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Pd(0)-catalyzed benzylation of indole through η^3-benzyl palladium intermediate

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ABSTRACT

An efficient method has been developed for the Pd(0)-catalyzed benzylation of indoles, which occurred with exclusive regioselectivity. When this reaction was performed in the presence of $Pd(PPh_3)_4$, it provided access to a broad range of substituted indoles bearing diarylmethanes at their 3-position in 90%–99% yields under mild conditions.

The chemistry of π-allyl palladium complexes has become one of the most successful areas of organic synthesis, as exemplified by the Tsuji-Trost reaction [1]. In contrast, reactions involving the η^3-benzyl palladium complexes generated from benzylic derivatives are much less common because they require the dearomatization of an aryl system. Despite the difficulties associated with the preparation of η^3-benzyl palladium complexes, these systems are considered to be useful intermediates in organic synthesis, because they can be used as special η^3-allyl-palladium species. In this way, η^3-benzyl palladium intermediates have been successfully substituted at their benzylic, *ortho*- and *para*-positions with a wide variety of different nucleophiles, including carbon [2–25], nitrogen [16,26–27], oxygen [16,28] and sulfur-based nucleophiles [16,29] (Fig. 1).

η^3-Benzyl palladium intermediates can be generated by the oxidative addition reactions of a wide range of benzylic derivatives, including carbonates [3–7,28–31], phosphates [8–10], carboxylates [11–15] and even fluorides [16], to Pd(0). Benzyl chlorides can also be treated as common precursors for the formation of η^3-benzyl palladium species because they are readily available with various commercial suppliers and stable [17–27]. Several elegant palladium-catalyzed benzylation processes have been developed during the course of the last dec-

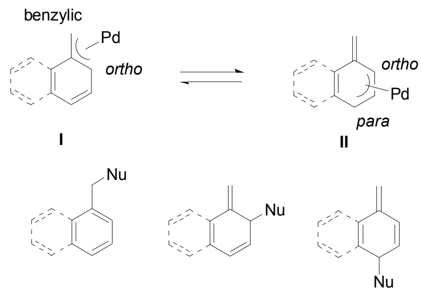

Fig. 1. η^3-Benzyl palladium intermediates and possible products.

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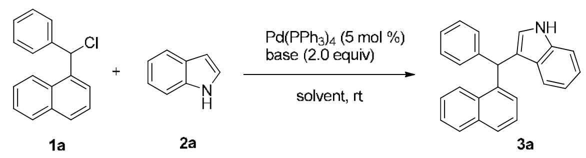
ade. In 2001, Yamamoto group [17] reported a facile palladium-catalyzed allylative dearomatization reaction involving the reaction of benzyl chloride with allyltributyltin at the *para*-position. Following on from this work, Bao group [19–27] reported their research towards the development of a series of reactions involving η^3-benzyl palladium intermediates. Despite these developments, there have been very few studies reported in the literature pertaining to the reaction of electron-rich arenes as nucleophiles with η^3-benzyl palladium intermediates [32,33]. In this study, it was envisioned that indole could be used as an effective nucleophile to attack benzylic systems and afford the corresponding triarylmethane compounds bearing an indole fragment, which could have numerous potential applications in organic synthesis [34–40]. It is noteworthy, however, that the use of indole in this way could also result in nucleophilic attack at the *ortho*- or *para*-position of the naphthyl ring, which would result in the formation of the corresponding dearomatized product through a catalytic dearomatization process [41–44]. Herein, we report the results of our recent study towards the Pd-catalyzed benzylation of indoles.

The reaction of 1-(chloro(phenyl)methyl)-naphthalene (**1a**) with indole (**2a**) was initially selected as a model reaction to allow for the optimization of the reaction conditions. Several different variables were evaluated, including the solvent, base and reaction time, in terms of their impact on the yield of the reaction, and the results are summarized in Table 1. Pleasingly, the reaction proceeded smoothly when it was conducted in CH$_3$CN at room temperature in the presence of 10 mol % Pd(PPh$_3$)$_4$ and 2.0 equivalents of Cs$_2$CO$_3$ to afford the triarylmethane product **3a** as a single regioisomer in 89% yield (Table 1, entry 1). Furthermore, none of the dearomatized product resulting from the nucleophilic attack of the indole on the naphthalene ring was observed. Encouraged by this preliminary result, we proceeded to evaluate the effects of several other solvents (i.e., toluene, 1,4-dioxane, Et$_2$O, DCM and THF) and bases (i.e., Cs$_2$CO$_3$, Li$_2$CO$_3$, Na$_2$CO$_3$, K$_2$CO$_3$, Et$_3$N and DBU) on the yield of the reaction (Table 1, entries 2–11). The highest yield of all of the conditions tested was achieved using a combination of THF with Cs$_2$CO$_3$, which provided the desired product in 99% yield (Table 1, entry 6). It is noteworthy that the reaction proceeded in only 60% yield when it was conducted without base (Table 1, entry 12). Furthermore, the reaction did not give any of the desired product when it was conducted in the absence of Pd(PPh$_3$)$_4$, which suggested that this reaction was proceeding via an η^3-benzyl palladium intermediate (Table 1, entry 13). Decreasing the amounts of catalyst and indole led to a reduction in the yield of the desired product (Table 1, entries 14–16). Based on these results, the optimized conditions were determined to be the following: 5 mol % Pd(PPh$_3$)$_4$, 2.0 equiv of Cs$_2$CO$_3$ and 2.0 equiv of indole in THF at room temperature.

