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Palladium(II)-Catalyzed Efficient C-3 Functionalization of Indoles with Benzylic and Allylic Alcohols under Co-Catalyst, Acid, Base, Additive and External Ligand-Free Conditions

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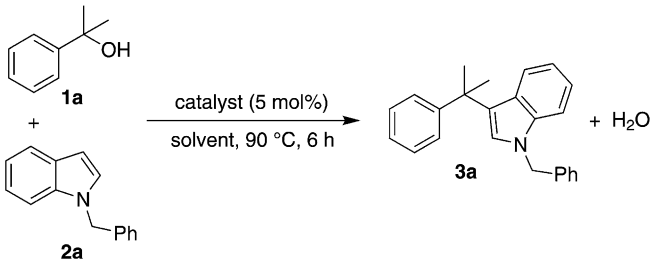
Abstract: The bis(acetonitrile)palladium(II) chloride complex, $PdCl_2(MeCN)_2$, efficiently catalyzes the regioselective alkylation of indoles with various benzylic and allylic alcohols under moisture and air insensitive conditions. Notably the reaction does not require any other co-catalyst, acid, base, additive, or external ligand.

Keywords: alkylation; allylic alcohols; benzylic alcohols; homogeneous catalysis; indoles; palladium(II) complex

The functionalization of indoles *via* low cost, selective, and eco-friendly strategies has attracted wide attention since structural motifs bearing the 'indole core' are frequently found in natural products, pharmaceuticals, and other functional synthetics.[1] Conventionally 3-alkylated indoles are synthesized from alkyl halides and surrogates by carbon-carbon bond forming reactions such as (i) acid- or base-promoted alkylation[1c,2] or (ii) transition metal-catalyzed alkylation.[1c,3] Among the transition metals, the palladium-catalyzed reactions of indoles with reactive electrophiles (halides, acetates, etc.) have become powerful tools to synthesize functionalized indoles.[1c,4] In contrast, examples of palladium-catalyzed C-alkylation of indole using an alcohol are few. Indeed the direct coupling of indole with an alcohol is considered to be synthetically attractive, mechanistically challenging and environmentally benign due to ready availability and significantly lower toxicity of alcohols (compared to alkylating agents like halides, acetates, etc.), and the fact that only stoichiometric amounts of water are generated as the side product in the alkylation reaction.[1c,5] One may also appreciate that a major difficulty in the direct alkylation reaction from an alcohol using a transition metal catalyst is the inertness of the OH group towards such activation.[1c,6] In light of the above, the available reports on the palladium-catalyzed syntheses of allylindoles from the corresponding alcohols are noteworthy.[7] In 1980 Billups et al. first reported that the reaction of indole and allyl alcohol in refluxing benzene under the catalytic influence of palladium acetylacetonate/PPh_3 gave rise to 3-allylindole in 45% yield along with 1-allylindole (7%) and 1,3-bisallylindole (9%).[7a] More recently Tamaru et al. achieved the desired transformation using $Pd(PPh_3)_4$ as the catalyst (5 mol%) and Et_3B (30–240 mol%) as the promoter.[7b] A closely related enantioselective variant of this approach was later proposed by Trost et al. using $Pd_2dba_3{\cdot}CHCl_3$ as the catalyst and 9-BBN-C_6H_{13} (105 mol%) as an additive.[7c] Pullarkat et al. employed a palladacycle catalyst (10 mol%) for the C-3 allylation of 2-substituted indoles.[7d] Breit et al. accomplished the allylation of indoles using the unique concept of self-assembling palladium phosphane catalysts.[7e] Recent reports on the development of multimetallic catalysts based on palladium for alcohol activation are also noteworthy.[7f,g]

In light of the above literature reports, we were pleasantly surprised with the serendipitous result when a simple monometallic palladium(II) complex, namely $PdCl_2(MeCN)_2$, catalyzed the alkylation of indole with benzylic and allylic alcohols with high efficiency and exclusive C-3 regioselectivity. We also noted that the reaction neither requires the assistance of external acid/base, additive and ligand, nor is it sensitive towards moisture and air. The details of our findings are presented below.

