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Iridium-Catalyzed C-Alkylation of Methyl Group on *N*-Heteroaromatic Compounds using Alcohols

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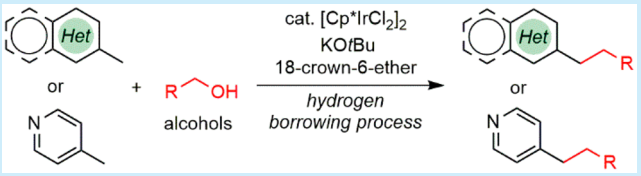
ABSTRACT: In this study, we developed a catalytic system for the C-alkylation of a methyl group on *N*-heteroaromatic compounds, including pyridine, pyrimidine, pyrazine, quinoline, quinoxaline, and isoquinoline, using alcohols based on a hydrogen-borrowing process with $[Cp^*IrCl_2]_2$ (Cp^*: η^5-pentamethylcyclopentadienyl) combined with potassium *t*-butoxide and 18-*crown*-6-ether as the catalyst precursor.



N-Heteroaromatic compounds, in particular, pyridine, pyrimidine, pyrazine, quinoline, quinoxaline, and isoquinoline, are important compounds in the fields of medicine, pesticides, and functional materials.[1] *N*-Heteroaromatic compounds are also considered important in synthetic organic chemistry because many natural products contain these skeletons. Various methods have been used to synthesize analogues of *N*-heteroaromatic compounds. One such method involves the initial introduction of a methyl group; then, a derivative with an analogous structure is synthesized by C-alkylation of the methyl group. This method is useful because the synthetic process is simple, and analogues of the *N*-heteroaromatic compound can be systematically synthesized. C-Alkylation is typically achieved using a compound, such as a halogenated alkyl in the presence of a strong base (Scheme 1a).[2] However, this method is neither environmentally friendly nor atom-efficient because a halogen salt is produced as a byproduct.

The hydrogen-borrowing process is an alternative method in which an alcohol is used as the alkylating reagent in a catalytic reaction.[3−6] This method is very environmentally friendly because the reaction generates only water, which is harmless, as a byproduct.

Several groups have reported the catalytic C-alkylation of methylated *N*-heteroaromatic compounds using alcohols based on the hydrogen-borrowing process (Scheme 1b). In 2010, Kempe et al. reported a pioneering work[7] where they successfully accomplished the C-alkylation of methylpyrimidine and methylpyrazine derivatives by employing an iridium catalyst. Obora et al. reported the C-alkylation of methylquinoline and methylquinoxaline derivatives using an iridium catalyst.[8] Lang et al.[9] and Oe et al.[10] also reported the C-alkylation of similar substrates using a ruthenium catalyst. Banerjee et al. reported a nickel-catalyzed system that enables the C-alkylation of methylpyrazine and methylquinoline derivatives.[11] Very recently, Kundu et al. reported a cobalt-catalyzed system for the C-alkylation of methylpyrazine, methylquinoline, and methylquinoxaline derivatives.[12] However, the types of *N*-heteroaromatic compounds that could be used as substrates in the reactions were relatively limited in those reports. There have been no successful examples of a versatile catalytic system that can be applied to a variety of substrates.[13,14]

In this study, we report a new, simple catalytic system to synthesize *N*-heteroaromatic compound analogues via C-alkylation using various primary alcohols. The advantages of this system are that many kinds of compounds with methyl groups, such as pyridine, pyrimidine, pyrazine, quinoline, quinoxaline, and isoquinoline, can be used as substrates, and the reaction does not produce any harmful compounds as byproducts (Scheme 1c).

The C-alkylation of 2-methylpyrazine (**1a**) with benzyl alcohol (**2a**) was carried out under various conditions to optimize the reaction conditions (Table 1). When the reaction of **1a** (1.0 mmol) with **2a** (1.0 mmol) was carried out in THF (1.0 mL) at 120 °C for 20 h in a sealed reactor in the presence of $[Cp^*IrCl_2]_2$ (Cp^*: η^5-pentamethylcyclopentadienyl) and KO*t*Bu, 2-(2-phenylethyl)pyrazine (**3a**) was obtained in 29% yield (entry 1). Catalysts $[Cp^*RhCl_2]_2$ and $[(cymene)RuCl_2]_2$ both exhibited very low catalytic activity (entries 2 and 3). $[IrCl(cod)]_2$ combined with PPh_3 also exhibited lower activity, providing **3a** in only 20% yield (entry 4). We anticipated that in this reaction, stronger basic conditions would lead to a higher yield of **3a**. Therefore, we examined the employment of the combination of a strong base containing potassium and 18-*crown*-6-ether, which is known to be effective for trapping the potassium ion.[15] When the reaction was carried out in the presence of 18-*crown*-6-ether (0.3 mmol), the yield of **3a** was

