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Transition-Metal-Catalyzed Regioselective Alkylation of Indoles with Alcohols

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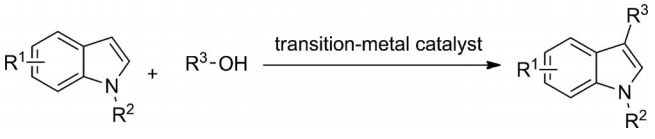
The regioselective alkylation of indoles with alcohols as alkylating reagents was developed by using Pd/C or $RuCl_2(PPh_3)_3$/DPEphos {DPEphos = bis[(2-diphenylphosphanyl)phenyl] ether}as catalysts. The reaction of indole with benzyl alcohol in the presence of Pd/C and K_2CO_3 at 80 °C for 24 h without any solvent under in air yielded 90 % of 3-benzylindole. The corresponding 3-benzylindole was obtained in 99 % yield when the reaction was catalyzed by $RuCl_2(PPh_3)_3$/DPEphos in the presence of K_3PO_4 at 165 °C for 24 h under argon. Several types of alcohols were treated with indoles under these conditions to give the corresponding 3-alkylated indoles in high yields (up to 99 %). This reaction may involve the catalyst-mediated transformation of alcohols to aldehydes, nucleophilic addition of indole to the resulting aldehydes accompanied by dehydration, and then hydrogenation.

Introduction

The development of a new efficient, selective, and green synthetic method for the preparation of 3-substituted indole derivatives has attracted much attention because of the important roles of these compounds, e.g., as versatile building blocks for the synthesis of therapeutic and biologically active compounds, medicines, and natural products.[1] Although the alkylation of indoles has traditionally been performed by using alkyl halides, this is not an ideal method, because of its poor regioselectivity.[2] The regioselective alkylation of indoles has been achieved in reactions with aldehydes,[3] α,β-unsaturated ketones,[4] and other reagents.[5] However, most of these reactions required large amounts of acids and/or expensive reagents, the yields were low, even after long reaction times, and dimerization of the indole sometimes occurred.

Recently, an environmentally friendly method, the so-called "borrowing hydrogen" methodology, has gained acceptance as an efficient green synthetic strategy in organic synthesis.[6,7] This strategy involves the in situ transformation of an alcohol into an aldehyde or ketone, followed by addition of a nucleophile to the resulting carbonyl compound, and then hydrogenation to form the desired product. The only by-product expected is water, so the reaction proceeds with a high atom efficiency. Therefore, the alkylation of indoles with alcohols could be an ideal C–C bond-formation process for the preparation of 3-substituted indoles.[8] An excellent example of this strategy for the alkylation of indoles with alcohols was reported by Grigg and co-workers in 2007 using $[Cp^*IrCl_2]_2$.[8c] However, the reaction was limited to aromatic alcohols, and low yields were observed when aliphatic alcohols were used, even after long reaction times. Aliphatic alcohols were found to be good alkylating agents in their further study on the alkylation of oxindole.[8d] In our current study, several transition metal catalysts have been screened, and we found that Pd/C and $RuCl_2(PPh_3)_3$/DPEphos showed high catalytic activities for the regioselective alkylation of indoles with various types of alcohols, including aliphatic alcohols (Scheme 1).



Scheme 1. This work: regioselective alkylation of indoles with alcohols.

Results and Discussion

Initially, benzyl bromide was treated with indole (**1a**) to give a complex mixture including 3-benzylindole, 1-benzylindole, and 1,3-dibenzylindole. In contrast, the reaction of benzyl alcohol (**2a**) and indole (**1a**) catalyzed by Pd/C proceeded at 150 °C to give 3-benzylindole (**3a**) in 70 % yield. Therefore, the alkylation with benzyl alcohol was ex-

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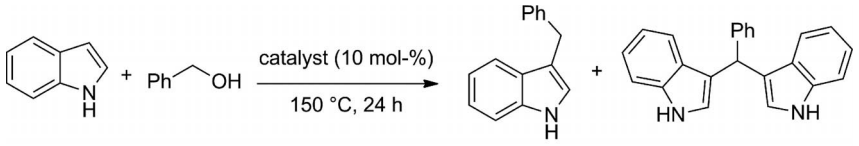
Table 1. Screening of transition metal catalysts.[a]



1a **2a** **3a** **4a**

Entry	Catalyst	KOH [mmol]	Conv. [%][b,c]	**3a** [%][c]	**4a** [%][c]
1	$[Ir(cod)Cl]_2$	0.1	100	41	34
2	$[Ir(cod)Cl]_2$	3.0	100	29	46
3	$[RuCl_2(p\text{-cymene})]_2$	0.2	53	trace	40
4	$RuCl(PPh_3)_3$	0.2	no reaction	–	–
5	$RuCl(PPh_3)_3$	3.0	100	62	32
6	$[RhCl(cod)]_2$	0.1	24	4	18
7	$[RhCl(cod)]_2$	3.0	100	24	64
8	$RhCl(PPh_3)_3$	0.1	100	35	40
9	Pd/C	none	72	70	0
10	Ru/C	none	92	68	0
11	Rh/Al_2O_3	none	100	12	61

[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (2 mL), catalyst (0.1 mmol), at 150 °C for 24 h, under air. [b] Based on indole. [c] Determined by ^{1}H NMR spectroscopy.

amined by using various metal catalysts (Table 1). Several homogeneous complexes, such as $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadiene), $RuCl_2(PPh_3)_3$, $[RhCl(cod)]_2$, and $RhCl(PPh_3)_3$, showed catalytic activities in the presence of base (KOH), and gave benzylated product **3a** in moderate yields along with significant amounts of by-product **4a**. Compound **4a** was the major product when $[RuCl_2(p\text{-cymene})]_2$ was used (Table 1, Entry 3). When heterogeneous Pd/C or Ru/C was used in the absence of KOH, the desired product (i.e., **3a**) was the major product (Table 1, Entries 9 and 10). Bis(3-indolyl)phenylmethane (**4a**) was formed as the major product when the reaction was catalyzed by Rh/Al_2O_3 without any base (Table 1, Entry 11).

On the basis of the above results, Pd/C was selected for further study. During our investigation, we found that when the amount of Pd/C was decreased to 5 mol-%, the reaction occurred without any decrease in yield. To enhance the yield of the product, the reaction temperature and additives were screened next (Table 2). The reaction proceeded smoothly at 150 °C, while at lower temperatures, the yield of product **3a** was decreased (Table 2, Entries 1–3). The addition of K_2CO_3 accelerated the reaction, even at 80 °C, and 1 equiv. of K_2CO_3 was sufficient for product **3a** to be obtained in excellent yield (Table 2, Entries 4 and 5). The addition of Cs_2CO_3 resulted in low yields of the product (Table 2, Entry 6). KOH also affected the reaction, and product **3a** was formed in good yield, even after 2 h, albeit accompanied by a considerable amount of by-product **4a** (Table 2, Entries 7 and 8). Interestingly, NaOH resulted in better selectivity for **3a** than did KOH (Table 2, Entry 9). When formic acid was used, almost equal amounts of product **3a** and by-product **4a** were formed (Table 2, Entry 11).

