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Palladium-Catalyzed C3-Benzylation of Indoles

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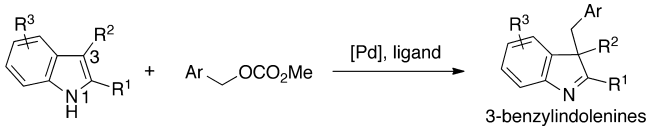
Supporting Information

ABSTRACT: A general method for regioselective C3-benzylation of indoles has been developed. Various 3-substituted indoles and benzyl methyl carbonates with different electronic properties react under mild conditions to afford a diverse range of 3-benzylindolenine products in good yields.

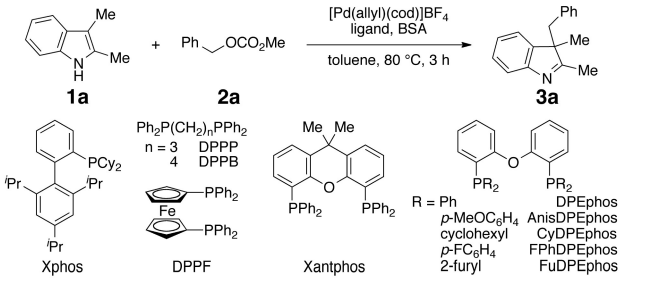
The prevalence of the indole nucleus in natural products, pharmaceutical ingredients, and organic materials has spurred considerable effort on the development of efficient and selective functionalizations of this primary heterocycle.[1] In the past few decades, Pd-catalyzed reactions of indoles have become powerful tools in the arsenal of synthetic chemists.[1a] While much attention has been focused on Pd-catalyzed indole allylation reactions,[2] the corresponding benzylation reaction of 3-substituted indoles[3] has not been reported. Such a fundamental transformation would allow access to 3-benzylindolenines bearing a newly formed quaternary center,[4] which constitute the core structures of many biologically active natural products and synthetic compounds.[5] In view of the centrality of the benzyl unit, there have been several recent reports on synthetic methods[6−8] involving π-benzyl-Pd intermediates,[9] although the Pd-catalyzed benzylation of nonstabilized nucleophiles using simple benzyl alcohol derivatives remains undeveloped. We report here a general, mild method for the Pd-catalyzed C3-benzylation of 3-substituted and 2,3-disubstituted indoles using benzyl carbonates (Scheme 1).

Scheme 1. Pd-Catalyzed Indole Benzylation



As anticipated, the benzylation of indoles proved more challenging than the corresponding allylation. Reaction conditions that are effective for allylation of 2,3-dimethylindole (**1a**) gave little or no benzylation product when benzyl methyl carbonate (**2a**) was used, even at 80 °C (Table 1, entries 1−5). It was observed that ligands bearing large bite angles[10] such as DPPF, Xantphos, and in particular DPEphos, are quite effective for the benzylation reaction (entries 6−8). Importantly, the reaction is completely C3-selective, with no N-benzyl product being formed. Evidently, the highly polarizable π-benzyl-Pd intermediate preferentially reacts at the carbon of the ambident indole. Evaluation of a series of synthetic DPEphos-type ligands

Table 1. Ligand Screening[a]



entry	ligand	yield (%)[b]	entry	ligand	yield (%)[b]
1[c]	PPh_3	<10[d]	7	Xantphos	68
2[c]	PBu_3	N. D.[e]	8[g]	DPEphos	82
3[f]	Xphos	20[d]	9[g]	AnisDPEphos	49
4	DPPP	<10[d]	10	CyDPEphos	13
5	DPPB	<10[d]	11[g]	FPhDPEphos	<10[d]
6	DPPF	36	12[g]	FuDPEphos	12[d]

[a]Reactions were carried out using 1.5 equiv of **2a**, 10 mol % [Pd(allyl)(cod)]BF_4, 11 mol % ligand, and 1.2 equiv of *N*,*O*-bis(trimethylsilyl)acetamide (BSA). [b]Isolated yields. [c]22 mol % ligand. [d]Yield was determined by ^{1}H NMR analysis. [e]**3a** was not detected. [f]5 mol % catalyst, 4.5 h reaction time. [g]1.5 h reaction time.

revealed that the yield diminished when either electron-rich (entries 9 and 10) or electron-deficient (entries 11 and 12) phosphine ligands were utilized. DPEphos was found to be optimal in providing the right balance between the rates of different steps in the catalytic cycle, resulting in the highest overall reaction rate.