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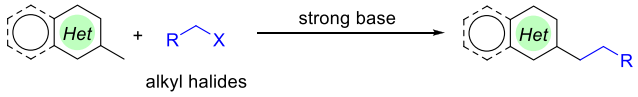
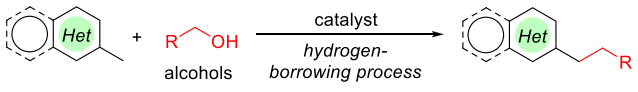
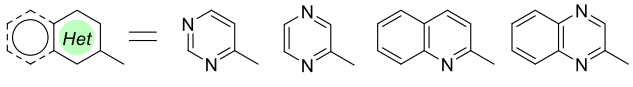
Scheme 1. C-Alkylation of Methyl Group on *N*-Heteroaromatic Compounds

a) Conventional method



b) Catalytic method based on hydrogen-borrowing process

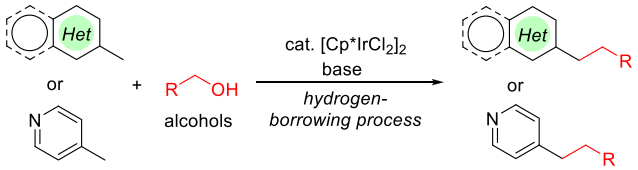




Researcher	Conditions	Substrate	Ref.
Kempe et al.	cat. $[IrCl(cod)]_2$ / $Py_2NP(i\text{-}Pr)_2$ KO*t*Bu (1.1 equiv), 110 °C	**A**, **B**	7
Obora et al.	cat. $[IrOH(cod)]_2$ / PPh_3 KO*t*Bu (0.5 equiv), 130 °C	**C**, **D**[a]	8
Lang et al.	cat. $RuCl_3$ KO*t*Bu (0.6 equiv), 130 °C	**C**, **D**[a]	9
Oe et al.	cat. $RuH(CO)(PPh_3)_3$ $InCl_3 \cdot 4H_2O$, 135 °C	**C**, **D**[a,b]	10
Banerjee et al.	cat. $NiBr_2$ / 1,10-phenanthroline KO*t*Bu (1.0 equiv), 140 °C	**B**, **C**[b]	11
Kundu et al.	cat. Co(NNN) KO*t*Bu (1.5 equiv), 150 °C	**B**, **C**, **D**	12

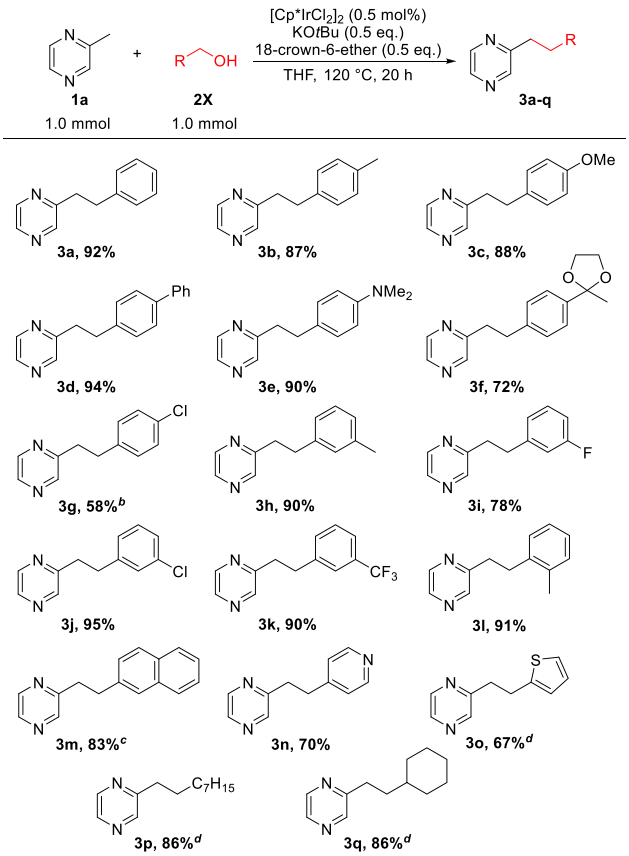
[a]4-methylquinoline was also applicable.
[b]1-methylisoquinoline was also applicable.

