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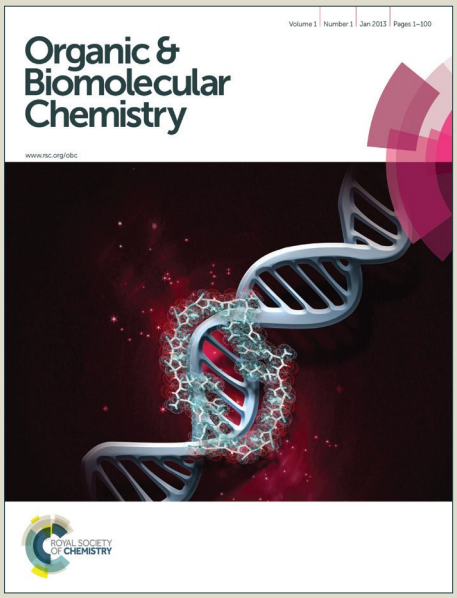

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Palladium-Catalysed Direct C-2 Methylation of Indoles

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A direct C-2 methylation reaction of indoles bearing a readily removable *N*-2-pyrimidyl moiety as a site-specific directing group has been developed with a palladium catalyst. This reaction relied on the use of KF to promote the efficient methylation. A moderate to good yield was achieved on a range of indole substrates.

Methyl group (Me) as the smallest alkyl group is one of the most common carbon fragments in organic compounds. In drug discovery and development, the conversion of C-H to C-Me can significantly improve the biological activity of a drug candidate, which is known as the "magic methyl" effect.[1] Capable catalytic and biocatalytic approaches such as transition-metal catalysed C-H methylation[2], new methylating reagents[3] and biocatalytic C-H methylation[4] have been developed to promote this industrially critical chemical transformation. Recently, transition-metal-catalysed directed C-H methylation has become a versatile strategy in selectively methylating C(sp^2)-H and C(sp^3)-H bonds.[5,6] Aryl systems have commonly been used in the studies of C(sp^2)-H methylation, whose site-specificity can be guided by different directing groups.[5] However, the C-H methylation of therapeutically important heterocycles, especially indoles, has been studied to a significantly less extent.[7]

2-Methylindoles are essential building blocks of a number of biologically active molecules.[8] Select medicinal molecules containing 2-methylindoles are shown in Figure 1. Panobinostat, Brivanib, and Cediranib are three FDA-approved drugs to treat various cancers by targeting different cellular targets[8a], while bioactive molecules containing 2-methylindoles are also being evaluated as drug candidates toward various diseases. MOMIPP is a promising drug candidate that effectively reduces the growth and viability of temozolomide-resistant glioblastoma and doxorubicin-resistant breast cancer cells.[8b] TG8-21 is a prostanoid receptor EP2 antagonist that could mitigate the inflammatory consequences of EP2 activation,[8c] while CRA-680 as a potent prostaglandin D2 receptor CRTH2 antagonist

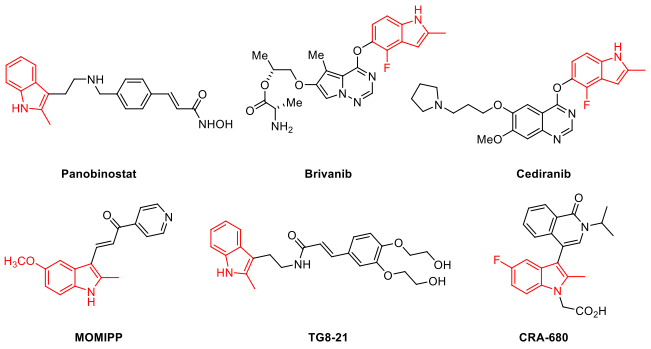

Figure 1 Select biologically active molecules and drug candidates containing 2-methyindoles.

