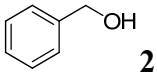
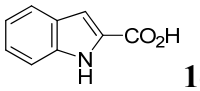
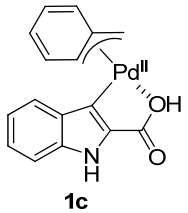
Entry	Indoles 1	Benzylic alcohols 2	D incorporation (%) [b]
1	 **1a**	 **2a**	65
2	**1a**	none	12

Table 2. *Cont.*

3	**1a**	 instead of **2a**	14
4	**1a**	 **2b**	80
5	**1a**	 **2c**	70
6	 **1b**	 **2a**	3
7	 **1c**	**2a**	81

[a] Reaction conditions: **1** (0.25 mmol), $Pd_2(dba)_3$ (2.5 mol%), TPPMS (10 mol%), benzyl alcohols **2** (3 equiv), D_2O (0.75 mL), 60 °C, 3 h under Ar in a sealed tube. [b] D incorporation was calculated by NMR integration.

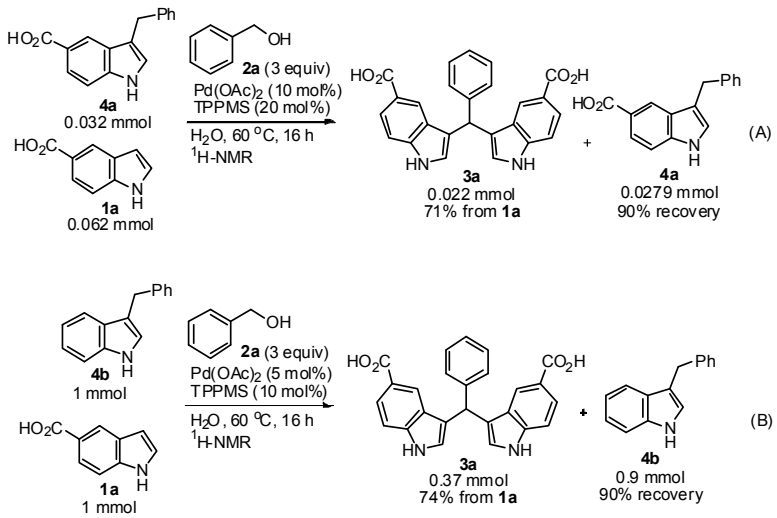
Figure 2. Role of carboxylic acid as a directing group.



1c

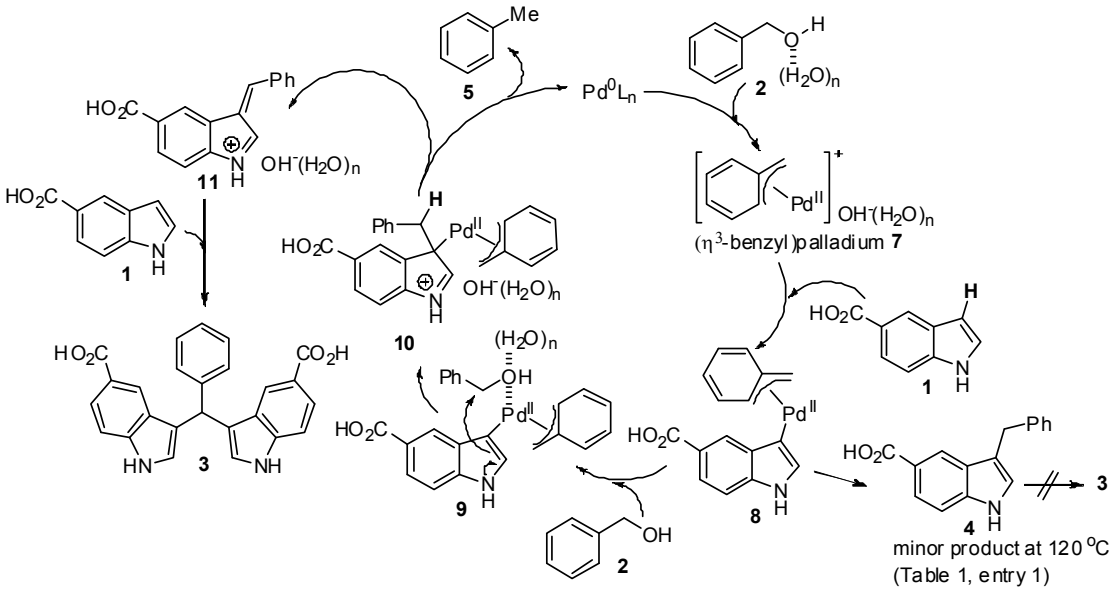
To confirm that 3-benzylindole **4a** was not the intermediate in our catalytic system, we tested the reaction of **4a** (Scheme 3, A). The reaction afforded desired **3a** (71% from **1a**) and recovery of 3-benzylated **4a** (90%). Use of 3-benzylindole **4b** instead of **4a** also resulted in recovery of 3-benzylated **4b** (90%) (Scheme 3, B). These results suggested that 3-benzylated **4a** is not the intermediate in our catalytic system.