c) **This Work**: Versatile catalytic system applicable for substrates **A** to **D** and 4-methylpyridine



First example of C-alkylation of 4-methylpyridine using alcohols in high yields

Scheme 2. Scope of Alcohols for C-Alkylation of 2-Methylpyrazine (1a)[a]



[a]Reaction was carried out with **1a** (1.0 mmol), primary alcohol (1.0 mmol), $[Cp^*IrCl_2]_2$ (0.5 mol %), KO*t*Bu (0.5 mmol), 18-*crown*-6-ether (0.5 mmol), and THF (1.0 mL) at 120 °C for 20 h. Isolated yields are shown. [b]*p*-Chlorobenzyl alcohol (1.5 mmol) was used. [c]Diglyme was used as a solvent. [d]**1a** (1.5 mmol) was used.

greatly improved to 84%, as expected (entry 5). Other bases were also examined. The reaction using KOH resulted in a moderate yield of **3a** (entry 6). The use of a weaker base (K_2CO_3) resulted in no reaction (entry 7). The combination of NaO*t*Bu and 15-*crown*-6-ether, which is known to be effective for trapping sodium ions, was not so effective, providing **3a** in only 40% yield (entry 8). We also examined the effect of solvent (entries 9−11); however, the yield of **3a** was not improved by using DME (1,2-dimethoxyethane), *tert*-butyl alcohol, or toluene. Finally, the best yield of **3a** (92%) was achieved by using 0.5 mmol each of KO*t*Bu and 18-*crown*-6-ether, which contributed the optimal conditions (entry 12).

With the optimized conditions in hand, we next explored the scope of the reaction of 2-methylpyrazine (**1a**) with primary alcohols (Scheme 2). Reactions of benzyl alcohols bearing electron-donating or electron-withdrawing substituents (methyl, methoxy, *N*,*N*-dimethylamino, phenyl, fluoro, chloro, and trifluoromethyl) on the aromatic ring proceeded smoothly to give the corresponding 2-(2-phenylethyl)pyrazine derivatives (**3b−l**) in good to excellent yields. An acetal group was tolerated under the reaction conditions, leading to the formation of **3f** in good yield (72%). Naphthalenemethanol, 4-pyridinemethanol, and 2-thiophenemethanol were also good C-alkylating reagents for this catalytic system, giving **3m−o** in 83, 70, and 67% yield, respectively. This catalytic system could also be applied to aliphatic alcohols such as 1-octanol and cyclohexanemethanol, leading to the formation of **3p** and **3q** in high yields. Thus the C-alkylation of **1a** with various primary alcohols was successful using the present catalytic system.

Next, we investigated the scope of alcohols for the C-alkylation of 4-methylpyridine (**1b**), as shown in Scheme 3.[16] Previously, the C-alkylation of **1b** with alcohols was attempted by Kempe et al.[7] and Lang et al.[9] However, the yields of C-alkylation were moderate or low. First, we tried the reaction of **1b** with **2a**. Fortunately, the reaction proceeded well to give 4-phenethylpyridine (**4a**) in 87% yield. This is an improvement over the yield of **4a** reported by Kempe et al. (45%)[7] and Lang et al. (29%),[9] respectively. The C-alkylations of **1b** with a variety of alcohols, such as *p*- and *o*-tolyl alcohol, *p*-methoxybenzyl alcohol, *p*-phenylbenzyl alcohol, *p*-*N*,*N*-dimethylaminobenzyl alcohol, *m*-chlorobenzyl alcohol, and naphthalenemethanols, gave the corresponding C-alkylated products (**4b−i**) in good to