can be used to treat allergic inflammatory diseases.[8d] Despite their validated importance in drug research, selective methylation protocols for the synthesis of 2-methylindoles remain poorly developed. Recently, Shi and co-workers reported one example of Rh(I)-catalysed decarbonylative C-2 methylation of indole with acetic acid (Scheme 1a).[7a] In 2015, Li and co-workers developed Rh(III)-catalysed oxidative C−H alkylation of diverse arenes bearing different *ortho*-directing groups using potassium alkyltrifluoroborates (Scheme 1b).[7b] These studies achieved C-2 methylation of a few *N*-(2-pyridine)indoles and *N*-(2-pyrimidyl)indoles with 42−94% yields. Since both protocols required expensive rhodium catalysts, it is strongly desired to develop new methods with cheaper transition metals. Herein, we report our work of Pd-catalysed direct C-2 methylation of indoles (Scheme 1c). The site-selectivity in this method was controlled by a removable *N*-pyrimidyl directing group.

Our study was inspired by a report of the methylation of 2-phenylpyridine.[5b] After extensive screening of a range of Pd catalysts, oxidants, ligands, additives and solvents (for detailed optimization studies, see the Supporting Information), we found that the desired C-2methylation of *N*-(2-pyrimidyl)indole (**1a**) was achieved using $Pd(OAc)_2$ as catalyst, $MeB(OH)_2$ as methyl source, Ag_2CO_3 and benzoquinone (BQ) as co-oxidant, KF as base or boronic acid activator, and *t*-AmylOH as solvent. The only product in the reaction was the methylated product **2a** (55% yield; Table 1, entry 1), and the rest was the unreacted starting material. A series of control experi-

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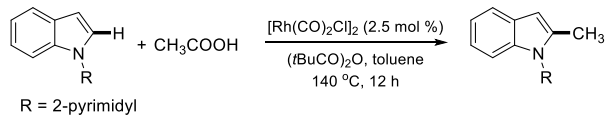
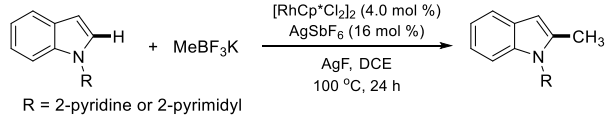
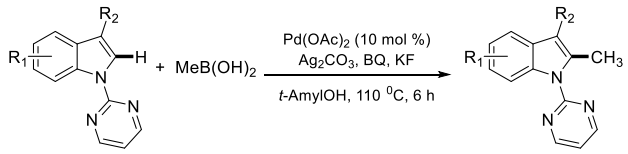
a) Rh(I)-catalyzed decarbonylative methylation of indoles with acetic acid



b) Rh(III)-catalyzed methylation of indoles with $MeBF_3K$



c) This work: Palladium-catalyzed methylation of indoles with $MeB(OH)_2$

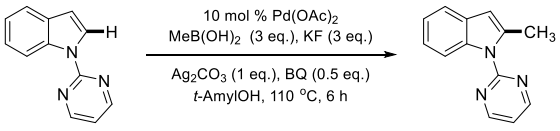


Scheme 1 Select approaches for site-specific C2-methylation of indoles.

ments were subsequently conducted to understand the role of each reactant (Table 1). In the absence of the Pd catalyst, no conversion was observed (entry 2). BQ proved to be crucial for the reductive elimination step (entry 3), and 0.5 equivalent of BQ provided the same conversion rate (entry 6). The removal of co-oxidant Ag_2CO_3 from the reaction led the yield reduction to 27% (entry 4). However, the higher amount of Ag_2CO_3 promoted a less effective reaction (entry 7). The absence of KF[5b] dropped the reaction yield by about three times, indicating its critical role in promoting the methylation (entry 5). CsF proved to be less efficient (entry 8), and the use of Ag_2O, which was effective in methylating 2-phenylpyridine[5b], gave a yield less than 10% (entry 11). The use of methylboroxine[5b] as the methyl resource gave an undesired yield (entry 9), while $MeBF_3K$[5h] showed no conversion at all (entry 10). Moreover, we applied Sanford's[5h] and Carretero's[5d] conditions to **1a**, and no methylation occurred (entry 12 and 13).

After establishing the optimized conditions, we extended the re-

Table 1 Control Experiments for the C-2 methylation.

