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Iridium catalysed C2 site-selective methylation of indoles using a pivaloyl directing group through weak chelation-assistance†

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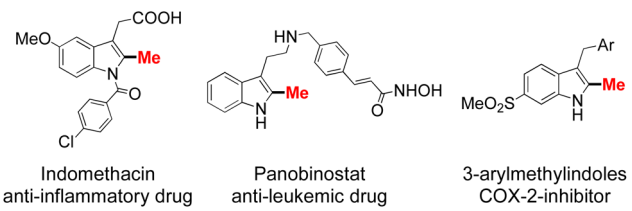
Here we present an iridium catalysed C2-selective methylation of indoles using methyltrifluoroborate as a source of methyl group. The iridium catalyst selectively discriminates the indole C2 and C4 C–H bonds by coordination with a pivaloyl directing group.

Numerous directing groups have been utilized to develop transition metal-catalysed C–C bond formation through C–H activation.[1] However, despite these advances, site-selective C–H bond activation, particularly for bonds of similar character, remains a challenge for transition metal catalysis.[2] This challenge has prompted the exploration of new synthetic disconnections and transformations. Indoles and their derivatives play a significant role as structural components in both medicinal chemistry and materials science.[3] Among them, C2 functionalized indoles are particularly noteworthy due to their prevalence in bioactive natural products and drugs, making new selective synthesis strategies extremely desirable to synthetic and medicinal chemists (Fig. 1).[4]

Over the last decade, several techniques have been devised to enable C2 C–H functionalization of indoles.[5] One well explored approach involves incorporating a directing group on the indole nitrogen to provide C2 selectivity.[6] Furthermore, directing groups at the C3 position have been used as tools for targeting the C4 and C2 positions,[7] where competition between the formation of five- and six-membered metallocycle is possible, though favoring functionalization at C4 over C2. Accordingly, methods for the regioselective functionalization of the C2 C–H bond in the presence of the C4 C–H bond is a challenge, and most attractive due their potential in synthetic applications. Previous efforts towards this goal have included an iridium-catalyzed C2/C4 regioselective heteroarylation, developed by You *et al.* that employed a pivaloyl directing group and carefully selected catalytic systems.[8] In a separate study, Ravikumar *et al.* reported a cobalt catalyzed regioselective C4 C–H functionalization of 3-pivaloyl indole, where the directing group.[9] Li *et al.* demonstrated the possibility of rhodium-catalyzed site-selective coupling of indoles with diazo esters to achieve C4 alkylation *versus* C2 annulation.[10] Moreover, Shi *et al.* have established an effective strategy for site-selective C4 arylation, utilizing a pivaloyl directing group positioned at the C3 position.[11] Additionally, Prabhu and colleagues have shown the crucial role of the electronic nature of the ketone directing groups in regulating the C2 and C4 functionalization of indoles.[12]

The introduction of the *magic methyl group* through transition metal catalyzed C–H methylation has been the focus of extensive research effort due to the importance of methylation for exploring the pharmacological properties of organic molecules.[13] This fundamental research has had a profound impact on the design of drug candidates with tailored physical properties in medicinal chemistry. According to a 2018 survey conducted by Njardarson, at least 73% of the top 200 marketed drugs contain a methyl substituent.[14] Various transition metals have been utilized in *ortho*-C–H methylation reactions using directing group strategies, with $MeB(OH)_2$, $MeBF_3K$, Me_3BO_3, DTBP, DCP, MeI, thiophenium salt serving as methyl sources.[15] For instance, Ackermann *et al.* have reported a cationic ruthenium(II)-complex enabled C2-C–H methylation on indoles using 2-pyrdine as a strongly coordinating directing group.[16] Li and co-workers developed rhodium(III) catalyzed C2-C–H methylation of arenes with alkylboron reagents.[17] To the best of our knowledge transition metal catalyzed regioselective C2 methylation of indoles with a directing group at the C3 position has not previously been demonstrated. Herein we disclose an



Indomethacin
anti-inflammatory drug

Panobinostat
anti-leukemic drug

3-arylmethylindoles
COX-2-inhibitor

Fig. 1 Examples of bioactive C2-functionalized indole derivatives.

