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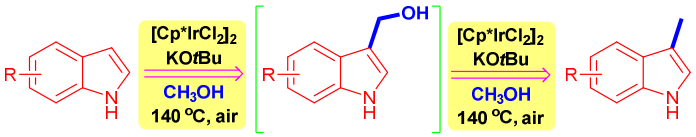

A $[Cp^*IrCl_2]_2$-catalyzed method for the direct methylation of indoles and pyrroles using the abundant and bio-renewable methanol as C1 feedstock.

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Iridium-catalyzed methylation of indoles and pyrroles using methanol as feedstock

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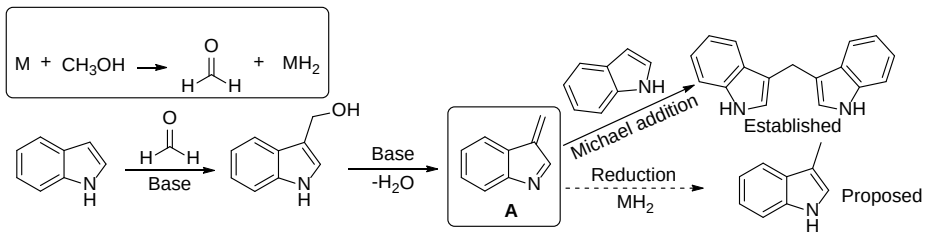
Iridium-catalyzed methylation of indoles and pyrroles using methanol as the methylating agent was achieved. This transformation takes place *via* borrowing hydrogen methodology under an air atmosphere, which constitutes a direct route to 3-methyl-indoles and methyl-pyrroles.

Borrowing hydrogen methodology, which is also known as hydrogen autotransfer, has emerged as an efficient synthetic strategy for the construction of C-N and C-C bonds in organic synthesis, especially as it represents an atom economic and green processes.[1-2] Since a pioneering work conducted by Grigg, who reported a ruthenium-catalyzed monoalkylation of arylacetonitriles using alcohols as alkylating agents *via* so-called borrowing hydrogen methodology,[3] the transition-metal-catalyzed alkylation of C-nucleophiles with alcohols has been investigated extensively by numerous research groups.[2] However, most of these reactions were restricted to activated (aromatic) alcohols and long-chain alkyl alcohols. The application of methanol in alkylation reactions based on hydrogen borrowing methodologies is less developed, although it is abundant and bio-renewable. It's believed that the relatively high energetic demand of methanol dehydrogenation (ΔH = +84 kJ mol^{-1}) compared to higher alcohols, e.g. ethanol (ΔH = +68 kJ mol^{-1}), led to the situation.[4] Nevertheless, some pioneering works using methanol as C1 feedstock for C-C bond formation were realized in recent years. In 2011, Krische and co-workers reported an iridium-catalysed direct C-C coupling of methanol and allenes to furnish higher alcohols.[5] Moreover, contributions from the groups of Donohoe,[6] Obora,[7] Andersson,[8] and Beller[9] have demonstrated methylation of ketones or alcohol in the presence of rhodium- or iridium-complexes.

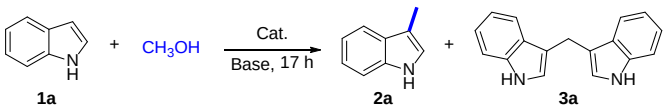
Based on the development of catalytic methanol dehydrogenation,[10] we envisioned the possibility of a direct coupling of indoles and methanol to achieve the methylation of indoles. Although some pioneering works upon coupling of indoles with benzylic alcohols or aliphatic alcohols have been developed, to the best of our knowledge, the methylation of indoles with methanol has not been achieved *via* hydrogen autotransfer.[11] For examples, the groups of Grigg,[12] Shimizu,[13] Piersanti[14], and Ohta[15] demonstrated the C3-alkylation of indoles with alcohols in the presence of homogeneous and heterogeneous transition-metal catalysts.[16] In addition, Beller and co-workers reported a N1-alkylation of indoles with alcohols through combination of Shvo's catalyst and *p*-toluenesulfonic acid.[17] In 2013, Li and co-workers described an iridium catalytic system for the synthesis of 3,3'-bisindolylmethanes, which utilized methanol as a surrogate of formaldehyde and proceeded *via* an "interrupted-hydrogen-borrowing" process.[18]

In fact, there are two potential paths by which the intermediate **A** can be converted into different products. The first way is the Michael addition with another indole to give the 3,3'-bisindolylmethane; the latter route is a reduction by the metal hydride to afford the 3-methylindole (Scheme 1). We speculated that the lack of metal hydride suspended the "hydrogen-returning" process, so the Michael addition became dominated. Our idea for producing 3-methylindole was to interrupt the Michael addition by accelerating the consumption of indole and the reduction of the intermediate **A**. According to this train of thoughts, increasing the loading of the catalyst, which promoted the formation of metal hydride with the concomitant release of formaldehyde, was a possible way to achieve this goal.