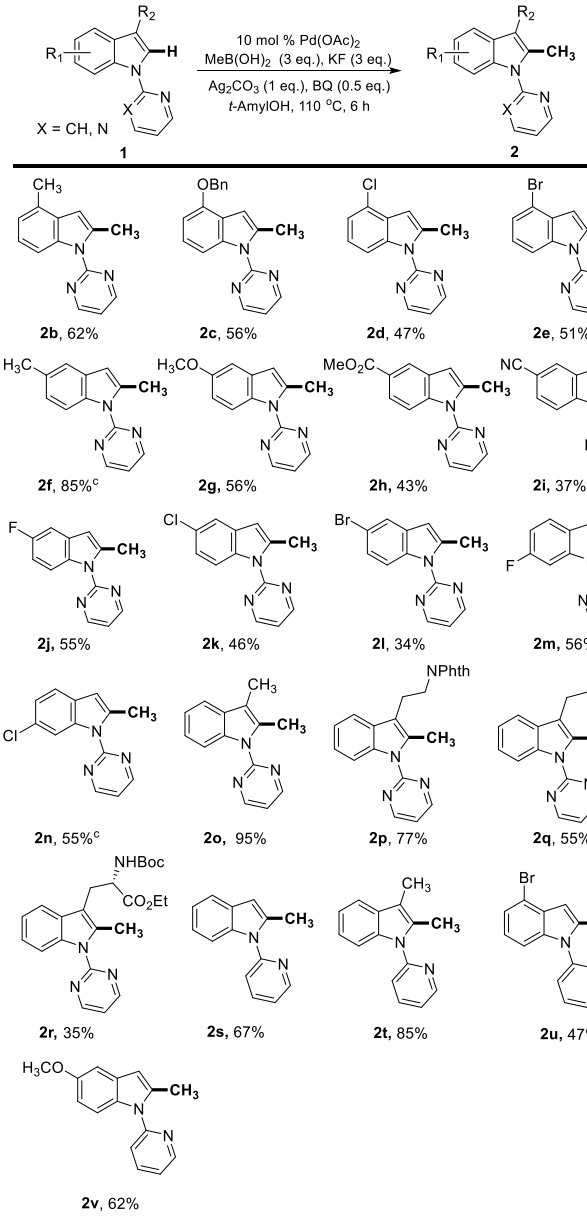


1a **2a**

entry	change from standard conditions	yield (%)[a,b]
1	none	55
2	no $Pd(OAc)_2$	nr
3	no BQ	10
4	no Ag_2CO_3	27
5	no KF (Yu's condition)	19
6	1 equiv BQ	53
7	2 equiv Ag_2CO_3	39
8	CsF instead of KF	32
9	methylboroxine instead of $MeB(OH)_2$	25
10	$MeBF_3K$ instead of $MeB(OH)_2$	nr
11	Yu's condition[c]	<10%
12	Sarford's condition[d]	nr
13	Carretero's condition[e]	nr

[a] Reaction conditions: **1a** (0.2 mmol), catalyst, methyl source and additives as specified, solvent (1M), 6 h. [b] Determined by ^1H NMR spectroscopy. nr = no reaction. [c] **1a** (0.2 mmol), 10 mol % $Pd(OAc)_2$, Ag_2O (1 equiv.), BQ (0.5 equiv.), $MeB(OH)_2$ (3 equiv.), *t*-AmylOH (1mL), 100 °C, 6 h. [d] **1a** (0.2 mmol), 10 mol % $Pd(OAc)_2$, MnF_3 (4 equiv.), CH_3BF_3K (2 equiv.), TFE/H_2O/AcOH (8:1:1), 25-40 °C, 6 h. [e] **1a** (0.2 mmol), 10 mol % $Pd(OAc)_2$, AgOAc (3 equiv.), BQ (0.5 equiv.), $MeB(OH)_2$ (2 equiv.), *t*-AmylOH, 100 °C, 20 h.

Table 2 The scope of C-2 methylation of indoles.[a,b]



[a] Reaction scale: 0.3 mmol. [b] Isolated yield. [c] 50 mol % $Pd(OAc)_2$ was used.