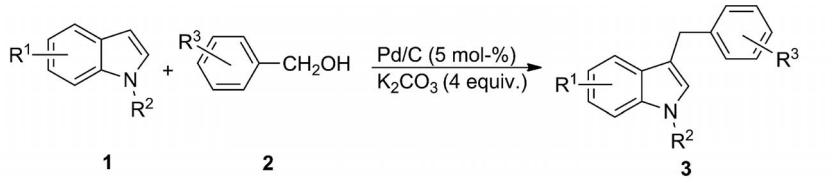
Table 2. Effect of additives on benzylation of indole catalyzed by Pd/C.[a]

Entry	Additive	Temp. [°C]	Time [h]	Conv. [%][b,c]	**3a** [%][c]	**4a** [%][c]
1	none	150	15	72	70	0
2	none	100	15	35	18	0
3	none	80	15	0	0	0
4	K_2CO_3 (4 equiv.)	80	24	100	90	0
5	K_2CO_3 (1 equiv.)	80	24	100	86	0
6	Cs_2CO_3 (2 equiv.)	80	24	100	55	22
7	KOH (4 equiv.)	80	2	100	72	22
8	KOH (1 equiv.)	80	2	100	77	23
9	NaOH (2 equiv.)	80	2	100	90	10
10	$(n\text{Bu})_3N$ (4 equiv.)	100	24	80	16	0
11	HCOOH (4 equiv.)	120	24	64	32	29

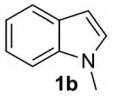
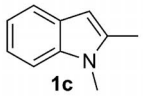
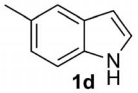
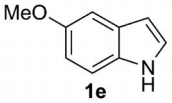
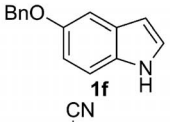
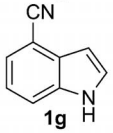
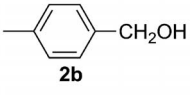
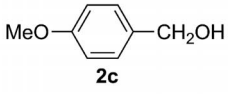
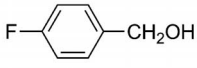
[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (2 mL), Pd/C (0.05 mmol), base, under air. [b] Based on indole. [c] Determined by ^{1}H NMR spectroscopy.

The effect on the reaction of substituents on the substrates was examined next (Table 3). Firstly, several types of indoles were tested. When 1-methylindole was used as a substrate, no product was obtained under the original conditions (Table 3, Entry 2), but running the reaction at a higher temperature and without base resulted in the formation of the product in moderate yield (Table 3, Entry 3). 1,2-Dimethylindole also gave the corresponding product in excellent yield when the reaction was run at higher temperature without any base (Table 3, Entry 5). 5-Methoxyindole showed good reactivity, and gave the product in 99% yield (Table 3, Entry 7), whereas 5-methylindole and 5-benzyloxyindole gave the corresponding products in moderate yields (Table 3, Entries 6 and 8). A lower yield was obtained with 4-cyanoindole (Table 3, Entry 9). Methyl, methoxy, or fluoro substituents at the *para*-position of the benzyl alcohol resulted in decreases in the product yields (Table 3, Entries 10–13).

Table 3. Benzylation of indoles catalyzed by Pd/C.[a]



1 2 3

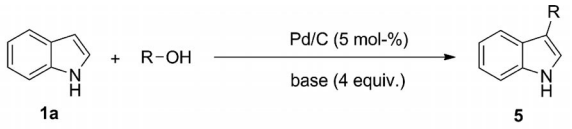
Entry	Indole	Benzyl alcohol	Temp. [°C]	Time [h]	Product	Yield [%][b]
1	**1a**	**2a**	80	24	**3a**	90
2	 **1b**	**2a**	80	24	**3b**	0
3[c]		**2a**	150	14	**3b**	52
4	 **1c**	**2a**	100	24	**3c**	0
5[c]		**2a**	150	24	**3c**	99
6[c]	 **1d**	**2a**	150	24	**3d**	60
7[c]	 **1e**	**2a**	150	24	**3e**	99
8	 **1f**	**2a**	80	24	**3f**	60
9	 **1g**	**2a**	100	24	**3g**	27
10	**1a**	 **2b**	80	24	**3h**	71
11	**1a**	 **2c**	80	24	**3i**	34
12	**1a**		80	72	**3i**	64
13	**1a**	 **2d**	80	24	**3j**	71

[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (2 mL), Pd/C (0.05 mmol), K_2CO_3 (4 mmol), under air. [b] Determined by ^1H NMR spectroscopy. [c] No base was used.

Various types of alcohols were also tested for this reaction (Table 4). The reaction of 2-phenyl-1-ethanol gave product **5a** in 66% yield at 150 °C after 72 h (Table 4, Entry 1). 1-Decanol could also be used for this reaction at 150 °C in the presence of KOH as a base (Table 4, Entry 2). The reactions using 2-phenyl-1-ethanol and 1-decanol as substrates also gave by-products derived from aldehydes. This indicates that the high acidity of the α-proton results in an aldol-type reaction when primary alcohols are used as alkylating agents. Next, secondary alcohols were used as alkylating agents. When 1-phenylethanol was used with K_2CO_3 as a base, no product was formed (Table 4, Entry 3), whereas KOH resulted in the formation of product **5a** in excellent yield (Table 4, Entry 4). Diphenylcarbinol showed a lower reactivity, and gave a 70% yield of the corresponding 3-substituted indole (i.e., **5d**; Table 4, Entry 6). The cyclic and heteroaromatic alcohols cyclohexanol and 2-pyridinemethanol gave the desired products in 88 and 99% yields, respectively (Table 4, Entries 8 and 9).

Having examined heterogeneous catalysis, we broadened our investigation to homogeneous catalysis. $RuCl_2(PPh_3)_3$ was chosen as the catalyst. Although we obtained a 62% yield of **3a** under air, we believed that the reaction would be better carried out under an inert gas, since the catalyst contained phosphanes, which are easily oxidized in air. Moreover, an inert gas would provide a greater opportunity

Table 4. Effect of alcohol structure on the alkylation of indole.[a]



Entry	Alcohol	Base	Temp. [°C]	Product	Yield [%][b]
1[c]	Ph–CH$_2$–CH$_2$–OH	K_2CO_3	150	**5a**	66
2	$C_{10}H_{21}OH$	KOH	150	**5b**	74
3	Ph–CH(CH$_3$)–OH	K_2CO_3	150	**5c**	0
4		KOH	150	**5c**	99
5	Ph–CH(Ph)–OH	K_2CO_3	150	**5d**	trace
6		KOH	100	**5d**	70
7	cyclohexyl–OH	KOH	150	**5e**	88
8	pyridyl–CH$_2$–OH	K_2CO_3	80	**5f**	99

[a] Reaction conditions: indole (1.0 mmol), Pd/C (0.05 mmol), alcohol (19 mmol), base (4 mmol), under air, 24 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Reaction time was 72 h.

to improve the performance of the catalyst, e.g., by the addition of easily oxidized ligands such as diphosphane ligands. We were glad to find that the corresponding 3-benzylindole was formed in 78% yield when the reaction was catalyzed by $RuCl_2(PPh_3)_3$ along with a DPEphos {bis[(2-diphenylphosphanyl)phenyl] ether} ligand (Table 5, Entry 3).

To support our attempts to enhance the efficiency of the catalytic reaction, the amount of catalyst was reduced to 5 mol-%, the amount of KOH to 1 mmol, and the amount of benzyl alcohol to 5 mmol (Table 6). However, the yield decreased to 50%, and the product was accompanied by 40% of bis(3-indolyl)phenylmethane (**4a**; Table 6, Entry 1). Several bases were screened to tune the catalyst performance. K_2CO_3 and Cs_2CO_3 showed similar activities, and **3a** was formed in 66 and 65% yields (Table 6, Entries 2–3). A better result was obtained when Na_2CO_3 was used, and 74% of **3a** was formed (Table 6, Entry 4). Finally, K_3PO_4 was found to give the best result, and the desired 3-benzylindole (**3a**) was formed in 80% yield (Table 6, Entry 6). In contrast, when Na_2HPO_4 or K_2SO_4 were used, bis(3-indolyl)phenylmethane (**4a**) was the major product, and only a trace amount of **3a** was detected (Table 6, Entries 7–8).