Further optimization of the reaction conditions was aimed at lowering the catalyst loading and the reaction temperature (Table 2). Benzyl acetate and benzyl alcohol afford the product in low yields (entries 1 and 2), and lowering the catalyst loading to 5 mol % slows the reaction considerably (entry 3). Examination of additives led to the observation that triethylborane (BEt_3) significantly promotes the reaction (entries 4 and 5).[2b] Indeed, in the presence of BEt_3, a 2.5 mmol scale reaction proceeds at 40 °C, giving the product in 83% yield (entry 6). To the best of our knowledge, this result represents the first example of a Pd-catalyzed benzylation reaction using a benzyl carbonate carried out below 60 °C. The

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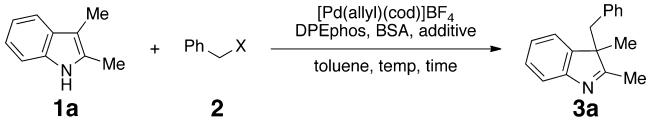
Table 2. Reaction Optimization[a]



entry	2	additive	temp (°C)	time	yield (%)[b]
1[c]	Ph–OAc	none	80	4.5 h	16[d]
2[e]	Ph–OH	1.1 equiv BEt_3	80	4.5 h	N. D.[f]
3	**2a**	none	80	4.5 h	37
4[g]	**2a**	0.5 equiv COD	80	4.5 h	41
5	**2a**	1.1 equiv BEt_3	80	45 min	91
6	**2a**	1.1 equiv BEt_3	40	48 h	83[h] (72[d,i])
7	**2a**	0.2 equiv BEt_3	40	24 h	60[d]

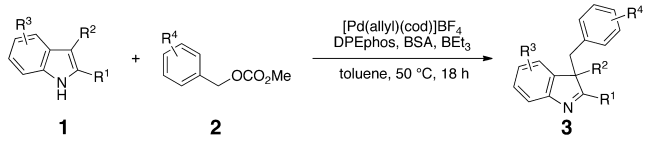
[a]Reactions were carried out using 0.50 mmol of **1a**, 1.5 equiv of **2**, 5 mol % $[Pd(allyl)(cod)]BF_4$, 5.5 mol % DPEphos, and 1.2 equiv of BSA. [b]Isolated yields. [c]10 mol % catalyst. [d]Yield was determined by ^1H NMR analysis. [e]Reaction was carried out using 10 mol % $Pd(PPh_3)_4$ in THF. [f]**3a** was not detected. [g]COD = 1,5-cyclooctadiene. [h]2.5 mmol scale reaction. [i]24 h reaction time.

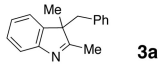
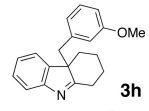
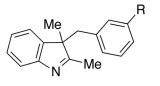
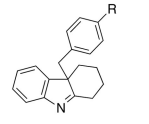
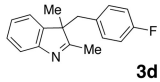
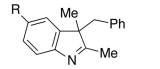
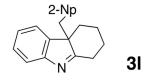
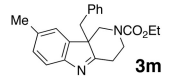
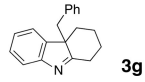
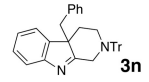
benzylation reaction also proceeds with substoichiometric BEt_3, albeit in lower yield (entry 7).[11]

The optimized conditions (1.2 equiv of **2**, 5 mol % catalyst, 1.2 equiv of BSA, 1.1 equiv of BEt_3, 50 °C) were found to be applicable to a diverse range of 2,3-disubstituted indoles and substituted benzyl methyl carbonates (Table 3). Both electron-rich and electron-deficient substituted benzyl carbonates were well-tolerated (entries 1−4). Substitutions on the indole modulated the reactivity, with the indole nucleophilicity being enhanced by a methoxy group and diminished by a chloro substituent (entries 5 and 6). Moreover, both carba- and heterocycle-fused indoles proved to be excellent substrates. The reactions between 1,2,3,4-tetrahydrocarbazole and various benzyl carbonates with different electronic properties afforded high yields (entries 7−11), with naphthylmethyl carbonate reacting faster than **2a** (entry 12). Notably, both tetrahydro-β-carboline and tetrahydro-γ-carboline derivatives were transformed to the respective heterocycle-fused benzylindolenines (entries 13 and 14).