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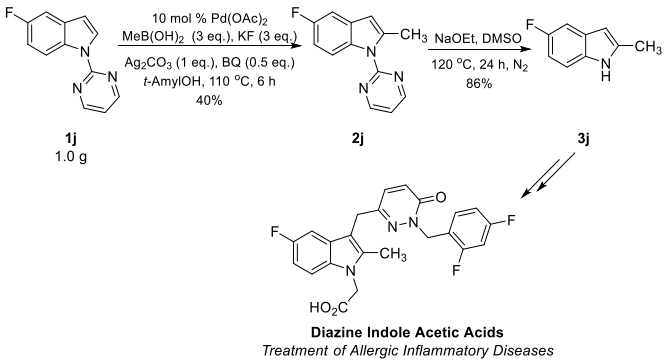
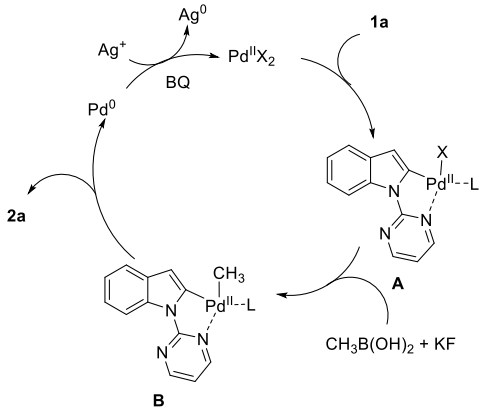
action to a range of indole substrates (Table 2). This reaction was compatible with different substitutions on the indole ring (C4-, C5-, or C6- positons) and regioselectively afforded 2-methylindoles in moderate to good yields. Both electron-donating groups (EDG) and electron-withdrawing groups (EWG) on indoles afforded C-2 methylated products. Electron-donating methyl (**2b** and **2f**), benzyloxy (**2c**) and methoxy (**2g**) groups usually gave slightly higher yields than electron-withdrawing ester (**2h**), cyano (**2i**) and halogen (**2d-2e** and **2j-2n**) groups. Notably, C-3 substituted indole substrates can have excellent yields (**2o** and **2p**), but *N*-pyrimidyl tryptophan derivative reached a yield of 35% (**2r**). Furthermore, a few examples of *N*-pyridyl indole substrates (**2s-2v**) were tested. These substrates gave comparable yields as the *N*-pyrimidyl indoles. However, the pyrimidyl group could be removed more easily than the pyridyl group. Remarkably, all reactions in the Table 2 had excellent mass balances: unreacted starting materials in these reactions including those with low yields were fully recovered.

Next, we demonstrated that this reaction was amenable to scale up. Under the optimal conditions, the C-2 methylation reaction of indole **1j** was carried out on a gram scale. Product **2j** was successfully obtained with a slightly decreased yield, and the starting material was fully recovered after the reaction (Scheme 2). Moreover, we attempted to remove the pyrimidyl directing group. Upon treatment of **2j** with NaOEt in DMSO under nitrogen atmosphere, 5-fluoro-2-methyl-1*H*-indole **3j** was isolated with excellent yield. This



Scheme 2 Gram scale synthesis and deprotection of the pyrimidyl group.



Scheme 3 Plausible reaction mechanism for the C-H methylation.

indole derivative is an important building block of CRA-680 (Figure 1) and other useful medication as shown in Scheme 2.[9]

The indole C-2 methylation may follow the same pathway previously proposed for the alkylation of thiophene.[10] Its plausible mechanism was shown in Scheme 3. First, the coordination of the pyrimidyl group of compound **1a** to Pd(II) is followed by the selective C-2 C-H bond activation, which gives the cyclopalladated intermediate **A**. Transmetallation of **A** with boronic acid generates the precursor **B** for a reductive elimination step, which releases product **2a** and produces the Pd(0). Reoxidation of Pd(0) by Ag_2CO_3 and BQ regenerates the Pd(II) catalyst to fulfil the catalytic cycle.

Conclusions

In conclusion, we have developed a Pd(II)-catalysed C-2 methylation of indoles directed by the removable 2-pyrimidyl group. It serves as a novel and alternative route for preparation of 2-methyl-1*H*-indoles. Further understanding of the reaction mechanism and applications of this approach to other synthetically useful substrates are ongoing in our laboratory.

Acknowledgements

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