Table 6. Effect of base on the benzylation of indole catalyzed by $RuCl_3(PPh_3)_3$/DPEphos.[a]

Entry	Base	Conv. [%][b,c]	**3a** [%][c]	**4a** [%][c]
1	KOH	100	50	40
2	K_2CO_3	94	66	22
3	Cs_2CO_3	100	65	28
4	Na_2CO_3	90	74	7
5	*t*BuOK	100	59	40
6	K_3PO_4	100	80	16
7	Na_2HPO_4	78	3	47
8	K_2SO_4	100	1	54

[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (5.0 mmol), $RuCl_2(PPh_3)_3$ (0.05 mmol), DPEphos (0.05 mmol), base (1 mmol), at 165 °C, under Ar, 24 h. [b] Based on indole. [c] Determined by ^{1}H NMR spectroscopy.

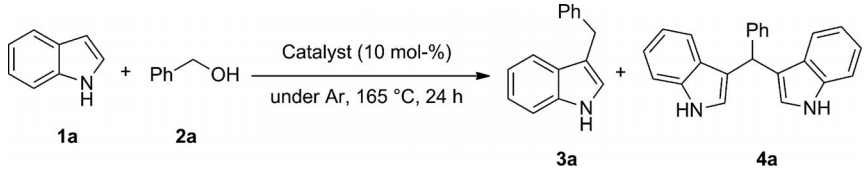
Next, the effects of the catalyst, the amount of base, and the temperature were investigated (Table 7). Initially, the amount of K_3PO_4 was reduced to 0.5 mmol; however, the yield of **3a** decreased to 69% (Table 7, Entry 2). The yield

Table 7. Optimization of reaction conditions.[a]

Entry	Catalyst [mol-%]	K_3PO_4 [mmol]	Temp. [°C]	Conv. [%][b,c]	**3a** [%][c]	**4a** [%][c]
1	5	1	165	100	80	16
2	5	0.5	165	100	69	24
3	5	2	165	100	89	4
4	5	3	165	100	87	2
5	2.5	2	165	100	99	trace
6	1.25	2	165	100	80	20
7	1.25	3	165	100	99	0
8	1.25	3	150	100	91	9
9	1.25	3	120	100	20	66

[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (5 mmol), $RuCl_2(PPh_3)_3$, DPEphos, K_3PO_4, under Ar, 24 h. [b] Based on indole. [c] Determined by ^{1}H NMR spectroscopy.

Table 5. Preliminary catalyst test.[a]

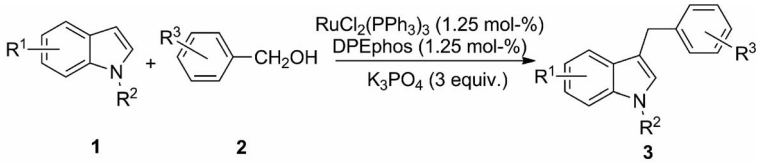


Entry	Catalyst	KOH [mmol]	Conversion [%][b,c]	**3a** [%][c]	**4a** [%][c]
1	$RuCl_3(PPh_3)_3$	0	100	44	56
2	$RuCl_3(PPh_3)_3$	3	100	52	38
3	$RuCl_3(PPh_3)_3$/DPEphos	3	100	78	12

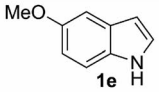
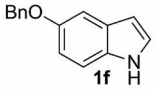
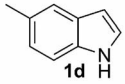
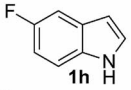
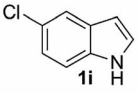
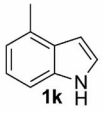
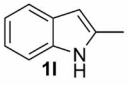
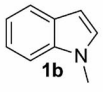
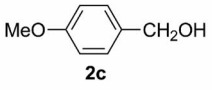
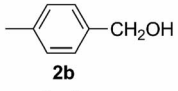
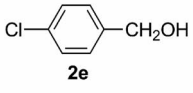
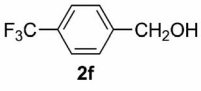
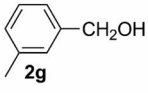
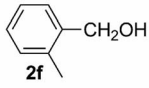
[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (2.0 mL), catalyst (0.1 mmol), KOH, at 165 °C, under Ar, 24 h. [b] Based on indole. [c] Determined by ^{1}H NMR spectroscopy.

increased to 89% when 2 mmol of K_3PO_4 was used (Table 7, Entry 3). Almost the same result was obtained when 3 mmol K_3PO_4 was used (Table 7, Entry 4). Thus, 2 mmol of K_3PO_4 was used in further optimization reactions. When the amount of catalyst was reduced to 2.5 mol-%, 99% of the corresponding product **3a** was formed

Table 8. Substituent effect on the benzylation of indoles catalyzed by $RuCl_2(PPh_3)_3$/DPEPhos.[a]



1 **2** **3**

Entry	Indole	Benzyl alcohol	Product	Yield [%][b]
1	 **1e**	**2a**	**3e**	99
2	 **1f**	**2a**	**3f**	92
3	 **1d**	**2a**	**3d**	99
4	 **1h**	**2a**	**3k**	98
5[c]	 **1i**	**2a**	**3l**	87
6	 **1k**	**2a**	**3m**	99
7	 **1l**	**2a**	**3n**	89
8[c]	 **1b**	**2a**	**3b**	74
9	**1a**	 **2c**	**3i**	90
10	**1a**	 **2b**	**3h**	99
11	**1a**	 **2e**	**3o**	80
12	**1a**	 **2f**	**3p**	67
13	**1a**	 **2g**	**3q**	76
14	**1a**	 **2f**	**3r**	90

[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (5.0 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol), K_3PO_4 (3.0 mmol), at 165 °C, under Ar, 24 h. [b] Determined by ^1H NMR spectroscopy. [c] Amount of benzyl alcohol was 7.0 mmol.

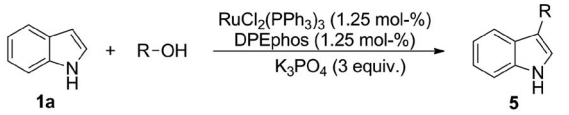
(Table 7, Entry 5), but when the catalyst loading was reduced further to 1.25 mol-%, the yield decreased to 80% (Table 7, Entry 6). However, increasing the amount of K_3PO_4 to 3 mmol with a catalyst loading of 1.25 mol-% gave **3a** in 99% yield (Table 7, Entry 7). The yield of **3a** decreased when the temperature was decreased, while the formation of bis(3-indolyl)phenylmethane (**4a**) increased (Table 7, Entries 8–9).

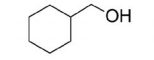
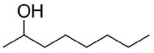
Under the optimized reaction conditions, the scope of substrates was studied. First, the substrate scope for the benzylation of indoles was investigated (Table 8). Indoles with electron-donating substituents such as methoxy, benzyloxy, and methyl, as well as electron-withdrawing substituents such as fluoro and chloro in the 5-position, gave excellent yields (87–99%) of the desired 3-substituted indoles (Table 8, Entries 1–5). Next, a methyl substituent was installed at several positions of the indole. The reaction proceeded smoothly to give excellent yields of the corresponding products when the methyl group was at the C-4 or C-2 position (Table 8, Entries 6 and 7). A 74% yield of the desired 3-substituted indole (i.e., **3b**) was observed when 1-methylindole was used (Table 8, Entry 8). 3-Benzylated indoles **3i** and **3h** were obtained in excellent yields when electron-donating groups, i.e., methoxy and methyl, were installed *para* to the benzyl alcohol (90 and 99%, respectively; Table 8, Entries 9 and 10). The yield decreased when electron-withdrawing groups were installed at the same position (Table 8, Entries 11 and 12). Product **3q** was obtained in 76% yield when the methyl substituent was moved to the *meta* position (Table 8, Entry 13), and an excellent yield of the product was obtained with *ortho*-methylbenzyl alcohol (Table 8, Entry 14).