Scheme 3. Pd-catalyzed benzylation of indole **1a** and 3-benzylindole **4**.



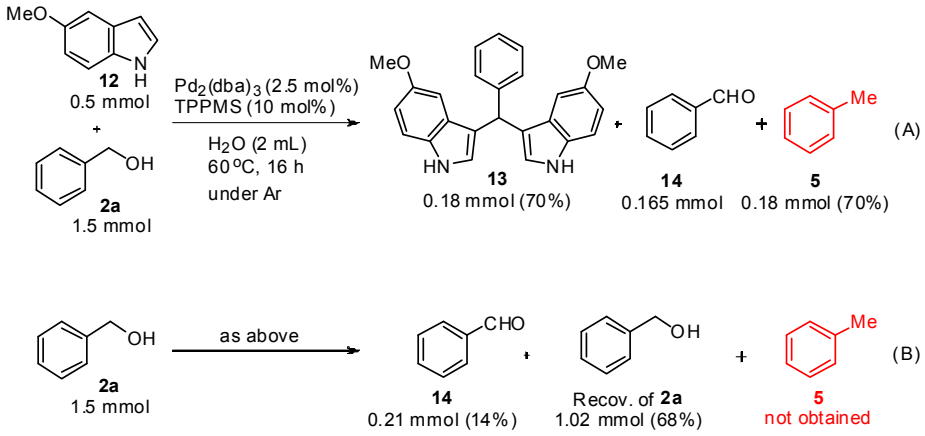
These results and our previous report [25–28] suggest the following mechanism for the formation of bis(indolyl)methanes **3** from indole carboxylic acid **1** and benzyl alcohol **2** in water (Scheme 4). Notably, activation of the C–H bond at the C3-position of indole carboxylic acid **1** with (η^3-benzyl)palladium **7** occurred to generate intermediate **8**, which did not form 3-benzylated **4** through reductive elimination (see Scheme 3). Instead, intermediate **8** reacted with benzyl alcohol **2** to give C3-benzylated **10**.

Scheme 4. Proposed mechanism.