Table 1. Catalysts screening.[a]



Entry	Catalyst	Solvent	Yield of **3a** [%][b]
1	pTSA	DCE	10
2	TfOH	DCE	35
3	TFA	DCE	0
4	$BF_3{\cdot}Et_2O$	DCE	27
5	$FeCl_3$	DCE	49
6	$InCl_3$	DCE	43
7	$Ti\{OCH(CH_3)_2\}_4$	DCE	15
8	$SnCl_4$	DCE	35
9	$[(PPh_3)AuCl]/AgOTf$	DCE	33
10	$Bi(OTf)_3$	DCE	22
11	$Cu(OTf)_2$	DCE	13
12	$Sc(OTf)_3$	DCE	37
13	$La(OTf)_3$	DCE	36
14	**$PdCl_2(MeCN)_2$**	**DCE**	**82**
15	$PdCl_2(bpy)$	DCE	0
16	$PdCl_2(PPh_3)_2$	DCE	18
17	$Pd(OAc)_2$	DCE	11
18	$Pd_2(dba)_3$	DCE	0
19	$Ru(PPh_3)_3Cl_2$	DCE	0
20	K_2PtCl_4	DCE	0
21	$PdCl_2(MeCN)_2$	MeCN	42
22	$PdCl_2(MeCN)_2$	MeOH	8
23[c]	none	H_2O	0
24	none	DCE	0

[a] A mixture of **1a** (0.30 mmol), **2a** (0.25 mmol), and catalyst (5 mol%) in 2 mL of solvent was stirred at 90 °C for 6 h.

[b] Yield by ^1H NMR using triphenylmethane as external standard.

[c] Carried out in deionized water at 80 °C.

In a model study we examined the reaction of 1-benzyl-1*H*-indole **2a** with 2-phenylpropan-2-ol **1a** in the presence of different Brønsted acids, Lewis acids, palladium and other transition metal catalysts (with 5 mol% loadings) at 90 °C for 6 h (Table 1).[8] Among the tested Pd complexes, only $PdCl_2(MeCN)_2$ showed promising catalytic activity in 1,2-dichloroethane (DCE) as the solvent and afforded the desired C-3 alkylated 1-benzyl-3-(2-phenylpropan-2-yl)-1*H*-indole **3a** as the only product (entries 14–18). Notably, it is not necessary to exclude air or moisture from this reaction. Lower conversion was observed in coordinating solvents like acetonitrile or methanol (entries 21 and 22).

Interestingly, all of the tested Lewis acids inclusive of $BF_3{\cdot}Et_2O$, $FeCl_3$, $InCl_3$, $Ti\{OCH(CH_3)_2\}_4$, $SnCl_4$ and transition metal catalysts $[(PPh_3)AuCl]/AgOTf$ were less effective (entries 4–9). Likewise, catalytic amounts of Brønsted acids like *p*TSA or TfOH (entries 1 and 2) and metal triflates (entries 10–13) gave lower yields, whereas TFA (entry 3) and late transition metal salts like $Ru(PPh_3)_3Cl_2$ or K_2PtCl_4 were totally inactive (entries 19 and 20). In a few of the cases where a Lewis or a Brønsted acid was used as catalyst, the observed low yield was due to the formation of unwanted side products (like α-methylstyrene, oligomers).[9]

Having established the optimum conditions, a number of *N*-substituted (alkyl-, benzyl-, allyl-, propargyl-)indoles as well as ring-substituted indoles were alkylated at 90 °C in DCE using various tertiary as well as secondary benzylic alcohols, giving rise to the desired products in good to excellent yields (Figure 1).[10] Significantly, in all cases where we have used *N*-unprotected indole, the reactions were completely C-3 selective, and no *N*-alkyl product was formed. Interestingly, γ-hydroxylactam could be used efficiently as an alkylating agent yielding the corresponding alkylated products **3q** and **3r** with quantitative conversions and excellent yields (Figure 1). The structure of **3q** was established by X-ray crystallographic analysis (Figure 2). It was also observed that alkylation of indole proceeded best with electron-rich alcohols, whereas electron-deficient 2-(4-chlorophenyl)propan-2-ol and primary benzyl alcohols were ineffective.

Next, we studied the coupling between substituted allylic alcohols and a diverse range of indoles using catalytic $PdCl_2(MeCN)_2$ (3 mol%) in DCE as solvent (Table 2). These results have been most gratifying as the reactions took place at room temperature and under additive- and ligand-free conditions for most cases.