Having obtained excellent results for the benzylation of indoles, we directed our attention to the scope of the alcohol component in this catalytic reaction. Several types of alcohols were tested (Table 9). The reaction proceeded well with primary aliphatic alcohols such as 1-decanol and cyclohexylmethanol to give the corresponding 3-substituted indoles in excellent yields (94 and 92%, respectively; Table 9, Entries 1 and 2). On the other hand, the secondary alcohol 2-octanol showed a lower reactivity and gave the corresponding 3-substituted indole (i.e., **5h**) in 74% yield (Table 9, Entry 3). We also found that the reaction of indole with secondary aryl alcohols gave the desired 3-substituted indoles in excellent yields (Table 9, Entries 4 and 5). Interestingly, a cyclic alcohol also acted as a good substrate. Thus, when cyclohexanol was used, 96% of the corresponding product was obtained (Table 9, Entry 6).

During the course of our investigations into the preparation of 3-benzylated indoles, bis(3-indolyl)phenylmethane derivatives were often observed as minor products. Although these compounds were not the desired products of our reaction, bis(3-indolyl)phenylmethanes are also useful materials.[9] In 2012, Liu and co-workers reported the one-pot ruthenium-catalyzed preparation of bis(3-indolyl)phenylmethanes by the reaction of indoles and benzylic alcohols.[9b] Surprisingly, we found that these compounds were obtained efficiently by using $RuCl_2(PPh_3)_3$/DPEphos

Table 9. Effect of alcohol structure on the alkylation of indole catalyzed by $RuCl_2(PPh_3)_3$/DPEPhos.[a]



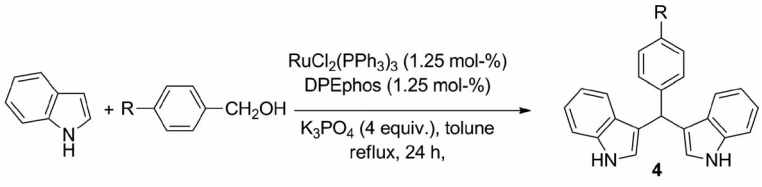
Entry	Alcohol	Product	Yield [%][b]
1	$C_{10}H_{23}OH$	**5b**	94
2		**5g**	92
3		**5h**	74
4		**5c**	93
5[c]		**5d**	93
6		**5e**	96

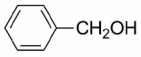
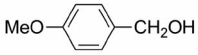
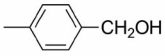
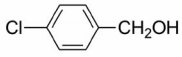
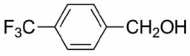
[a] Reaction conditions: indole (1 mmol), alcohol (5 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol), K_3PO_4 (3.0 mmol), at 165 °C, under Ar, 24 h. [b] Determined by ^1H NMR spectroscopy. [c] Reaction time was 30 h.

under reflux conditions in toluene. Several types of benzyl alcohols were examined (Table 10). The reaction yielded the corresponding bis(3-indolyl)phenylmethane in 90% yield when benzyl alcohol was used (Table 10, Entry 1). Excellent yields were also observed when electron-donating substituents were installed at the *para* position of the benzyl alcohol (Table 10, Entries 2 and 3). The yields were slightly decreased when electron-withdrawing substituents such as chloro and trifluoromethyl groups were used (Table 10, Entries 4 and 5).

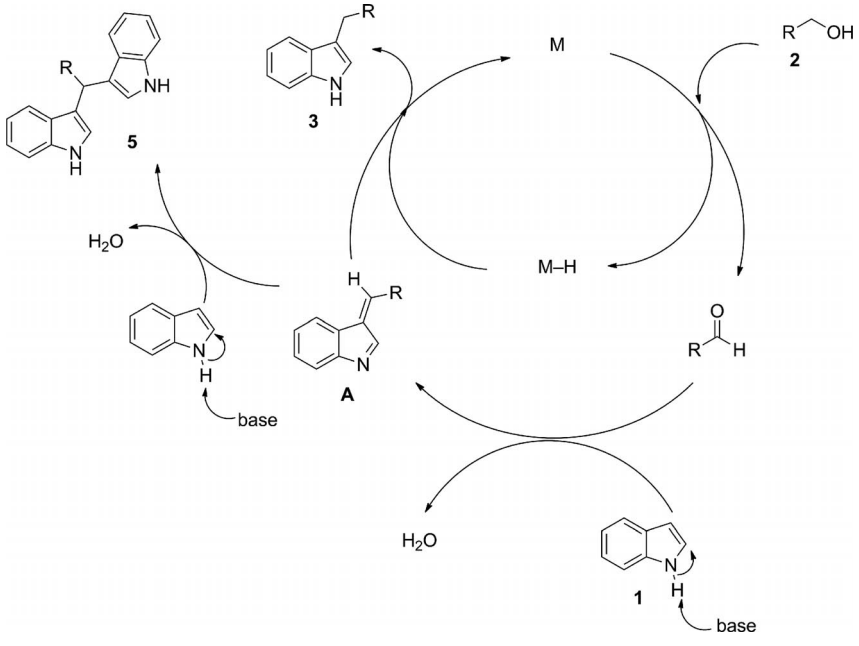
A plausible reaction mechanism (Scheme 2) is proposed as follows. Initially, alcohol **2** is dehydrogenated to give the aldehyde by the catalyst, i.e., Pd/C or $RuCl_2(PPh_3)_3$. The base activates the C-3 position of the indole for nucleophilic reaction. Next, the indole attacks the intermediate aldehyde, and this is followed by dehydration to give intermediate **A**. The carbon–carbon double bond is then hydrogenated to give 3-substituted indole **3**. When the reduction of **A** is slow, bis(3-indolyl)phenylmethane **4** is formed by further nucleophilic reaction of the indole.[8c] *N*-Alkylated products were not detected in our reactions, possibly due to the presence of the base. Under these conditions, *N*-alkylation of the indole by the carbonyl compound arising from the alcohol starting material by the borrowing hydrogen mechanism apparently cannot take place. In 2010, Beller, Williams and co-workers investigated the detailed mechanism of the *N*-alkylation of indoles with alcohols. They found that the *N*-alkylation of indoles with alcohols proceeded smoothly by transformation of the indole into the indoline in the presence of *p*-toluenesulfonic acid (0.025 mol-%).[10]

Table 10. Formation of bis(3-indolyl)phenylmethane derivatives catalyzed by $RuCl_2(PPh_3)_3$/DPEphos.[a]



Entry	Alcohol	Product	Yield [%][b]
1		**4a**	90
2		**4b**	91
3		**4c**	87
4		**4d**	70
5		**4e**	70

[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (2.0 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol), K_3PO_4 (4.0 mmol), reflux in toluene (1 mL), under Ar, 24 h. [b] Determined by ^1H NMR spectroscopy.



Scheme 2. Plausible reaction mechanism.

Conclusions

We report that Pd/C and $RuCl_2(PPh_3)_3$/DPEphos effectively catalyze the alkylation of indole with alcohols to give 3-substituted indoles with high selectivities. Various types of substrates were examined and were found to give the corresponding 3-substituted indoles in high yield. Moreover, bis(3-indolyl)phenylmethane derivatives could be selectively formed by using $RuCl_2(PPh_3)_3$/DPEphos under different reaction conditions.