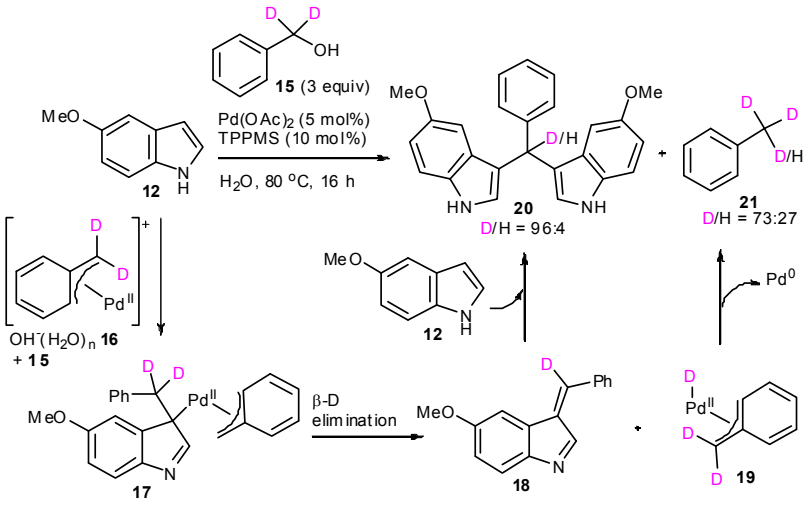
Furthermore, toluene **5** should be formed from the (η^3-benzyl)palladium complex through reductive elimination in our catalytic system (see Scheme 4). We were delighted to observe that indeed toluene **5** was obtained in the reaction mixture (Sceme 5, A). In contrast, the reaction of benzyl alcohol **2a** in the absence of indole **12** gave benzaldehyde **14** (14%) and recovery of SM **2a** (68%) with no toluene **5** detected (Scheme 5, B). This observation suggested that benzaldehyde **14** should not be the intermediate in our catalytic system.

Scheme 5. ^{1}H NMR experiments to monitor the reaction.



Next, we utilized ^{1}H NMR experiments to monitor the reaction using benzyl-α,α-d_2 alcohol **15**. The reaction afforded desired deuterated **20** (D/H = 96:4) and deuterated toluene **21** (D/H = 73:27) (Scheme 6). This observation clearly explained that β-D elimination of intermediate **17** occurred to generate intermediate **18**, followed by addition of indole **12** to give desired deuterated **20** along with deuterated toluene **21** with regeneration of Pd(0) through reductive elimination.β

Scheme 6. Pd-catalyzed reaction with benzyl-α,α-d_2 alcohol **15**.

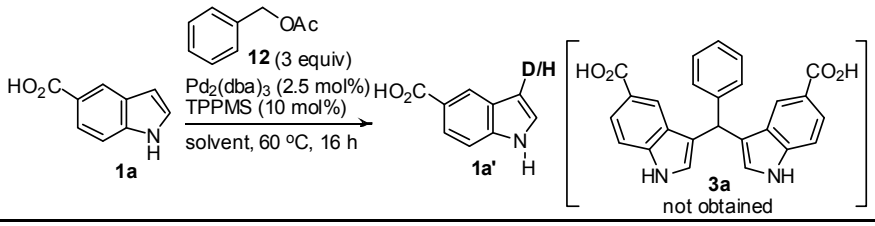


Finally, we investigated the reaction using benzyl acetate **22** instead of benzyl alcohol **2** because oxidative addition of the benzylic ester to a Pd(0) species could occur to form (η^3-benzyl)palladium **7** [39,40]. As expected, 65% deuterium incorporation was observed using benzyl acetate **22** in D_2O (Table 3, entry 1). To our surprise, the reaction did not afford desired product **3a**. These results suggested that the C3-palladated indole could not react with benzyl acetate **22** (Figure 3, intermediate **23**). It is known that the reactivity of benzyl acetate **22** with nucleophiles is high compared with benzyl alcohols **2**. Next, the reactions using benzyl acetate **22** and benzyl alcohol **2a** in organic solvents such as 1,4-dioxane or CD_3OD instead of water were examined, which also did not afford desired product **3a** (entry 2 and 3). Interestingly, 89% deuterium incorporation was observed when CD_3OD was used. These results suggested that C3-palladated indole could not react with benzyl alcohol **2a** after C–H activation of indole **1** occurred in CD_3OD, and organic solvents could not activate the benzyl alcohol **2a** (Figure 3, intermediate **24**). Therefore, we have demonstrated an important role of water for water-promoted sp^3 C–O bond activation of benzyl alcohols **2** in our catalytic system (Figure 3, intermediate **9**) [15–17].