The allylation reaction with alcohol **4g** was sluggish at room temperature but the rate increased significantly at 90 °C (entry 14). In our hands, aliphatic allylic alcohols were inactive even at higher temperatures. The formation of regioisomers (α and γ) was noticed in the case of alcohols **4e**–**4g**. Note that the use of propargylic alcohol **4h** as an alkylating agent gave the desired alkylation product **5n** in 12% yield only (entry 15, Table 2).

During the course of this experimentation we noticed that whenever $PdCl_2(MeCN)_2$ was added to a solution of only indole or to a mixture containing indole and the electrophile in DCE or DCM as solvent, a dark red color was formed. The color change was also visualized even when indole and $PdCl_2(MeCN)_2$ were mixed in the solid state (please see Figure S1 in the Supporting Information). Prompted by this observation, we carried out the reaction of indole and

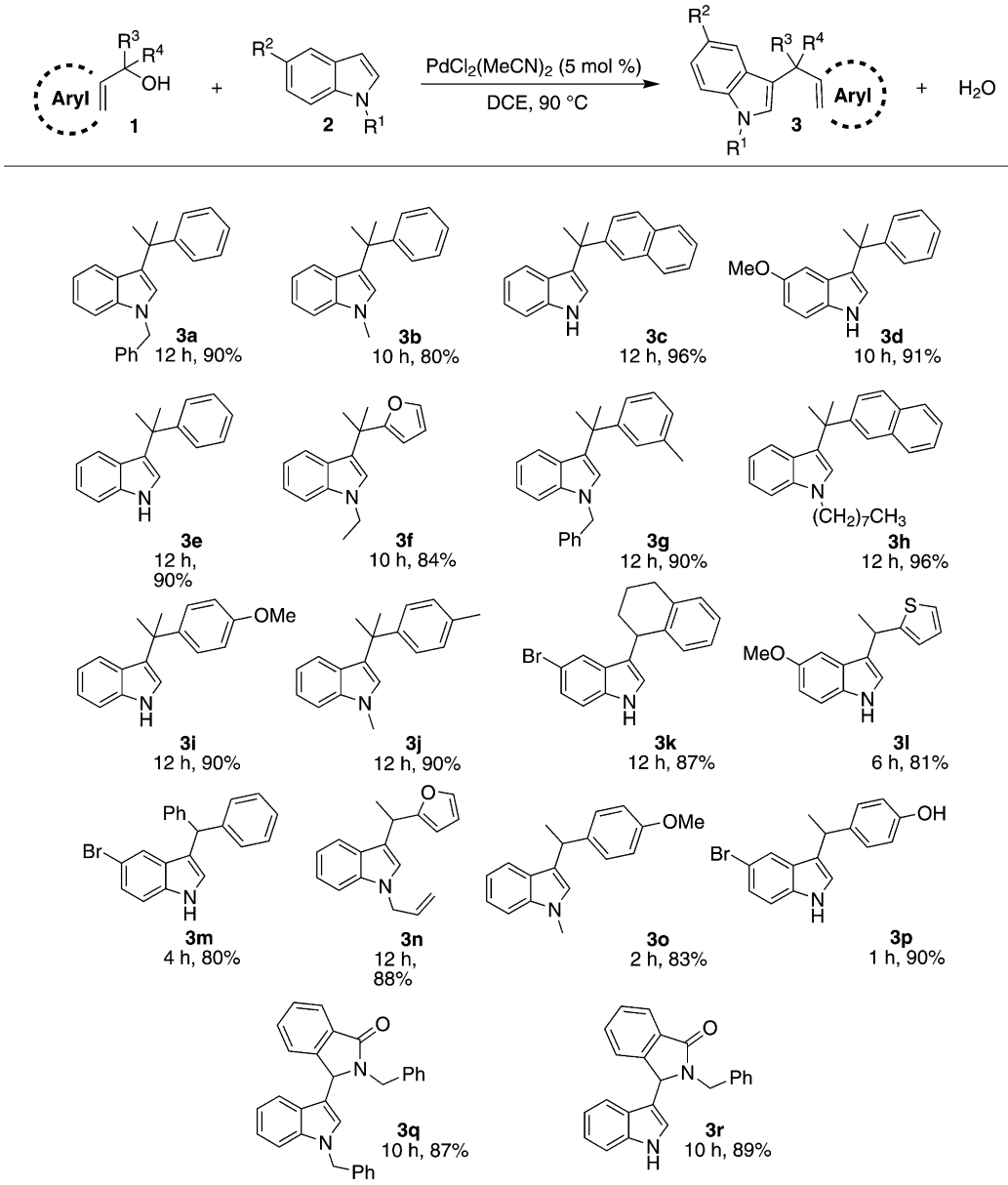


Figure 1. Substrate scope of the direct benzylation of indoles.