The benzylation reactions of 3-substituted indoles are more challenging because the 3-alkyl-3-benzylindolenine products are prone to rearrangement to 3-alkyl-2-benzylindoles as a result of the high migratory aptitude of the benzyl group. Jackson synthesized **3o** in only 4% yield via 3-methylindolylmagnesium iodide, and the preparation of 3-(*p*-methoxybenzyl)-3-methylindolenine failed completely.[12] In contrast, 3-methylindole (**1b**) nicely underwent the Pd-catalyzed benzylation reaction, furnishing the desired product **3o** in 88% yield. The unwanted rearrangement was completely avoided under these reaction conditions (Table 4, entry 1). In addition, **1b** reacted smoothly with substituted benzyl carbonates **2b** and **2c**. Although the 3-benzyl-3-methylindolenine products were in equilibrium with the corresponding cyclic trimers (1,3,5-triazinanes),[13] they could be transformed cleanly to indoline derivative **3p** by reduction and 2-benzylindole derivative **3q** via acid-catalyzed rearrangement, respectively (entries 2 and 3). The intramolecular trapping of the indolenine C═N bond by a pendant nucleophile is of particular interest since the resulting

Table 3. Benzylation of 2,3-Disubstituted Indoles[a]



entry	product	yield (%)[b]	entry	product	yield (%)[b]
1	 **3a**	86	8	 **3h**	89
2	 R = OMe **3b**	80	9	 R = OMe **3i**	88
3	F **3c**	77	10	Cl **3j**	71
4	 **3d**	79	11	CF_3 **3k**	90
5	 R = OMe **3e**	91	12[c]	 **3l**	95
6	Cl **3f**	78	13	 **3m**	86
7	 **3g**	90	14[d]	 **3n**	89

[a]Reactions were carried out using 0.50 mmol of **1**, 1.2 equiv of **2**, 5 mol % $[Pd(allyl)(cod)]BF_4$, 5.5 mol % DPEphos, 1.2 equiv of BSA, and 1.1 equiv of BEt_3 at 50 °C for 18 h. [b]Isolated yields. [c]8 h reaction time. Np = naphthyl. [d]Tr = triphenylmethyl.

heterocycle-fused indoline is found as a core structure of many natural products. *N*-tosyltryptamine (**1c**) and tryptophol (**1d**) participated nicely in the reaction, giving the corresponding cis-fused pyrrolo- and furanoindolines in high yields (entries 4 and 5). The fact that a sulfonamide and an alcohol were tolerated reflects the high chemoselectivity of the reaction. The reaction between indole (**1e**) and 1.0 equiv of **2a** afforded 3-benzylindole (**3t**) in 69% yield along with a small amount of 3,3-dibenzylindolenine (**3u**) (entry 6). The use of excess **2a** afforded **3u** as the sole product in high yield (entry 7). Finally, in contrast to 1-phenylethyl methyl carbonate (**2d**) (entry 8), 1-(naphthalen-2-yl)ethyl methyl carbonate (**2e**) showed excellent reactivity (entries 9 and 10).

To probe the reactivity differences between allyl, naphthylmethyl, and benzyl carbonates, a series of competition studies was carried out (Scheme 2). The Pd-catalyzed reactions of **1f** with mixtures of **4** and **2a** or **4** and **2f** produced allylation product **5** exclusively (eqs 1 and 2). When **1f** was subjected to a mixture of equal amounts of **2a** and **2f**, product **3l** was isolated predominantly, together with a <2% yield of **3g** (eq 3). The dramatic decrease in reactivity for Pd-catalyzed indole alkylation reactions in going from **4** to **2f** to **2a** correlates with the increased disruption of π-conjugation or aromaticity in the formation of the corresponding η^3-palladium complexes. In comparison with many reports of Pd-catalyzed benzylation reactions employing extended π-systems, the indole benzylation reaction described above represents a rare example of Pd-