Table 1
Optimization of the reaction conditions [a].

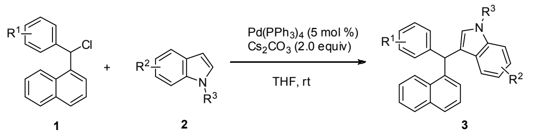


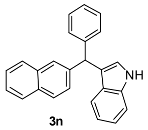
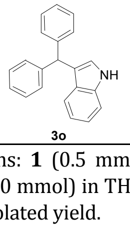
Entry	Solvent	Base	Time (h)	Yield [b] (%)
1	CH$_3$CN	Cs$_2$CO$_3$	15	89
2	toluene	Cs$_2$CO$_3$	3.0	91
3	1,4-dioxane	Cs$_2$CO$_3$	25	65
4	Et$_2$O	Cs$_2$CO$_3$	25	70
5	DCM	Cs$_2$CO$_3$	4.0	97
6	THF	Cs$_2$CO$_3$	2.0	99
7	THF	Li$_2$CO$_3$	2.5	94
8	THF	Na$_2$CO$_3$	2.5	88
9	THF	K$_2$CO$_3$	2.0	80
10	THF	Et$_3$N	30	85
11	THF	DBU	20	65
12	THF	—	2.0	60
13 [c]	THF	Cs$_2$CO$_3$	12	—
14 [d]	THF	Cs$_2$CO$_3$	24	83
15 [e]	THF	Cs$_2$CO$_3$	30	75
16 [f]	THF	Cs$_2$CO$_3$	4.0	85

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), base (1.0 mmol) and Pd(PPh$_3$)$_4$ (0.025 mmol) in solvent (3 mL) at room temperature under an argon atmosphere. [b] Isolated yield. [c] No Pd(PPh$_3$)$_4$. [d] 1.5 equiv of **2a** and Cs$_2$CO$_3$. [e] 1.0 equiv of **2a** and Cs$_2$CO$_3$. [f] Pd(PPh$_3$)$_4$ (2.5 mol %).

With the optimized conditions in hand, we proceeded to evaluate the scope of this reaction using a variety of different substituted indoles and benzyl chloride-type compounds. The results of these experiments are summarized in Table 2. The electronic properties of the indole ring had no discernible impact on the outcome of the reaction, with indoles **2** bearing an electron-donating (i.e., 7-Me or 5-MeO) or electron-withdraw-

Table 2
Pd-catalyzed benzylation of indoles [a].



Entry	**3**, R^1, R^2, R^3	Time (h)	Yield [b] (%)
1	**3a**, H, H, H	2.0	99
2	**3b**, H, 7-Me, H	5.0	90
3	**3c**, H, 5-MeO, H	2.0	91
4	**3d**, H, 4-Br, H	3.0	93
5	**3e**, H, 5-Br, H	2.0	96
6	**3f**, H, 6-Br, H	3.0	94
7	**3g**, H, 6-F, H	2.5	90
8	**3h**, H, 6-Cl, H	4.0	96
9	**3i**, H, H, Me	3.0	99
10	**3j**, 4-^{t}Bu, H, H	2.0	98
11	**3k**, 4-Me, H, H	2.0	98
12	**3l**, 4-F, H, H	2.0	91
13	**3m**, 4-Br, H, H	2.5	94
14	 NH **3n**	3.0	98
15	 NH **3o**	20	trace

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), Pd(PPh$_3$)$_4$ (0.025 mol) and Cs$_2$CO$_3$ (1.0 mmol) in THF (3 mL) at room temperature under Ar atmosphere. [b] Isolated yield.