This domino process includes C–H activation/benzylation at the C3-position of the indole-carboxylic acid and benzylic C–H functionalization. C3-Benzylation of unprotected indole carboxylic acids is extremely rare. Carter and co-workers reported the only reaction of indole-5-carboxylic acid with 4-methoxybenzylbromide using EtMgBr to afford 3-benzylated indole-5-carboxylic acid [41]. Synthesis of bis(indolyl)methanes having carboxylic acids from benzyl alcohol and indole is also extremely rare. Itoh and co-workers reported the only one-pot synthesis from indole-3-butyric acid with benzyl alcohols using catalytic iodine and oxygen under visible light

irradiation [42]. Indole carboxylic acids and their analogs are key units in a wide range of relevant pharmacophores with a broad spectrum of activities [41–46].

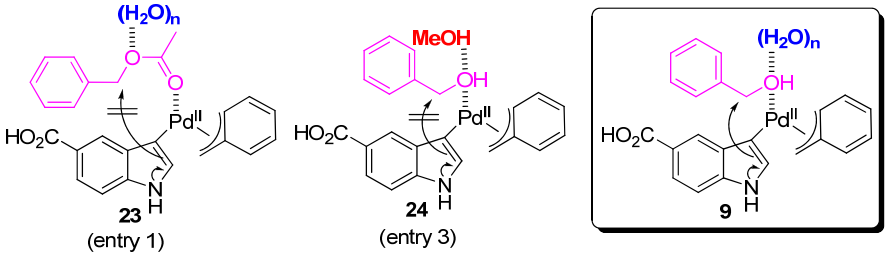
Table 3. Use of benzyl acetate **12** [a].



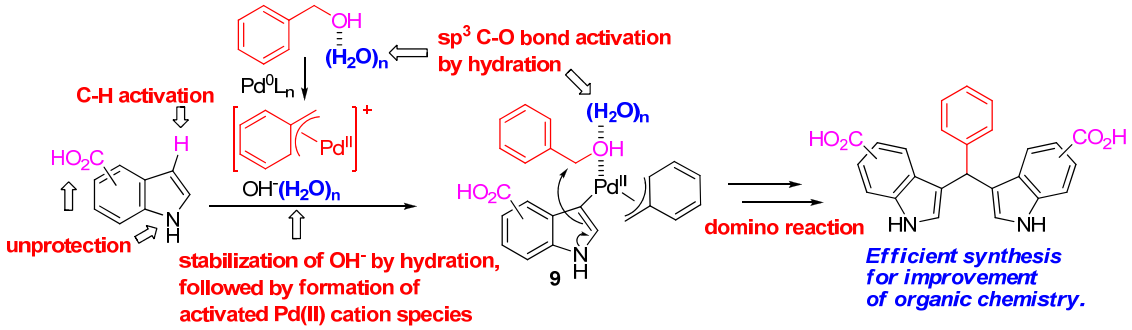
Entry	Solvent	Additive	D incorporation (%) [b]
1	D_2O	none	65
2	1,4-dioxane	benzyl alcohol **2a** (3 equiv)	-
3	CD_3OD	benzyl alcohol **2a** (3 equiv)	89

[a] Reaction conditions: **1a** (0.5 mmol), $Pd_2(dba)_3$ (2.5 mol%), TPPMS (10 mol%), benzyl acetate **12** (3 equiv), solvent (1.5 mL), 60 °C, 16 h in a sealed tube. [b] D incorporation was calculated by NMR integration.

Figure 3. Role of water for water-promoted sp^3 C–O bond activation of benzyl alcohols **2**.



Scheme 7. Development of unprotected syntheses, new activated catalysts, and new reaction fields.