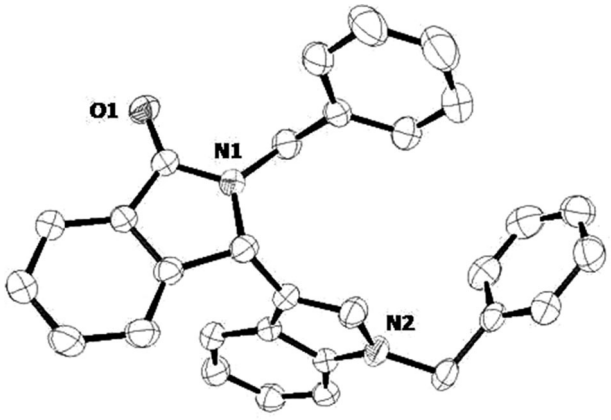
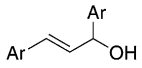
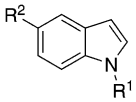
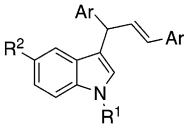
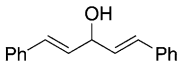
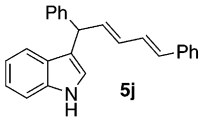
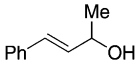
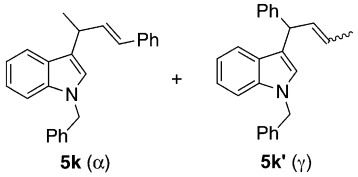
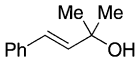
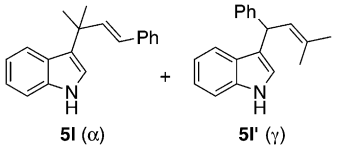
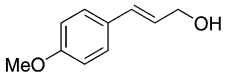
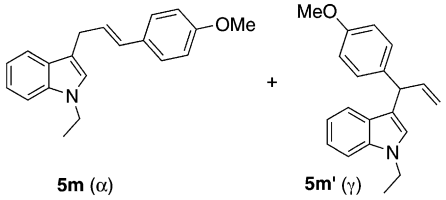
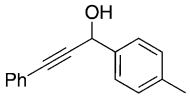
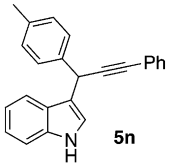


Figure 2. ORTEP diagram of compound **3q** with 30% probability thermal ellipsoids.

$PdCl_2(MeCN)_2$ in dicholoromethane at room temperature and isolated a dark red solid in 55% yield (Scheme 1). The complex of indole with $PdCl_2(MeCN)_2$ conformed to a composition $C_{16}H_{14}Cl_4N_2Pd_2$ (hereafter complex **1**). Shul′man et al. had earlier proposed the formation of a halide-bridged Pd(II) dimer of general formula $Pd_2(indole)_2X_4$ (X = halogen) from the reaction of Pd(II) with indole.[11]

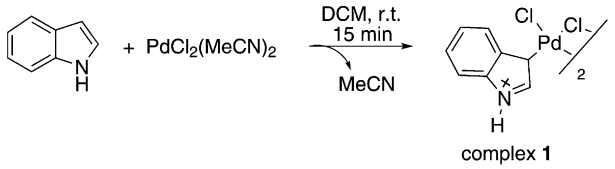
In our view, complex **1** is overall a neutral complex; the formal oxidation number of palladium being two. The chloride ligand could be in the outer-sphere or in the inner-sphere. When in the outer sphere, one can write it as a chloride anion. X-ray crystallography can provide the answer to this issue. So far we have failed to grow crystals of the desired quality for structure

Table 2. Pd(II)-catalyzed alkylation of indoles.[a]

Entry	4	Alcohol	Indole	Time [h]	Product 5	Yield of 5 [%]
						