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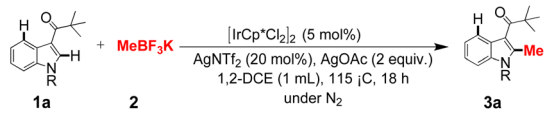
efficient protocol *via* bench stable $[Cp^*IrCl_2]_2$ catalyzed C2 selective C–H methylation using commercially available potassium trifluoromethylborate as a methyl source under mild reaction conditions and with wide substrate scope.

Recently, we reported a tandem iridium-catalysed decabonylative C–H activation of indoles using a sacrificial electron rich ketone for bis-arylsulfenylation reactions.[18] Using this efficient iridium(III) catalytic system as a starting point, we pondered whether the catalytic conditions could be applicable to the C2-selective methylation of indoles by switching the inherently preferred regioselectivity. We initiated our studies with a screening of potential directing groups (ESI, Table S1,†) using potassium trifluoromethyl borate (**2**) to investigate potential for the iridium catalysed C2-selective methylation reactions. The dominant 3-pivaloyl-*N*-methyl indole (**1a**) was used in subsequent studies (Table 1).

The best identified conditions for this reaction were 5 mol% of $[Cp^*IrCl_2]_2$ as catalyst, 20 mol% of silver bistrifluoromethanesulfonate as additive, 2 equivalents of silver acetate as oxidant, in 1,2-dichloroethane as solvent at 115 °C for 23 h under nitrogen atmosphere. To our delight the desired product was obtained in 89% isolated yield (Table 1, entry 1). When we screened fluoro-alcohol-based solvents, which are known to promote C–H activation reactions[19] the isolated yields decreased from 89% to 70% (Table 1, entries 2–3). Reactions performed using the solvents *t*-amylOH, acetonitrile and dimethoxyethane all produced lower yields (Table 1, entries 4–6). As expected, the absence of a silver additive resulted in no product formation, as it is crucial for the formation of the iridium complex with the indole substrate (Table 1, entry 7). Conducting the reaction at lower temperature (80 °C) did not improve the yield and at RT the reaction was highly compromised, producing only traces of the product (Table 1, entries 8–9). Next, we focused our attention on screening potential methyl donors. While we didn't observe product formation with methylboronic acid, due to poor solubility, the soluble boroxine delivered the product in 49% yield (Table 1, entry 10–11). When reactions were performed under air, the product was obtained in 80% yield, which is sufficient for use in up-scaled syntheses (Table 1, entry 12). On account of the cost of iridium, less expensive ruthenium and palladium catalysts were tested, though found to be impotent with respect to the reaction under these conditions used (Table 1, entries 13–14). In the case of rhodium(III) catalysis, the product was obtained in 67% yield (Table 1, entry 15). Unfortunately, the non-noble metal Co(III) catalyst did not support the reaction (Table 1, entry 16). Moreover, in the absence of AgOAc no product was obtained (Table 1, entry 17), and the use of silver carbonate in place of silver acetate resulted in lower yield. Even the use of silver oxide was not efficient (Table 1, entries 18–19). Control experiments verified that the iridium catalyst and an excess of potassium trifluoromethyl borate are both essential to obtain the very good, isolated yields (Table 1, entries 20–21).

Table 1 Optimization conditions[a]