In general, almost all of the compounds that have been synthesized based on protection/deprotection steps and known organic transformations tend to be inefficient in organic solvents. To enable efficient synthesis for improvement of organic chemistry, it is essential to develop *synthesis without protecting groups*, *newly activated catalysts* that work for activating unreactive bonds such as C–H bonds, and *new reaction fields*. In our catalytic system, water plays an important

role in activation of unreactive molecules and stabilization of hydroxide ion by hydration, followed by formation of activated Pd(II) cation species [47]. Nucleophilic attack of indoles to hydrated benzyl alcohols also could occur (Scheme 7). In organic solvents, elimination of naked hydroxide ion is unfavorable. Thus, our catalytic system should have a broad impact on Pd-catalyzed reactions.

3. Experimental Section

General procedure: A mixture of indole carboxylic acid **1** (0.5–1 mmol), palladium(II) acetate (5 mol%), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 10 mol%) and benzyl alcohol **2** (3–5 equiv) in H_2O (2–4 mL) was heated at 60–80 °C for 16 h in a sealed tube. After cooling, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (100 mL × 3). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc) to give desired product **3**.

3,3'-(Phenylmethylene)bis(1*H*-indole-5-carboxylic acid) 3a (Table 1, entry 2) Following the general procedure, **3a** was obtained as a red solid. 93 mg (91%); mp 212–214 °C; IR (KBr) (cm^{-1}) 3424, 1680; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.98 (s, 1H), 6.87 (s, 2H), 7.20 (t, *J* = 6.4 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.69 (dd, *J* = 8.4 Hz, 2H), 8.01 (s, 2H), 11.2 (s, 2H), 12.3 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.3, 119.3, 120.8, 121.8, 122.4, 125.3, 126.1, 128.2, 139.1, 144.3, 168.3; MS (EI): *m*/*z* (%) 410 (M^+, 100); Anal. Calcd for $C_{25}H_{18}N_2O_4$ 0.6H_2O: C, 71.28; H, 4.59; N, 6.65. Found: C, 71.22; H, 4.59; N, 6.37.

3,3'-(*p*-Tolylmethylene)bis(1*H*-indole-5-carboxylic acid) 3b Following the general procedure, **3b** was obtained as a red solid. 88 mg (83%); mp 222–224 °C; IR (KBr) (cm^{-1}) 3411, 1682; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H), 5.93 (s, 1H), 6.85 (d, *J* = 1.6 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.69 (dd, *J* = 8.8, 1.6 Hz, 2H), 8.00 (d, *J* = 0.8 Hz, 2H), 11.2 (s, 2H), 12.3 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.6, 111.3, 119.5, 120.8, 121.9, 122.3, 125.2, 126.1, 128.1, 128.8, 134.9, 139.2, 141.3, 168.3; MS(EI): *m*/*z* (%) 424 (M^+, 37.2), 161 (100); Anal. Calcd for $C_{26}H_{20}N_2O_4$ 0.6H_2O: C, 71.75; H, 4.91; N, 6.44. Found: C, 71.80; H, 4.80; N, 6.35.

3,3'-((4-Ethylphenyl)methylene)bis(1*H*-indole-5-carboxylic acid) 3c Following the general procedure, **3c** was obtained as a red solid. 101 mg (92%); mp 206–208 °C; IR (KBr) (cm^{-1}) 3414, 1679; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, *J* = 7.6 Hz, 3H), 2.56 (q, *J* = 7.6 Hz, 2H), 5.94 (s, 1H), 6.87 (d, *J* = 2.0 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.68 (dd, *J* = 8.4, 1.2 Hz, 2H), 8.01 (d, *J* = 0.8 Hz, 2H), 11.2 (s, 2H), 12.3 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.4, 27.7, 111.2, 119.5, 120.8, 121.8, 122.3, 125.2, 126.1, 127.6, 128.1, 139.1, 141.2, 141.5, 168.3; MS(EI): *m*/*z* (%) 438 (M^+, 13.6), 161 (100); Anal. Calcd for $C_{27}H_{22}N_2O_4$ 0.6H_2O: C, 72.18; H, 5.20; N, 6.24. Found: C, 72.25; H, 4.95; N, 6.18.