1[b]	**4a**	Ar = C_6H_5	R^1 = H, R^2 = H	4	**5a**	0
2	**4a**		R^1 = H, R^2 = H	4	**5a**	80
3	**4a**		R^1 = H, R^2 = Br	10	**5b**	92
4	**4a**		R^1 = H, R^2 = OMe	10	**5c**	95
5	**4a**		R^1 = Me, R^2 = H	4	**5d**	81
6	**4a**		R^1 = -$CH_2C\equiv CH$, R^2 = H	2	**5e**	88
7	**4a**		R^1 = -$(CH_2)_7CH_3$, R^2 = H	6	**5f**	95
8	**4b**	Ar = 4-MeC_6H_4	R^1 = -CH_2Ph, R^2 = H	4	**5g**	80
9	**4c**	Ar = 4-BrC_6H_4	R^1 = -Me, R^2 = H	5	**5h**	66
10	**4c**		R^1 = -CH_2C=CH_2, R^2 = H	6	**5i**	70
11	**4d**		R^1 = H, R^2 = H	6	 **5j**	83
12	**4e**		R^1 = -CH_2Ph, R^2 = H	12	 **5k** (α) **5k'** (γ)	65 (α/γ = 72:28)
13	**4f**		R^1 = H, R^2 = H	8	 **5l** (α) **5l'** (γ)	82 (α/γ = 54:46)
14[c]	**4g**		R^1 = Et, R^2 = H	3	 **5m** (α) **5m'** (γ)	60 (α/γ = 74:26)
15[d]	**4h**		R^1 = H, R^2 = H	10	 **5n**	12

[a] All reactions were carried out with alcohol (0.6 mmol), indole (0.5 mmol) and $PdCl_2(MeCN)_2$ (3 mol%) in 2 mL of DCE at room temperature (30 °C).
[b] Carried out without catalyst.
[c] Carried out at 90 °C.
[d] Carried out with 5 mol% catalyst at 90 °C.

determination. However, ^{1}H and ^{13}C NMR spectra of complex **1** in $CDCl_3$ showed characteristic features. Noticeably, the proton resonance of 1-NH in complex **1** did not disappear but showed a shift from 8.13 ppm in the free indole to 10.59 ppm (Figure 3). The identification of the 1-NH proton was also supported by a deuterium exchange experiment. Therefore we ruled out N to Pd coordination in complex **1**. The res-

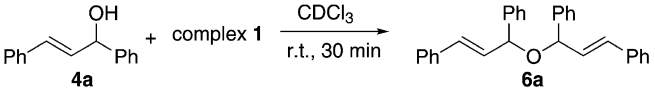


Scheme 1. Preparation of Pd(II) complex **1**.

onance of 3-CH in complex **1** appeared at 6.34 ppm, an upfield shift with respect to that of free indole (6.57 ppm). The ^{13}C NMR chemical shift values for C-3 in free indole and complex **1** appeared at 102.8 and 77.4 ppm, respectively. We propose that this dramatic change is due to the conversion of an aromatic carbon to a tetrahedral carbon (please see the Supporting Information).[12] The ^{1}H signal for 2-CH in complex **1** appeared at 8.22 ppm; a downfield shift from that of free indole. The ^{13}C resonance for C-2 (analogous to an imine carbon) in complex **1** was also downfield shifted to 142.8 ppm (please see the Supporting Information).[13]

The above findings support that in complex **1** palladation occurred at the 3-C atom of the indole ring.[12] To our gratification complex **1** could be successfully utilized as a catalyst for the coupling of indole with alcohols. We presume that the labile nature of the acetonitrile ligand in $PdCl_2(MeCN)_2$ might be the key to the formation of complex **1** which, in turn, accounts for its promising reactivity in the alkylation reactions. It also explains the inactivity or less reactivity of other Pd(II) complexes with strong donor ligands (like PPh_3, bipy or acetate) (Table 1, entries 15–17). Complex **1** is partially soluble and stable in solvents like DCM, DCE and $CHCl_3$ but is unstable in methanol and showed poor reactivity in MeOH/acetonitrile (Table 1, entries 21 and 22). On the other hand, reaction of allyl alcohol **4a** with 1 equiv. of complex **1** in $CDCl_3$ at room temperature yielded the corresponding symmetrical diallyl ether **6a** (as a 1:1 mixture of diastereomers) along with unreacted alcohol **4a** (Scheme 2). The formation of **6a** from alcohol **4a** provided initial support towards the activation of alcohol by Pd(II) *via* a typical Friedel–Crafts-type pathway.[14]

Although detailed mechanistic studies must be awaited, on the basis of the above results, in particular the observed enhanced reactivity of 2° and 3° electron-rich aryl alcohols compared to 1° or electron-poor aryl alcohols, we tentatively suggest that an elec-



Scheme 2. Formation of diallyl ether **6a** from allyl alcohol **4a** and complex **1**.