Experimental Section

General Remarks: Nuclear magnetic resonance spectra were measured by using Varian Mercury plus 300-4N spectrometers with

tetramethylsilane as the internal standard for ^{1}H NMR spectra, and $CDCl_3$ at δ = 77 ppm for ^{13}C NMR spectra. Mass spectra (GC–MS) were recorded with a Shimadzu QP5000 instrument. High-resolution mass spectra (FAB) were recorded by using a JEOL JMS-700 instrument with *meta*-nitrobenzyl alcohol as the matrix and PEG-200 as the calibration standard. Commercially available compounds were used without further purification.

Benzylation of Indoles Catalyzed by Pd/C: Indole (1.0 mmol), K_2CO_3 (1.0 mmol), Pd/C (0.05 mmol), and benzyl alcohol (2.0 mL) were mixed in a Schlenk tube (80 mL), and then the mixture was stirred at 80 °C for 24 h. The reaction mixture was diluted with diethyl ether, and the catalyst was removed by filtration through a Celite pad. The filtrate was concentrated under reduced pressure. The excess benzyl alcohol was removed by Kugelrohr distillation. The crude product was purified by column chromatography or recrystallization from hexane to give the corresponding 3-benzylated indole.

Benzyation of Indoles Catalyzed by $RuCl_2(PPh_3)_3$/DPEphos: Indole (1.0 mmol), K_3PO_4 (3.0 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol), and benzyl alcohol (5 mmol) were mixed in an argon-purged Schlenk tube (20 mL). The mixture was degassed by three cycles of the freeze–pump–thaw method, then it was purged with argon and stirred at 165 °C for 24 h. The reaction mixture was filtered, and the solvent was evaporated under reduced pressure. The excess benzyl alcohol was removed by Kugelrohr distillation. The crude product was purified by column chromatography or recrystallization from hexane to give the corresponding 3-benzylated indole.

3-Benzyl-1*H*-indole (3a):[11] White solid; m.p. 104–107 °C. ^{1}H NMR ($CDCl_3$): δ = 4.12 (s, 2 H, -C*H*-Ph), 6.91 (d, *J* = 2.4 Hz, 1 H, -NH-C*H*=), 7.07 (t, *J* = 6.9 Hz, 1 H, Ar), 7.15–7.30 (m, 6 H, Ar), 7.35 (d, *J* = 8.1 Hz, 1 H, Ar), 7.51 (d, *J* = 7.8 Hz, 1 H, Ar), 7.94 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.5, 110.9, 115.6, 118.9, 119.1, 121.8, 122.1, 125.7, 127.2, 128.1, 128.4, 136.2, 141.0 ppm. GC–MS: *m*/*z* = 207. HRMS (FAB, *m*-NBA): calcd. for $C_{15}H_{13}N$ 207.1048; found 207.1038.

3-Benzyl-1-methyl-1*H*-indole (3b):[12] White solid; m.p. 51–53 °C. ^{1}H NMR ($CDCl_3$): δ = 3.80 (s, 3 H, -NCH_3), 4.11 (s, 2 H, -CH_2-Ph), 6.75 (s, 1 H, -NH-CH-), 7.07 (t, *J* = 6.9 Hz, 1 H, Ar), 7.15–7.30 (m, 6 H, Ar), 7.35 (d, *J* = 8.1 Hz, 1 H, Ar), 7.51 (d, *J* = 7.8 Hz, 1 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.5, 108.9, 114.1, 118.6, 119.0, 121.4, 125.6, 126.9, 127.6, 128.1, 128.5, 136.9, 141.2 ppm. GC–MS: *m*/*z* = 221. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{15}N$ 221.1205; found 221.1192.

3-Benzyl-1,2-dimethyl-1*H*-indole (3c):[13] Pale brown solid; m.p. 48–50 °C. ^{1}H NMR ($CDCl_3$): δ = 2.37 (s, 3 H, -NCH_3-CCH_3), 3.65 (s, 3 H, -NCH_3-CCH_3), 4.08 (s, 2 H, -CH_2-Ph), 7.01 (t, *J* = 7.3 Hz, 1 H, Ar), 7.08–7.27 (m, 7 H, Ar), 7.40 (d, *J* = 7.3 Hz, 1 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.4, 29.5, 30.3, 108.3, 109.6, 118.1, 118.6, 120.3, 125.4, 127.7, 128.0, 128.1, 133.3, 136.4, 141.7 ppm. GC–MS: *m*/*z* = 235. HRMS (FAB, *m*-NBA): calcd. for $C_{17}H_{17}N$ 235.1361; found 235.1363.

3-Benzyl-5-methyl-1*H*-indole (3d):[14] Brown solid; m.p. 108.5–113 °C. ^{1}H NMR ($CDCl_3$): δ = 2.40 (s, 3 H, Ar-CH_3), 4.06 (s, 2 H, -CH_2-Ph), 6.81 (d, *J* = 2.4 Hz, 1 H, -NH-C*H*=), 7.10–7.51 (m, 8 H, Ar), 8.05 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.6, 31.4, 110.5, 115.1, 118.5, 122.3, 123.4, 125.6, 127.5, 128.1, 128.4, 134.5, 141.1 ppm. GC–MS: *m*/*z*= 221. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{15}N$ 221.1205; found 221.1214.

3-Benzyl-5-methoxy-1*H*-indole (3e):[8c] White solid; m.p. 61–62 °C. ^{1}H NMR ($CDCl_3$): δ = 3.80 (s, 3 H, -OCH_3-), 4.08 (s, 2 H, Ph-CH_2-), 6.82–6.88 (m, 2 H, Ar), 6.93 (s, 1 H, -NH-C*H*=), 7.15–7.37 (m, 6 H, Ar), 7.85 (s, 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.6, 55.8, 100.9, 111.6, 111.9, 115.3, 123.0, 125.7, 127.7, 128.1, 128.5, 131.5, 140.9, 153.7 ppm. GC–MS: *m*/*z* = 237. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{15}NO$ 237.1154; found 237.1136.

3-Benzyl-5-benzyloxy-1*H*-indole (3f): Brown solid; m.p. 97.5–101 °C. ^{1}H NMR ($CDCl_3$): δ = 4.06 (s, 2 H, -CH-CH_2-Ph), 5.03 (s, 2 H, -O-CH_2-Ph), 6.86 (d, *J* = 2.1 Hz, 1 H, Ar), 6.91 (dd, *J* = 7.8, 2.4 Hz, 1 H, Ar), 7.02 (s, 1 H, Ar), 7.16–7.38 (m, 9 H, Ar), 7.43 (d, *J* = 7.8 Hz, 2 H, Ar), 7.82 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.6, 70.8, 102.6, 111.6, 112.7, 115.4, 123.0, 125.7, 127.4, 127.5, 128.1, 128.3, 128.4, 131.6, 137.4, 140.5, 140.9, 152.9 ppm. GC–MS: *m*/*z* = 313. HRMS (FAB, *m*-NBA): calcd. for $C_{22}H_{19}NO$ 313.1468; found 313.1474.

3-Benzyl-4-cyano-1*H*-indole (3g): Pale pink solid; m.p. 126.5–129 °C. ^{1}H NMR ($CDCl_3$): δ = 4.37 (s, 2 H, -CH_2-Ph), 6.88 (s, 1 H, -NH-C*H*=), 7.16–7.41 (m, 6 H, Ar), 7.45 (d, *J* = 7.2 Hz, 1 H, Ar), 7.52 (d, *J* = 8.1 Hz, 1 H, Ar), 8.51 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.1, 102.1, 115.8, 116.3, 119.2, 121.4, 125.6, 125.9, 126.2, 128.2, 128.8, 130.9, 140.3 ppm. GC–MS: *m*/*z* = 223. HRMS (FAB, *m*-NBA): calcd. for $C_{15}H_{13}NO$ 223.0998; found 223.0983.