3,3'-((4-Methoxyphenyl)methylene)bis(1*H*-indole-5-carboxylic acid) 3d Following the general procedure, **3d** was obtained as a red solid. 59 mg (54%); mp 241–243 °C; IR (KBr) (cm^{-1}) 3400, 1681; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.72 (s, 3H), 5.92 (s, 1H), 6.84 (d, *J* = 2.0 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.69 (dd, *J* = 8.4, 1.6 Hz, 2H), 8.01 (s, 2H), 11.2 (s, 2H), 12.3 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.3, 54.9, 111.2, 113.6, 119.7, 120.8, 121.9, 122.3, 125.2, 126.1, 129.1, 136.2, 139.2, 157.5, 168.3; MS(EI): *m*/*z* (%) 440 (M^+, 12.5), 161

(100); Anal. Calcd for $C_{26}H_{20}N_2O_5$ $0.7H_2O$: C, 68.93; H, 4.76; N, 6.18. Found: C, 68.92; H, 4.62; N, 6.05.

3,3'-((3-Methoxyphenyl)methylene)bis(1*H*-indole-5-carboxylic acid) 3e Following the general procedure, **3e** was obtained as a pale brown solid. 60 mg (54%); mp 258–260 °C; IR (KBr) (cm^{-1}) 3425, 3291, 1697; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.68 (s, 3H), 5.96 (s, 1H), 6.78 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.85–6.95 (m, 4H), 7.22 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 8.02 (s, 2H), 11.2 (s, 2H), 12.3 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.9, 111.0, 111.3, 114.5, 119.2, 120.7, 120.9, 121.9, 122.4, 125.3, 126.1, 129.2, 139.1, 146.0, 159.2, 168.4; MS (EI): *m*/*z* (%) 440 (M^+, 17.0), 161 (100); Anal. Calcd for $C_{26}H_{20}N_2O_5$ $0.5H_2O$: C, 69.48; H, 4.71; N, 6.23. Found: C, 69.50; H, 4.57; N, 6.20.

3,3'-((4-Fluorophenyl)methylene)bis(1*H*-indole-5-carboxylic acid) 3f Following the general procedure, **3f** was obtained as a red solid. 56 mg (52%); mp 210–212 °C; IR (KBr) (cm^{-1}) 3428, 1680; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.02 (s, 1H), 6.86 (d, *J* = 2.0 Hz, 2H), 7.12 (dd, *J* = 8.8, 8.8 Hz, 2H), 7.38 (dd, *J* = 8.8, 5.6 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.69 (dd, *J* = 8.4, 1.6 Hz, 2H), 8.00 (s, 2H), 11.2 (s, 2H), 12.3 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.3, 111.3, 114.9 (*J* = 22 Hz), 119.3, 120.9, 121.8, 122.4, 125.3, 126.0, 130.0 (*J* = 7 Hz), 139.2, 140.4 (*J* = 3 Hz), 160.6 (*J* = 242 Hz), 168.3; MS (EI): *m*/*z* (%) 428 (M^+, 48.7), 252 (100); Anal. Calcd for $C_{25}H_{17}FN_2O_4$ $0.8H_2O$: C, 67.81; H, 4.23; N, 6.33. Found: C, 67.96; H, 4.12; N, 6.41.