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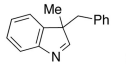
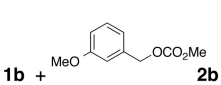
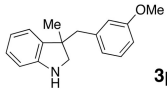
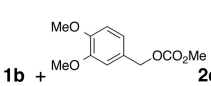
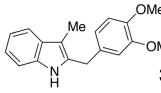
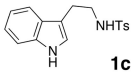
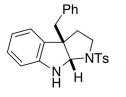
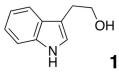
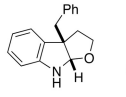
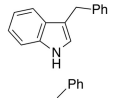
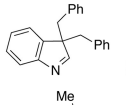
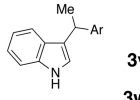
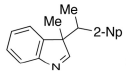
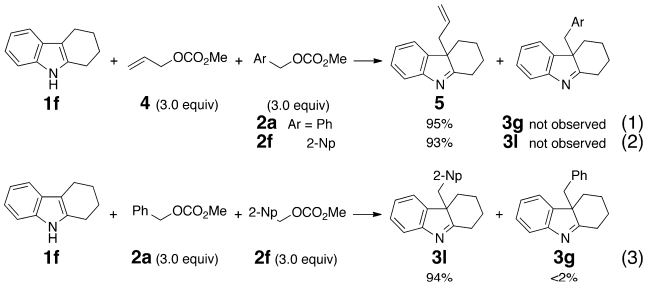
Table 4. Benzylation of Indole and 3-Substituted Indoles[a]

entry	substrate	product	yield (%)[b]
1	 **1b** + **2a**	 **3o**	88
2	 **1b** + **2b**	 **3p**	83[c]
3	 **1b** + **2c**	 **3q**	73[d]
4[e]	 **1c** + **2a**	 **3r**	92
5[f]	 **1d** + **2a**	 **3s**	88[g]
6[h]	 **1e** + **2a**	 **3t**	69[i]
7[f,j]		 **3u**	94
8[h]	**1e** + Ar = Ph **2d**	 **3v**	N. D.[k]
9[h]	2-Np **2e**	**3w**	93
10	**1b** + **2e**	 **3x**	94 (5.8:1 dr)

[a]The reaction conditions were the same as in Table 3. [b]Isolated yields. [c]Reduction of the indolenine product using $NaBH_4$ in AcOH yielded **3p**. [d]Treatment of the indolenine product with CF_3COOH yielded **3q**. [e]Ts = *p*-toluenesulfonyl. [f]2.2 equiv of BSA was used. [g]The reaction was quenched with K_2CO_3 in MeOH. [h]1.0 equiv of **2** was used. [i]The product was isolated as a 5:1 mixture of **3t** and **1e**. The yield of **3t** was determined by ^1H NMR analysis. **3u** was isolated in 15% yield as a side product. [j]2.2 equiv of **2a** was used. [k]**3v** was not detected.

Scheme 2. Competition Studies[a]

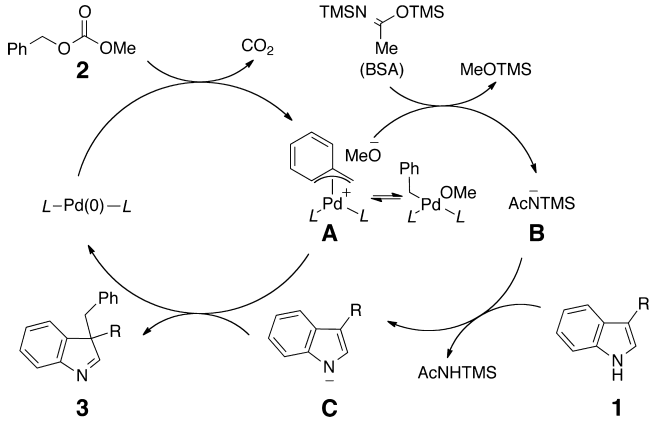


[a]The reaction conditions were the same as in Table 3.

catalyzed benzylation of nonstabilized nucleophiles using simple benzyl alcohol derivatives.

A plausible mechanism for the benzylation reaction is shown in Scheme 3.[14] It is likely that BEt_3 facilitates the formation of π-benzyl-Pd (**A**) by binding to the carbonyl group of benzyl carbonate **2**.[15,16] BSA is proposed to play a dual role: it silylates the methoxide, thereby removing it from the π-benzyl-Pd

Scheme 3. Proposed Reaction Mechanism[a]



[a]*L* = ligand; TMS = trimethylsilyl.

cation, and the resulting amide anion (**B**) subsequently deprotonates indole **1** to generate the indolyl anion (**C**).

In conclusion, we have developed the first general method for the regioselective C3-benzylation of 3-substituted indoles. This Pd-catalyzed transformation is effective for indoles and benzyl carbonates possessing sterically and electronically diverse substituents and affords the C3-benzyl indolenine products in high yields. The mild reaction conditions provide future opportunities to apply this methodology to complex molecules and develop an enantioselective variant of this reaction.[6g,17]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) A reaction with (*R*)-BINAP as the ligand gave **3g** in 37% ee. See the SI for details.

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