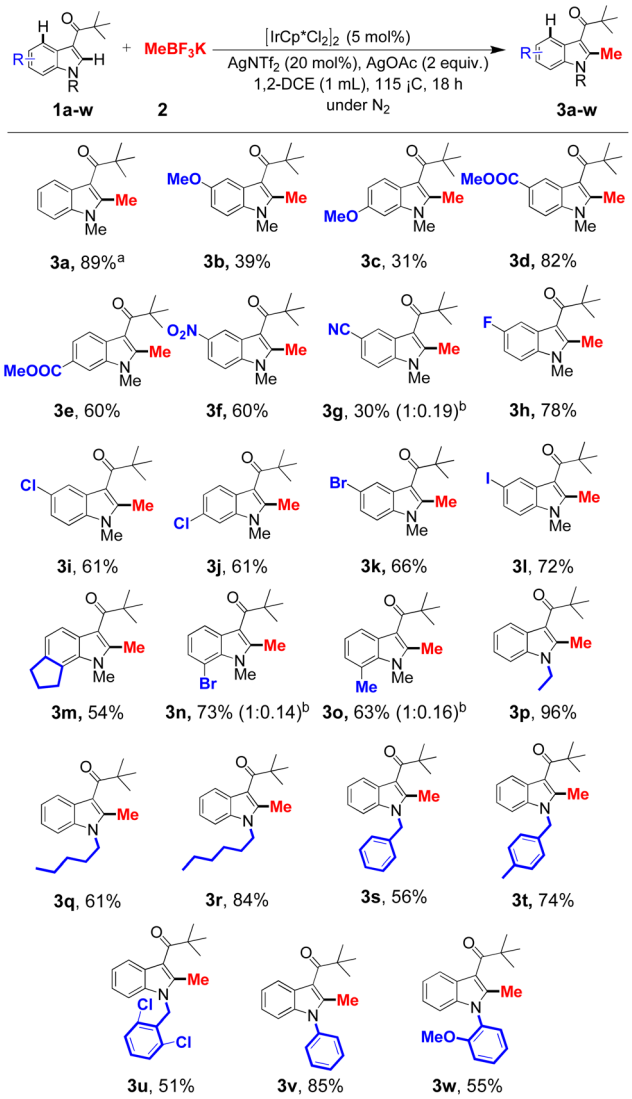


1a 2 3a

	Variation from standard conditions	
1	None	89%[b]
2	HFIP as solvent	76%
3	TFE as solvent	75%
4	*t*-AmylOH as solvent	70%
5	Acetonitrile as solvent	NR
6	DME as solvent	58%
7	No $AgNTf_2$	NR
8	Reaction at 80 °C	75%
9	Reaction at RT	Trace
10	$MeB(OH)_2$ instead of $MeBF_3K$	NR
11	$Me(BO)_3$ instead of $MeBF_3K$	49%[c]
12	Under air	80%
13	$[Ru(p\text{-cymene})Cl_2]_2$ as catalyst	NR
14	$Pd(OAc)_2$	NR
15	$[Rh(Cp^*Cl_2)]_2$ as catalyst	67%
16	$[Co(Cp^*CO)I_2]$ as catalyst	NR
17	No AgOAc	NR
18	Ag_2CO_3 instead of AgOAc	63%
19	Ag_2O instead of AgOAc	NR
20	No $[IrCp^*Cl_2]_2$	NR
21	3 equiv. of $MeBF_3K$	80%

[a] Reaction conditions: **1** (0.34 mmol), **2** (5 equiv.), $[IrCp^*Cl_2]_2$ (5 mol%), $AgNTf_2$ (20 mol%), AgOAc (2 equiv.), 1,2-DCE (1 mL), 115 °C, 18 h, N_2 atmosphere; NR = no reaction; yields are isolated yields. [b] Isolated yields. [c] 50% dissolved in THF (5 equiv.).

Next, with optimized conditions in hand, we explored the substrate scope using potassium methyltrifluoroborate and its use for targeting a range of methylated indole derivatives was investigated with respect to substitution of the arene ring (Scheme 1). Initial studies showed that the unsubstituted indole could react under the standard reaction conditions, furnishing the C4-methylated indole (**3a**) in good yield. Subsequent studies with a range of substituents indicated a subtle interplay between steric and electronic effects on reaction yields. The presence of a strongly electron donating methoxy substituent at the 5-position of indole gave the desired product (**3b**) in 39% yield with a comparable yield in the case of reactions performed with the 6-methoxy derivative (**3c**, 31%), albeit lower than that of the unsubstituted indole. In contrast, electron-withdrawing substituents were observed to be better tolerated, with the 5- and 6-methyl carboxylate substituted indoles (**1d–1e**) affording the C4-methylated products (**3d–3e**) in 80% and 60% yield, and the NO_2 group substituted indole yielding the product (**3f**) in 60% yield. However, the electron withdrawing cyano (CN) group at 5-position gave low yield (30%, **3g**), this is suspected to arise from competition by the cyano group for coordination with the metal center. Some support for this hypothesis is provided by studies using halogens at the 5- and 6-position, where the fluoro (**1h**), chloro (**1i–j**), bromo (**1k**) and iodo (**1l**) derivatives, afforded good to very good yields (**3h–l**, 61–78%) of the corresponding methylated products. The ready accessibility of halogenated derivatives highlights the potential of this methodology for applications in late-stage transformations. A fused ring substrate (**1m**) delivered the corresponding expected product (**3m**) in moderate yield. C7 bromo- and methyl-substituted