3,3'-((4-Chlorophenyl)methylene)bis(1*H*-indole-5-carboxylic acid) 3g Following the general procedure, **3g** was obtained as a pale brown solid. 75 mg (67%); mp 211–213 °C; IR (KBr) (cm^{-1}) 3435, 1679; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.03 (s, 1H), 6.87 (d, *J* = 2.0 Hz, 2H), 7.36 (s, 4H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.69 (dd, *J* = 8.4, 1.2 Hz, 2H), 8.00 (s, 2H), 11.2 (brs, 2H), 12.4 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.4, 111.3, 118.9, 120.9, 121.7, 122.4, 125.4, 126.0, 128.2, 130.1, 130.6, 139.1, 143.4, 168.3; MS(EI): *m*/*z* (%) 446 (M^++2, 17.3), 444 (M^+, 45.2), 252 (100); Anal. Calcd for $C_{25}H_{17}ClN_2O_4$ $0.3H_2O$: C, 66.69; H, 3.94; N, 6.22. Found: C, 66.56; H, 3.97; N, 6.20.

3,3'-(Thiophen-2-ylmethylene)bis(1*H*-indole-5-carboxylic acid) 3h Following the general procedure, **3h** was obtained as a brown solid. 54 mg (52%); mp 228–230 °C; IR (KBr) (cm^{-1}) 3392, 1682; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.29 (s, 1H), 6.90–7.00 (m, 2H), 7.09 (s, 2H), 7.34 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 8.09 (s, 2H), 11.3 (brs, 2H), 12.4 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.5, 111.3, 119.3, 120.9, 121.9, 122.4, 124.1, 124.9, 125.0, 125.8, 126.6, 139.1, 148.8, 168.3; MS(EI): *m*/*z* (%) 416 (M^+, 18.7), 161 (100); Anal. Calcd for $C_{23}H_{16}N_2O_4S$ $1.0H_2O$: C, 63.58; H, 4.18; N, 6.45. Found: C, 63.86; H, 4.08; N, 6.18.

3,3'-(Naphthalen-2-ylmethylene)bis(1*H*-indole-5-carboxylic acid) 3i Following the general procedure, **3i** was obtained as a pale brown solid. 110 mg (96%); mp 222–224 °C; IR (KBr) (cm^{-1}) 3419, 1676; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.17 (s, 1H), 6.91 (s, 2H), 7.40–7.48 (m, 4H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.76–7.88 (m, 4H), 8.05 (s, 2H), 11.2 (brs, 2H), 12.3 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.3, 119.2, 120.9, 121.8, 122.4, 125.5, 125.9, 126.0, 126.1, 127.4, 127.5, 127.6, 127.7, 131.8, 133.1, 139.2, 142.0, 168.3; MS (EI): *m*/*z* (%) 460 (M^+, 98.1), 161 (100); Anal. Calcd for $C_{29}H_{20}N_2O_4$ $1.0H_2O$: C, 72.79; H, 4.63; N, 5.85. Found: C, 72.75; H, 4.49; N, 5.75.

3,3'-(Phenylmethylene)bis(1*H*-indole-4-carboxylic acid) 3j Following the general procedure, **3j** was obtained as a red solid. 53 mg (52%); mp 266–268 °C; IR (KBr) (cm^{-1}) 3413, 3063, 1682; ^{1}H

NMR (400 MHz, DMSO-d_6): δ 6.24 (s, 2H), 6.86 (s, 1H), 7.00 (d, *J* = 4.0 Hz, 2H), 7.05–7.15 (m, 4H), 7.18 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 11.0 (d, *J* = 4.0 Hz, 2H), 12.0 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 41.4, 115.0, 119.6, 120.3, 121.0, 123.4, 125.1, 126.2, 126.9, 127.5, 129.2, 138.1, 146.7, 168.9; MS(ESI): *m*/*z* (%) 410 (M^+); Anal. Calcd for $C_{25}H_{18}N_2O_4$ 0.3H_2O: C, 72.21; H, 4.51; N, 6.74. Found: C, 72.29; H, 4.44; N, 6.62.