3-(4-Methylbenzyl)-1*H*-indole (3h):[15] Pale yellow solid; m.p. 89.5–91 °C. ^{1}H NMR ($CDCl_3$): δ = 2.31 (s, 3 H, -CH_3), 4.07 (s, 2 H, -CH_2-C_6H_4-), 6.89 (d, *J* = 2.1 Hz, 1 H, -NH-C*H*=), 7.03–7.08 (m, 3 H, Ar), 7.14–7.19 (m, 3 H, Ar), 7.34 (d, *J* = 8.1 Hz, 1 H, Ar), 7.51 (d, *J* = 8.1 Hz, 1 H, Ar), 7.94 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.0, 31.1, 110.8, 115.9, 119.0, 119.1, 121.8, 122.0, 128.3, 128.4, 128.8, 128.9, 135.0, 137.9 ppm. GC–MS: *m*/*z* = 221. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{15}N$ 221.1205; found 221.1192.

3-(4-Methoxybenzyl)-1*H*-indole (3i):[8c] Pale yellow solid; m.p. 80.5–83 °C. ^{1}H NMR ($CDCl_3$): δ = 3.77 (s, 3 H, -CH_3), 4.05 (s, 2 H, -CH_2-C_6H_4-), 6.83 (d, *J* = 8.1 Hz, 2 H, Ar), 6.86 (d, *J* = 2.1 Hz, 1 H, -NH-C*H*), 7.07 (t, *J* = 7.5 Hz, 1 H, Ar), 7.14–7.22 (m, 3 H, Ar), 7.34 (d, *J* = 8.1 Hz, 1 H, Ar), 7.51 (d, *J* = 8.1 Hz, 1 H, Ar), 7.88 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.7, 55.2, 110.9, 113.6, 116.1, 119.0, 119.1, 121.8, 122.0, 127.2, 129.4, 133.1, 136.2, 157.5 ppm. GC–MS: *m*/*z* = 237. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{15}NO$ 237.1154; found 237.1172.

3-(4-Fluorobenzyl)-1*H*-indole (3j):[15] White solid; m.p. 87–89 °C. ^{1}H NMR ($CDCl_3$): δ = 4.08 (s, 2 H, -CH_2-C_6H_4-), 6.87–6.97 (m, 3 H, Ar), 7.07 (t, *J* = 6.9 Hz, 1 H, Ar), 7.15–7.24 (m, 3 H, Ar), 7.36 (d, *J* = 8.1 Hz, 1 H, Ar), 7.47 (d, *J* = 7.8 Hz, 1 H, Ar), 7.97 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.8, 110.9, 114.7, 115.0, 115.5, 118.9, 119.2, 122.0, 127.1, 129.8, 136.3, 136.5, 161.0 ppm. GC–MS: *m*/*z* = 225. HRMS (FAB, *m*-NBA): calcd. for $C_{15}H_{12}NF$ 225.0954; found 225.0978.

3-Benzyl-5-fluoro-1*H*-indole (3k):[8c] Colorless micro-needles; m.p. 122–126 °C. ^{1}H NMR ($CDCl_3$): δ = 4.05 (s, 2 H, CH_2-Ph), 6.88 (dd, *J* = 8.85, 2.7 Hz, 1 H, Ar), 6.95 (s, 1 H, NH-C*H*), 7.10 (dd, *J* = 9.75, 2.7 Hz, 1 H, Ar), 7.14–7.31 (m, 6 H, Ar), 7.90 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.52, 103.89, 104.19, 110.20, 110.56, 111.52, 124.06, 125.99, 128.37, 128.58, 132.90, 140.74, 159.23 ppm. HRMS (FAB, *m*-NBA): calcd. for $C_{15}H_{12}FN$ 225.0954; found 225.0969.

3-Benzyl-5-chloro-1*H*-indole (3l):[16] Colorless micro-needles; m.p. 82–84 °C. ^{1}H NMR ($CDCl_3$): δ = 4.05 (s, 2 H, CH_2-Ph), 6.91 (s, 1 H, NH-C*H*), 7.13 (dd, *J* = 8.7, 1.8 Hz, 1 H, Ar), 7.13–7.31 (m, 6 H, Ar), 7.47 (d, *J* = 1.8 Hz, 1 H, Ar), 7.92 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.68, 112.02, 115.62, 118.60, 122.34,

123.68, 125.08, 126.02, 128.40, 128.56, 134.73, 140.65 ppm. GC–MS: *m*/*z* = 241.

3-Benzyl-4-methyl-1*H*-indole (3m):[15] Pale yellow solid; m.p. 84–86 °C. ^{1}H NMR ($CDCl_3$): δ = 2.54 (s, 3 H, -CH_2-CH_3), 4.28 (s, 2 H, CH_2-Ph), 6.75 (s, 1 H, NH-C*H*-), 6.78 (d, *J* = 8.7 Hz, 1 H, Ar), 7.02 (t, *J* = Hz, 1 H8.1 Ar), 7.15–7.29 (m, 6 H), 7.85 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.13, 33.30, 108.98, 115.97, 120.92, 122.14, 123.18, 125.79, 126.06, 128.29, 128.56, 131.10, 136.96, 141.93 ppm. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{15}N$ 221.1204; found 221.1192.

3-Benzyl-2-methyl-1*H*-indole (3n):[8c] Colorless micro-needles; m.p. 115–118 °C. ^{1}H NMR ($CDCl_3$): δ = 2.33 (s, 3 H,NH-C-CH_3), 4.05 (s, 2 H, -CH_2-Ph), 6.98–7.09 (m, 2 H, Ar), 7.11–7.15 (m, 1 H, Ar), 7.18–7.25 (m, 5 H, Ar), 7.36 (d, *J* = 7.5 Hz, 1 H, Ar), 7.66 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.80, 30.12, 109.98, 110.16, 110.56, 118.39, 119.27, 121.01, 125.68, 128.29, 128.92, 131.67, 135.28, 141.68 ppm. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{15}N$ 221.1204; found 221.1214.

3-(4-Chlorobenzyl)-1*H*-indole (3o):[8c] White solid; m.p. 101–102 °C. ^{1}H NMR ($CDCl_3$): δ = 4.07 (s, 2 H, -CH_2-C_6H_4-), 6.91 (s, 1 H, NH-C*H*=), 7.04 (t, *J* = 8.1 Hz, 1 H, Ar), 7.16–7.25 (m, 5 H, Ar), 7.37 (d, *J* = 7.8 Hz, 1 H, Ar), 7.47 (d, *J* = 7.8 Hz, 1 H, Ar), 7.95 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.97, 111.12, 115.26, 119.03, 119.53, 122.19, 122.34, 127.24, 128.40, 129.99, 131.58, 136.44, 139.65 ppm. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{12}ClN$ 241.0658; found 241.0638.

3-[4-(Trifluoromethyl)benzyl]-1*H*-indole (3p):[17] White solid; m.p. 95–97 °C. ^{1}H NMR ($CDCl_3$): δ = 4.17 (s, 2 H, -CH_2-C_6H_4-), 6.94 (s, 1 H, NH-C*H*=), 7.11 (t, *J* = 7.8 Hz, 1 H, Ar), 7.22 (t, *J* = 8.1 Hz, 1 H, Ar), 7.39 (d, *J* = 9.3 Hz, 3 H, Ar), 7.40–7.54 (m, 3 H, Ar), 7.99 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.44, 111.18, 114.66, 118.95, 119.56, 122.26, 122.44, 125.21, 125.27, 127.19, 128.88, 136.44, 145.35 ppm. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{12}F_3N$ 275.0922; found 275.0924.