Scheme 1. Chemoselectivity in the Coupling of Indole and Methanol.

Table 1. Iridium-Catalyzed Methylation of Indole with Methanol under Various Reaction Conditions.[a]



Entry	Cat. (mol %)	Atmos-phere	Conversion (%)[b]	Yield (%)[b] 2a	3a
1	$[Cp^*IrCl_2]_2$ (0.2)	N_2	100	57	33
2	$[Cp^*IrCl_2]_2$ (0.5)	N_2	100	74	12
3	$[Cp^*IrCl_2]_2$ (1)	N_2	100	84	2
4	$[Cp^*IrCl_2]_2$ (1)	O_2	100	92	0
5	$[Cp^*IrCl_2]_2$ (1)	Air	100	90	2
6	$IrCl_3 \cdot 3H_2O$ (2)	Air	100	76	14
7	$[Ir(cod)Cl]_2$ (1)	Air	95	27	24
8	$[Ir(cod)Cl]_2$ (1)/PPh_3 (2)	Air	97	45	18
9	$(PPh_3)_2(CO)IrCl$ (2)	Air	90	82	4
10	$[Ru(p\text{-cymene})_2Cl_2]_2$ (1)	Air	45	15	26
11	$[Cp^*RhCl_2]_2$ (1)	Air	100	89	3
12[c]	$[Cp^*IrCl_2]_2$ (1)	Air	89	50	18
13[d]	$[Cp^*IrCl_2]_2$ (1)	Air	87	33	35
14[e]	$[Cp^*IrCl_2]_2$ (1)	Air	80	65	6
15	-	Air	0	0	0
16[f]	$[Cp^*IrCl_2]_2$ (1)	Air	0	0	0

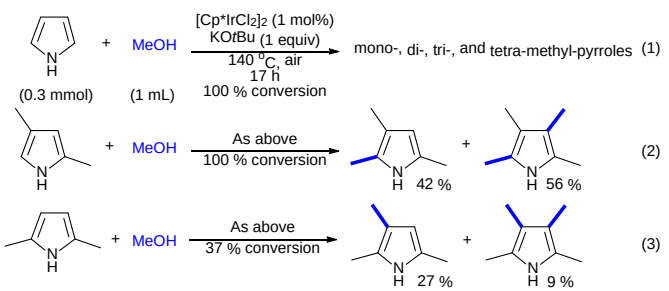
[a] Indole **1a** (0.3 mmol), methanol (1 mL), catalyst, KO*t*Bu (1 equiv), 140 °C for 17 h. [b] Determined by GC analysis. [c] 120 °C. [d] 100 °C, 24 h. [e] KO*t*Bu (0.5 equiv). [f] Base-free condition.

In an initial series of experiments, we surveyed the effect of the catalyst loadings on the selectivity by using $[Cp^*IrCl_2]_2$ as catalyst (Table 1, entries 1-3). In the presence of $[Cp^*IrCl_2]_2$ (0.2 mol%) and KO*t*Bu (1 equiv), a 57% yield of methylated product **2a** was obtained, along with bisindolylmethane **3a** as a side product in 33% yield (entry 1). Notably, with a higher catalyst loading (0.5 mol%), a better yield of **2a** was achieved, and the yield was improved to 84% upon increasing the catalyst loading to 1 mol% (entries 2-3). This is in line with our assumption mentioned above. It is worth mentioning that an atmosphere of oxygen was found to be beneficial to the methylation,[6] and even under the air, the methylation could be accomplished in 90% yield (entries 4-5). A quick screening of common hydrogen transfer catalysts showed that $[Cp^*IrCl_2]_2$ and it's Rh analogs were the optimal catalysts in both activity and selectivity among the testing catalysts (entries 6-11). With regard to the base, LiO*t*Bu, KO*t*Bu, and Cs_2CO_3 were found to be equally effective for this transformation (see Table S1, Supporting Information). A decrease in temperature or the amount of base led to unreacted indole, with inferior yield of the desired product (entries 12-14). Omission of the catalyst or base resulted in no desired product formation (entries 15-16).