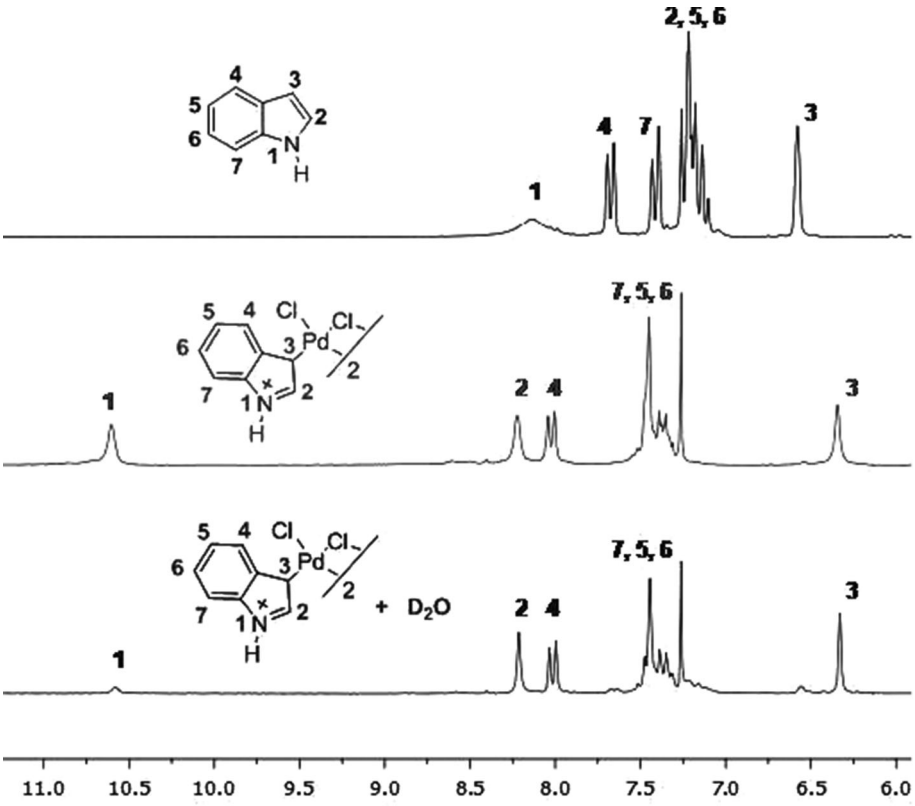


Figure 3. ^{1}H NMR spectrum of indole and complex **1**.

trophilic mechanism involving the intermedicacy of a carbenium ion may be operating in the present Pd(II)-catalyzed alkylation of indole.[5f,14,15] In the case of *N*-unprotected indoles, one cannot completely rule out the possibility of a pathway involving Brønsted acid-type catalysis.[16,17] Such a pathway may operate in tandem with the proposed Friedel–Crafts alkylation.

In summary, $PdCl_2(MeCN)_2$ has been found to be an effective catalyst for regioselective functionalization of indoles with benzylic and allylic alcohols. Co-catalysts, acid/base, additive, external ligand are not required in this alkylation, which is thus of great promise. The easy handling of the catalyst makes the reaction more attractive, simple and practical.

Experimental Section

Syntheses and Characterization of $[(C_8H_7N)PdCl_2]_2$ (Complex 1)

Solid $PdCl_2(MeCN)_2$ (130 mg, 0.5 mmol) was added in one portion to a stirred solution of indole (59 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) resulting in a sharp color change. After 15 min, petroleum ether (30 mL) was added while stirring was continued for a further period of 5 min. The dark red solid was separated by filtration, washed with petroleum ether and dried in vacuum; yield: 55%. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.34$ (s, 1H), 7.31–7.52 (m, 3H), 8.02. (d, 1H, $J = 7.6$ Hz), 8.22 (br s, 1H), 10.59 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 77.4$, 114.3, 125.10, 125.14, 128.2, 130.6, 134.4, 142.8; anal. calcd. for $C_{16}H_{14}Cl_4N_2Pd_2$: C 32.63, H 2.40, N 4.76; found: C 32.29, H 2.21, N 4.93.