3-(3-Methylbenzyl)-1*H*-indole (3q): Pale brown solid; m.p. 48–49 °C. ^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 3 H, -C_6H_4-CH_3), 4.07 (s, 2 H, -CH_2-C_6H_4-), 6.89 (s, 1 H, NH-C*H*=), 6.98 (d, *J* = 9.3 Hz, 1 H, Ar), 7.04–7.10 (m, 3 H, Ar), 7.13–7.20 (m, 2 H, Ar), 7.35 (d, *J* = 8.1 Hz, 1 H, Ar), 7.54 (d, *J* = 9 Hz, 1 H, Ar), 7.89 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.45, 31.51, 111.03, 115.95, 119.17, 119.34, 122.01, 122.28, 125.73, 126.63, 127.50, 128.22, 129.47, 136.41, 137.86, 141.13 ppm. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{15}N$ 221.1204; found 221.1192.

3-(2-Methylbenzyl)-1*H*-indole (3r): Pale pink solid; m.p. 52–53 °C. ^{1}H NMR ($CDCl_3$): δ = 2.32 (s, 3 H, -C_6H_4-CH_3), 4.06 (s, 2 H, -CH_2-C_6H_4-), 6.70 (s, 2 H, NH-C*H*-), 7.07–7.23 (m, 6 H, Ar), 7.36 (d, *J* = 8.1 Hz, 1 H, Ar), 7.57 (d, *J* = 8.1 Hz, 1 H, Ar), 7.88 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.47, 29.23, 111.04, 115.18, 119.03, 119.30, 122.02, 122.35, 125.91, 126.14, 127.53, 129.37, 130.09, 136.42, 139.05 ppm. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{15}N$ 221.1204; found 221.1192.

Synthesis of Bis(3-indolyl)phenylmethane Derivatives Catalyzed by $RuCl_2(PPh_3)_3$: Indole (1.0 mmol), benzyl alcohol (2.0 mmol), K_3PO_4 (4.0 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol), and toluene (1 mL) were mixed in an argon-purged Schlenk tube (20 mL). The mixture was degassed by using three cycles of the freeze–pump–thaw method, then it was purged with argon and stirred at 120 °C for 24 h. The reaction mixture was filtered and concentrated in vacuo, and the residue was purified by column chromatography.

Bis(3-indolyl)phenylmethane (4a):[9b] Pink solid. ^{1}H NMR ($CDCl_3$): δ = 5.87 (s, 1 H, Ph-C*H*), 6.63 (s, 2 H, -NH-C*H*=), 6.99 (t, *J* = 7.8 Hz, 2 H, Ar), 7.15 (t, *J* = 7.0 Hz, 2 H, Ar), 7.19–7.39 (m, 9 H, Ar), 7.90 (s, 2 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 40.1, 110.8, 119.0, 119.5, 119.7, 121.7, 123.4, 125.9, 126.9, 128.0, 128.5, 136.4, 143.8 ppm. GC–MS: *m*/*z* = 322. HRMS (FAB, *m*-NBA): calcd. for $C_{23}H_{18}N_2$ 322.1470; found 322.1471.

Bis(3-indolyl)(4-methoxyphenyl)methane (4b):[9b] Orange solid. ^{1}H NMR ($CDCl_3$): δ = 3.81 (s, 3 H, -OCH_3), 5.83 (s, 1 H, Ph-C*H*), 6.65 (s, 2 H, -NH-C*H*=), 6.83 (d, *J* = 8.7 Hz, 2 H, Ar), 7.02 (t, *J* = 7.2 Hz, 2 H, Ar), 7.18 (t, *J* = 8.4 Hz, 2 H, Ar), 7.36 (d, *J* = 8.1 Hz, 2 H, Ar), 7.40 (d, *J* = 9.6 Hz, 2 H, Ar), 7.89 (s, 2 H, N*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 39.3, 55.2, 111.0, 113.5, 119.2, 119.8, 120.1, 121.9, 123.5, 127.0, 129.6, 136.2, 136.7, 157.9 ppm.

Bis(3-indolyl)(4-methylphenyl)methane (4c):[9b] Orange solid. ^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3 H, -CH_3), 5.83 (s, 1 H, Ph-C*H*), 6.60 (s, 2 H, -NH-C*H*=), 7.01 (t, *J* = 6.9 Hz, 2 H, Ar), 7.08 (d, *J* = 8.1 Hz, 2 H, Ar), 7.17 (t, *J* = 8.1 Hz, 2 H, Ar), 7.22 (d, *J* = 8.4 Hz, 2 H, Ar), 7.32 (d, *J* = 9.3 Hz, 2 H, Ar), 7.39 (d, *J* = 7.8 Hz, 2 H), 7.79 (s, 2 H, N*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.0, 39.7, 110.9, 119.1, 119.8, 119.9, 121.8, 123.5, 127.0, 128.5, 128.8, 135.4, 136.6, 140.9 ppm.

(4-Cholorophenyl)bis(3-indolyl)methane (4d):[9b] Orange solid. ^{1}H NMR ($CDCl_3$): δ = 5.85 (s, 1 H, Ph-C*H*), 6.64 (s, 2 H, -NH-C*H*=), 7.03 (t, *J* = 8.1 Hz, 2 H, Ar), 7.08 (d, *J* = 8.1 Hz, 2 H, Ar), 7.15–7.22 (m, 4 H, Ar), 7.37 (d, *J* = 8.7 Hz, 4 H, Ar), 7.92 (s, 2 H, N*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 39.6, 111.1, 119.1, 119.3, 119.8, 122.0, 123.5, 126.8, 128.3, 130.0, 131.7, 136.6, 142.5 ppm.

Bis(3-indolyl)[4-(trifluoromethyl)phenyl]methane (4e):[9b] Brown solid. ^{1}H NMR ($CDCl_3$): δ = 5.83 (s, 1 H, Ph-C*H*), 6.57 (s, 2 H, -NH-C*H*=), 7.02 (t, *J* = 8.7 Hz, 2 H, Ar), 7.13–7.22 (m, 4 H, Ar), 7.35 (t, *J* = 8.4 Hz, 4 H, Ar), 7.82 (s, 2 H, N*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.9, 39.5, 111.1, 119.1, 119.2, 119.7, 122.0, 123.5, 126.8, 128.3, 130.0, 131.7, 136.5, 142.5 ppm.

Alkylation of Indoles Catalyzed by Pd/C: Indole (1.0 mmol), K_2CO_3 (1.0 mmol), Pd/C (0.05 mmol), and alcohol (19 mmol) were mixed in a Schlenk tube (80 mL), and then the mixture was heated at 80 °C for 24 h. The reaction mixture was diluted with diethyl ether, and the catalyst was removed by filtration through a Celite pad. The filtrate was concentrated under reduced pressure. The excess alcohol was removed by Kugelrohr distillation. The crude product was purified by column chromatography or recrystallization from hexane to give the corresponding 3-substituted indole.

Alkylation of Indoles Catalyzed by $RuCl_2(PPh_3)_3$/DPEphos: Indole (1.0 mmol), K_3PO_4 (3.0 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol), and the corresponding alcohol (5 mmol) were mixed in an argon-purged Schlenk tube (20 mL). The mixture was degassed by using three cycles of the freeze–pump–thaw method, then it was purged with argon and stirred at 165 °C for 24 h. The reaction mixture was filtered, and the solvent was evaporated under reduced pressure. The excess alcohol was removed by Kugelrohr distillation. The crude product was purified by column chromatography or recrystallization from hexane to give the corresponding 3-substituted indole.