To study the general applicability of the present system, the methylation of a variety of indoles with methanol was investigated under the optimized conditions (Table 1, entry 5), and the results are summarized in Table 2. The cross coupling of C-2 substituted indoles **1b**-**1c** and methanol afforded the corresponding C-3 methylated products **2b**-**2c** with 82-91% yields. Reactions of indoles bearing electron-donating or electron-withdrawing groups on the phenyl ring also proceeded smoothly. The 4-, 7-methyl-indoles **1d**-**1e** and 5-methoxyl-indole **1f** participated in the reaction, and the corresponding products **2d**-**2f** were obtained in 84–85% yields. The halide substituents such as fluoro- (**1g**-**1h**), chloro- (**1i**-**1j**) and bromo- (**1k**-**1m**), were tolerant under the conditions, affording the corresponding products in good yields (**2g**-**2m**). In the case of substrate bearing an ester group, a slightly longer reaction time was required to obtain good yield (**2n**). Notably, nitro group survived under the conditions, although it is easily reduced in the presence of alcohols (hydrogen donor) and transition metal catalysts (**2o**-**2p**). Similarly, the methylation of 5-cyanoindole (**1n**) gave the desired product **2n** in 87% yield. The coupling was also applied to indole bearing an amino, except for C-3 methylation, *N*-methylation of amino was also observed (**2r**). In addition, 7-azaindole successfully yielded 62% of the desired product **2s**. Consistent with prior observations, *N*-methyl indole **1t** failed to undergo methylation, which indicated an indole anion involved mechanism.[13]

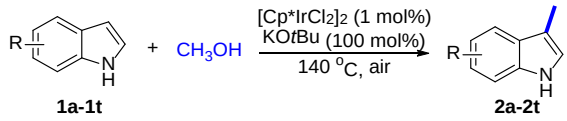
Except for indoles, we also investigated the reaction of pyrroles with methanol (Scheme 2). Unlike the indoles, pyrrole shown inferior selectivity, which afforded methylated products consisting of the mono-, di-, tri-, and tetra-methyl-pyrroles under the present conditions (Eqn 1). Although this, it was observed that the methylation occured preferentially at the α position (C2 or C5) of pyrroles (Eqns 2-3).

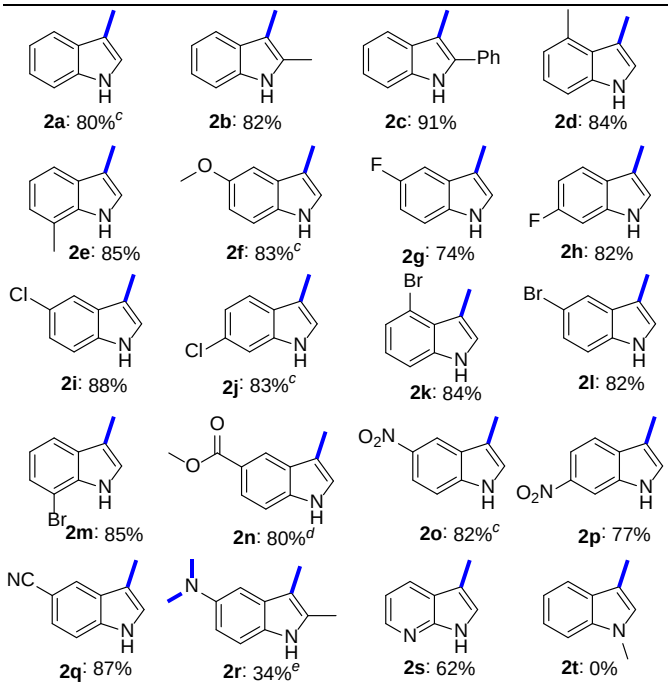
An additional mechanistic experiment starting from the possible intermediate (1*H*-indol-3-yl)methanol gave 94% yield of the desired product, which again verified the reaction process outlined in



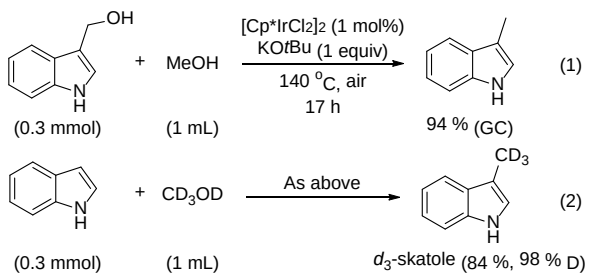
Scheme 2. Methylation of pyrroles.

Table 2. Coupling of a Variety of Indoles with Methanol.[a,b]





[a] Reaction conditions: **1** (0.3 mmol), 1 mL methanol, KO*t*Bu (0.3 mmol), 140 °C for 17 h under air. [b] Isolated yield. [c] Reaction was carried out on1 mmol scale. [d] 24 h. [e] **2r** was separated by preparative HPLC.



Scheme 3. Mechanistic Experiments.

Scheme 1 (Scheme 3, Eqn 1). Furthermore, this methodology also provides a simple and straightforward approach for the synthesis of d_3-skatole, which is widely used in the deuterium isotope techniques, such as the metabolism kinetics (Eqn 2).[19]

In summary, we have developed a $[Cp^*IrCl_2]_2$-catalyzed method for the direct methylation of indoles and pyrroles using the abundant and bio-renewable methanol as C1 feedstock. The methyaltion of indoles was selectively occurred at the C3 position, while the methyaltion of pyrroles was occurred at both the α position (C2 or C5) and the β position (C3 or C4).

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Electronic Supplementary Information (ESI) available: Experimental procedures and analytical data for products. See DOI: 10.1039/c000000x/

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