3,3'-(Phenylmethylene)bis(1*H*-indole-6-carboxylic acid) 3k Following the general procedure, **3k** was obtained as a pale brown solid. 62 mg (60%); mp 280–283 °C; IR (KBr) (cm^{-1}) 3376, 3011, 1672; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.91 (s, 1H), 7.07 (d, *J* = 2.0 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.26–7.40 (m, 7H), 7.49 (dd, *J* = 8.4, 1.2 Hz, 2H), 8.02 (s, 2H), 11.2 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 113.7, 118.4, 118.6, 119.3, 123.2, 126.0, 127.3, 128.2, 129.7, 135.9, 144.4, 168.4; MS (EI): *m*/*z* (%) 410 (M^+, 56.5), 161 (100); Anal. Calcd for $C_{25}H_{18}N_2O_4$ 0.4H_2O: C, 71.90; H, 4.54; N, 6.71. Found: C, 71.81; H, 4.50; N, 6.47.

3,3'-(Phenylmethylene)bis(1*H*-indole-7-carboxylic acid) 3l Following the general procedure, **3l** was obtained as a pink solid. 78 mg (76%); mp 198–200 °C; IR (KBr) (cm^{-1}) 3453, 3035, 1668; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.94 (s, 1H), 6.79 (s, 2H), 6.99 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.30 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.72 (d, *J* = 7.6 Hz, 2H), 10.9 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 113.5, 117.9, 118.3, 123.9, 124.5, 125.3, 126.1, 128.1, 128.2, 128.3, 135.3, 144.3, 168.0; MS (EI): *m*/*z* (%) 410 (M^+, 100); Anal. Calcd for $C_{25}H_{18}N_2O_4$ 0.7H_2O: C, 70.98; H, 4.62; N, 6.62. Found: C, 70.86; H, 4.55; N, 6.51.

3,3'-(Phenylmethylene)bis(1*H*-indole-2-carboxylic acid) 3m Following the general procedure, **3m** was obtained as a purple solid. 46 mg (45%); mp 231–234 °C; IR (KBr) (cm^{-1}) 3390, 3063, 1677; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.50 (d, *J* = 8.0 Hz, 2H), 6.61 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.05–7.10 (m, 4H), 7.20–7.25 (m, 3H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.46 (s, 1H), 11.6 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 112.6, 119.0, 121.8, 123.4, 123.6, 125.2, 125.8, 127.2, 127.9, 128.7, 136.0, 144.7, 162.9; MS (EI): *m*/*z* (%) 410 (M^+, 15.5), 252 (100); Anal. Calcd for $C_{25}H_{18}N_2O_4$•1.0H_2O: C, 70.08; H, 4.71; N, 6.54. Found: C, 69.85; H, 4.59; N, 6.24.

3-Benzyl-1*H*-indole-5-carboxylic acid 4a (Table 1, entry 1) Following the general procedure, **4a** was obtained as an off-white solid. 38 mg (15%); mp 184–186 °C; IR (KBr) (cm^{-1}) 3442, 2966, 2640, 1673; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.08 (s, 2H), 7.10–7.20 (m, 1H), 7.20–7.35 (m, 5H),7.39 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 8.09 (s, 1H), 11.2 (brs, 2H), 12.3 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.7, 111.1, 115.2, 120.8, 121.2, 122.3, 124.8, 125.7, 126.5, 128.2, 128.3, 138.9, 141.4, 168.3; MS (EI): *m*/*z* (%) 251 (M^+, 100); HRMS(EI): *m*/*z* calcd for $C_{16}H_{13}NO_2$ [M^+], 251.0946 found 251.0944.

4. Conclusions

In summary, we have demonstrated a novel method for the direct construction of C–C bonds of unprotected indole carboxylic acid **1** and various benzyl alcohols **2** by Pd-catalyzed domino reactions in water. In our (η^3-benzyl)palladium system, the domino reactions achieved C–H activation of the C3-position of indole, nucleophilic attack of indoles to hydrated benzyl alcohols, and benzylic C–H functionalization. Notably, water activated unreactive molecules such as hydroxyl groups and stabilized hydroxide ions by hydration, followed by formation of activated Pd(II) cation species.

Conflict of Interest

The authors declare no conflict of interest.

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