3-(2-Phenylethyl)-1*H*-indole (5a):[18] White solid; m.p. 108.5–112.5 °C. ^{1}H NMR ($CDCl_3$): δ = 3.05–3.07 [m, 4 H, -(CH_2)$_2$-], 6.91 (d, *J* = 2.4 Hz, 1 H, -NH-C*H*=), 7.07–7.41 (m, 8 H, Ar), 7.63 (d, *J* = 7.1 Hz, 1 H), 7.87 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.2, 36.4, 110.9, 116.0, 118.7, 119.0, 121.1, 121.7, 125.6, 127.2, 128.1, 128.3, 136.1, 142.2 ppm. GC–MS: *m*/*z* = 221. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{15}N$ 221.1205; found 221.1214.

3-Decyl-1*H*-indole (5b):[19] Yellow oil. ^{1}H NMR ($CDCl_3$): δ = 0.86–1.47 [m, 17 H, -(C*H*$_2$)$_7$-C*H*$_3$], 1.70 [quintet, J = 7.8 Hz, 2 H, -C*H*$_2$-(CH$_2$)$_7$-CH$_3$], 2.74 [t, J = 7.8 Hz, 2 H, -C*H*$_2$-(CH$_2$)$_8$-CH$_3$], 6.95 (s, 1 H, -NH-C*H*=), 7.09 (t, J = 7.5 Hz, 1 H, Ar), 7.16 (t, J = 7.5 Hz, 1 H, Ar), 7.33 (d, J = 7.5 Hz, 1 H, Ar), 7.60 (d, J = 7.5 Hz, 1 H, Ar), 8.00 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 25.1, 29.3, 29.5, 29.7 (×3), 30.1, 31.9, 110.8, 117.0, 118.8 (×2), 120.8, 121.6, 127.4, 136.1 ppm. GC–MS: *m*/*z* = 257. HRMS (FAB, *m*-NBA): calcd. for $C_{18}H_{27}N$ 257.2144; found 257.2125.

3-(1-Phenylethyl)-1*H*-indole (5c):[19] White solid; m.p. 70–71 °C. ^{1}H NMR ($CDCl_3$): δ = 1.63 (d, J = 7.0 Hz, 3 H, -CH-C*H*$_3$), 4.31 (q, J = 7.0 Hz, 1 H, -C*H*-CH$_3$), 6.95–7.05 (m, 2 H, Ar), 7.10–7.36 (m, 8 H, Ar), 10.86 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.4, 36.9, 110.8, 119.0, 119.5, 120.9, 121.3, 121.8, 125.7, 126.7, 127.2, 128.1, 136.4, 146.6 ppm. GC–MS: *m*/*z* = 221. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{15}N$ 221.1205; found 221.1214.

3-(Diphenylmethyl)-1*H*-indole (5d):[20] White solid; m.p. 125–126 °C. ^{1}H NMR ($CDCl_3$): δ = 5.66 [s, 1 H, -C*H*(Ph)$_2$], 6.53 (s, 1 H, Ar), 7.01 (t, J = 7.0 Hz, 1 H, Ar), 7.10–7.35 (m, 13 H, Ar), 7.91 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 48.7, 110.9, 119.2, 119.7, 121.9, 123.8, 126.0, 126.8, 128.1, 128.3, 128.8, 136.4, 143.7 ppm. GC–MS: *m*/*z* = 283. HRMS (FAB, *m*-NBA): calcd. for $C_{21}H_{17}N$ 283.1361; found 283.1363.

3-Cyclohexyl-1*H*-indole (5e):[21] Brown solid; m.p. 72–77 °C. ^{1}H NMR ($CDCl_3$): δ = 1.18–2.12 [m, 10 H, -(C*H*$_2$)$_5$-], 2.93 (br., 1 H, C*H*-), 6.92 (s, 1 H, -NH-C*H*=), 7.08 (t, J = 7.5 Hz, 1 H, Ar), 7.16 (t, J = 7.5 Hz, 1 H, Ar), 7.33 (d, J = 7.5 Hz, 1 H, Ar), 7.65 (d, J = 7.5 Hz, 1 H, Ar), 7.91 (br., 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.5, 26.9, 34.0, 35.4, 110.9, 118.7, 119.1 (×2), 121.6, 123.0, 126.6, 136.2 ppm. GC–MS: *m*/*z* = 199. HRMS (FAB, *m*-NBA): calcd. for $C_{14}H_{17}N$ 199.1361; found 199.1362.

3-(Pyridin-2-ylmethyl)-1*H*-indole (5f):[22] White solid; m.p. 89–90 °C. ^{1}H NMR ($CDCl_3$): δ = 4.31 (s, 2 H, -C*H*$_2$-), 7.04–7.20 (m, 6 H, Ar), 7.35 (d, J = 8.1 Hz, 1 H, Ar), 7.51 (d, J = 7.8 Hz, 1 H, Ar), 8.08 (br., 1 H, -N*H*-), 8.55 (d, J = 3.9 Hz, 1 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.5, 111.0, 113.4, 118.9, 119.1, 120.9, 121.7 (×2), 122.6, 126.2, 136.3, 148.7, 161.0 ppm. GC–MS: *m*/z = 208. HRMS (FAB, *m*-NBA): calcd. for $C_{14}H_{12}N_2$ 208.1000; found 208.1004.

3-(Cyclohexylmethyl)-1*H*-indole (5g): White solid; m.p. 64–66 °C. ^{1}H NMR ($CDCl_3$): δ = 0.94–1.03 (m, 2 H, -Cy), 1.15–122 (m, 2 H, -Cy), 1.56–1.73 (m, 6 H, -Cy), 2.63 (d, J = 6.9 Hz, 2 H, CH-C*H*$_2$-), 6.93 (s, 1 H, -NH-C*H*=), 7.07–7.19 (m, 2 H, Ar), 7.35 (d, J = 1.8 Hz, 1 H, Ar), 7.61 (d, J = 7.8 Hz, 1 H), 7.85 (s, 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.3, 26.5, 33.0, 33.5, 38.7, 110.8, 115.4, 118.9, 119.1, 121.6, 121.8, 127.9, 136.1 ppm. GC–MS: *m*/*z* = 213.

3-(1-Methylheptyl)-1*H*-indole (5h):[5b] Pale yellow oil. ^{1}H NMR ($CDCl_3$): δ = 0.83–0.90 (m, 3 H, -CH$_2$-C*H*$_3$), 1.25–131 (m, 8 H, -C$_4$*H*$_8$-CH$_3$), 1.35 (d, J = 6.9 Hz, 3 H, CH-CH$_3$), 1.58–1.62 (m, 1 H), 1.75–1.80 (m, 1 H), 3.05 (m, 1 H, CH$_3$-C*H*), 6.94 (s, 1 H, -NH-C*H*=), 7.06–7.19 (m, 2 H, Ar), 7.36 (d, J = 6.9 Hz, 1 H, Ar), 7.66 (d, J = 3.8 Hz, 1 H), 7.86 (s, 1 H, -N*H*-) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 21.3, 22.6, 27.6, 29.5, 30.80, 31.87, 37.65, 111.0, 118.9, 119.4, 119.7, 121.7, 122.9, 126.9, 136.4 ppm. HRMS (FAB, *m*-NBA): calcd. for $C_{16}H_{23}N$ 229.1830; found 229.1850.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds **3a**–**3r**, **4a**–**4e**, and **5a**–**5h**.

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