Procedures for the Catalytic C3-Functionalization of Indole

a) Representative Procedure for the Benzylation of Indoles with Benzylic Alcohols: A mixture of phenylpropan-2-ol **1a** (82 mg, 0.60 mmol), 1-benzyl-1*H*-indole **2a** (103.4 mg, 0.5 mmol), $PdCl_2(MeCN)_2$ (6.5 mg, 0.025 mmol) in 2 mL of DCE was stirred at 90 °C for the appropriate time. Then, the solvent was removed under reduced pressure, and the mixture was subjected to column chromatography over silica gel (100–200 mesh, eluent: petroleum ether 60–80 °C/ethyl acetate, 50:1 v/v) to afford the desired alkylated product **3a** as a colorless oil; yield: 146 mg (90%).

b) Representative Procedure for the Alkylation of Indoles with Allylic Alcohols: A mixture of (*E*)-1,3-diphenylprop-2-en-1-ol **4a** (126 mg, 0.60 mmol), 1*H*-indole (58.5 mg, 0.5 mmol), $PdCl_2(MeCN)_2$ (3.9 mg, 0.015 mmol) in 2 mL of DCE was stirred at room temperature (30 °C) for the appropriate time. Then, the solvent was removed under reduced pressure, and the mixture was subjected to column chromatography over silica gel (100–200 mesh, eluent: petroleum ether 60–80 °C/ethyl acetate, 9:1 v/v) to afford the alkylated product **5a** as a yellow solid; yield: 124 mg (80%).

X-Ray Crystallography

CCDC 918766 (**3q**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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[9] In presence of a Lewis acid, 3° benzylic alcohols are known to undergo elimination reactions and the resulting styrenes are often dimerized/polymerized. Please see: a) F. Howard, S. Sawadjoon, J. S. M. Samec, *Tetrahedron Lett.* **2010**, *51*, 4208; b) H. B. Sun, B. Li, R. Hua, Y. Yin, *Eur. J. Org. Chem.* **2006**, 4231.

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[11] V. M. Shul′man, T. V. Zagorskaya, I. M. Cheremisina, G. K. Parygina, E. A. Kravtsova, *Zh. Neorg. Khim.* **1972**, *17*, 2498.

[12] The NMR features observed by us are very similar to those of indole-Pd(II) complexes reported earlier. Please see: N. V. Kaminskaia, G. M. Ullmann, D. B. Fulton, N. M. Kostić, *Inorg. Chem.* **2000**, *39*, 5004.

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[15] Recently Yuan et al. reported that the $PdCl_2$-mediated allylation with allyl acetate involves the *in situ* generation of Pd(0). It is suggested that the latter catalyzes the allylation *via* Tsuji–Trost mechanism. Please see: F. Yuan, L. Gaoa, F. Han, *Tetrahedron* **2012**, *68*, 6837. Note that allyl acetates are much stronger electrophiles than allyl alcohols. In our case a Pd(0) complex like $Pd_2(dba)_3$ did not show any reactivity in the model reaction (Table 1, entry 18). Thus we tentatively rule out a Tsuji–Trost pathway. In the case of allylic alcohols, a prior activation of the allylic π-bond by Pd(II) is a possibility and is worthy of future investigation.

[16] We thank one of the reviewers for this insightful suggestion.

[17] In this context the studies by Focante and others demonstrating the dramatic enhancement of CH-acidity in indoles and other *N*-heteroaromatics upon reaction with boron electrophiles may be considered as an interesting parallel. For details, please see: a) F. Focante, P. Mercandelli, A. Sironi, L. Resconi, *Coord. Chem. Rev.* **2006**, *250*, 170; b) S. Guidotti, I. camurati, F. Focante, L. Angellini, G. Moscardi, L. Resconi, R. Leardini, D. Nanni, P. Mercandelli, A. Sironi, T. Beringhelli, D. Maggioni, *J. Org. Chem.* **2003**, *68*, 5445.