Scheme 1 Reaction conditions: **1** (0.34 mmol), **2** (5 equiv.), $[IrCp^*Cl_2]_2$ (5 mol%), $AgNTf_2$ (20 mol%), AgOAc (2 equiv.), 1,2-DCE (1 mL), 115 °C, 18 h, N_2 atmosphere. [a]Isolated yields. [b]Ratio of C2 & C4

indoles afforded the products (**3n–o**) in good yield. Subsequently the effect of substituents on the nitrogen was studied (**1p–1u**). Interestingly, and to our surprise, the *N*-ethyl indole provided C4 methylated product (**3p**) in 96% isolated yield. When we used *N*-pentyl and *N*-hexyl substituted indoles, the products (**3q–r**) were isolated in 61% and 84% respectively. Finally, various benzyl and phenyl derivatives were also incorporated to provide the target products (**3s–3w**) in very good to moderate yields.

We then focussed on the mechanism of the iridium catalysed methylation reaction using a series of isotope experiments (Scheme SI-1†). Based upon our supporting experimental findings together with previous studies,[18] a plausible catalytic cycle for the iridium(III) catalysed methylation reaction can be presented (Fig. 2). The first step being the coordination of the iridium catalyst by the pivaloyl carbonyl group through weak coordination, followed by the formation of either a five- or a six-membered iridiacycle *via* C–H metalation at C2 and C4 positions, respectively. However, the iridium catalyst preferably defaults to the energetically more favourable five-membered iridacycle for the subsequent transmetalation with potassium methyltrifluoroborate (**2**). Thereafter, the reductive elimination liberates the product (**3**) and finally the reduced iridium(I) was re-oxidized with silver to regenerate the catalytically active iridium(III) catalyst.

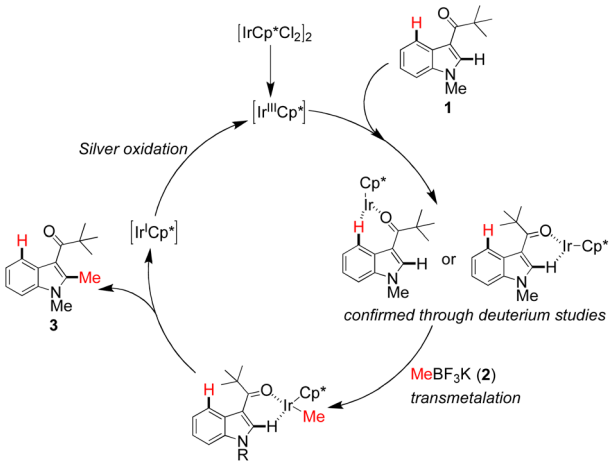


Fig. 2 Plausible reaction mechanism.

In conclusion, we have developed the first iridium(III) catalyzed C2-selective methylation of an indole, with the reaction performed *via* a transmetalation reaction. The iridium catalyst, with the help of a simple carbonyl directing group, facilitates the preferential transformation of the five-membered iridacycle over its six-membered counterpart, thus providing discrimination between two indole C–H bonds. Mechanistic studies indicated that the C–H bond iridium metalation step is reversible. Collectively, this opens for the possibility to use this reaction as a tool for use in the efficient, selective methylation reaction in drug development and other areas. Further studies to apply this catalysis to various other substrates is undergoing in our laboratory.

Author contributions

SK and TZ performed the synthesis and analysis. IAN and SK conceived the project. All authors contributed to the writing of the manuscript and gave approval for submission.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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