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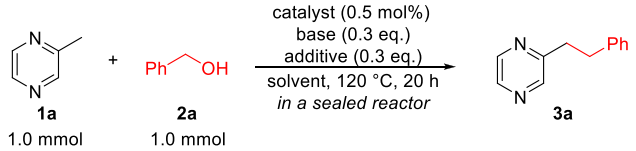
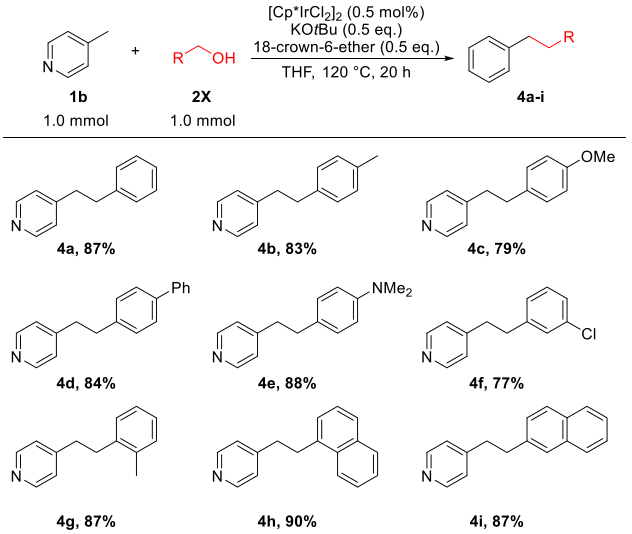
Table 1. C-Alkylation of 2-Methypyrazine (1a) with Benzyl Alcohol (2a) under Various Conditions[a]



entry	catalyst	base	additive	solvent	yield of 3a[b]
1	$[Cp^*IrCl_2]_2$	KO*t*Bu		THF	29
2	$[Cp^*RhCl_2]_2$	KO*t*Bu		THF	13
3	$[(cymene)RuCl_2]_2$	KO*t*Bu		THF	4
4[c]	$[IrCl(cod)]_2/PPh_3$	KO*t*Bu		THF	20
5	$[Cp^*IrCl_2]_2$	KO*t*Bu	18-*crown*-6-ether	THF	84
6	$[Cp^*IrCl_2]_2$	KOH	18-*crown*-6-ether	THF	47
7[d]	$[Cp^*IrCl_2]_2$	K_2CO_3	18-*crown*-6-ether	THF	N.R.
8	$[Cp^*IrCl_2]_2$	NaO*t*Bu	15-*crown*-5-ether	THF	40
9	$[Cp^*IrCl_2]_2$	KO*t*Bu	18-*crown*-6-ether	DME	71
10	$[Cp^*IrCl_2]_2$	KO*t*Bu	18-*crown*-6-ether	*t*BuOH	83
11	$[Cp^*IrCl_2]_2$	KO*t*Bu	18-*crown*-6-ether	toluene	47
12[e]	$[Cp^*IrCl_2]_2$	KO*t*Bu	18-*crown*-6-ether	THF	92

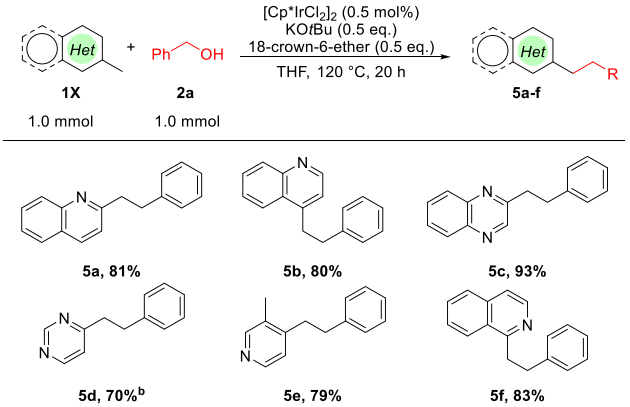
[a]Reaction was carried out with **1a** (1.0 mmol), **2a** (1.0 mmol), catalyst (0.5 mol %), base (0.3 mmol), additive (0.3 mmol), and solvent (1.0 mL) at 120 °C for 20 h. [b]GC yield determined by using biphenyl as an internal standard. [c]PPh_3 (2 mol %) was used. [d]18-*crown*-6-ether (0.6 mmol) was used. [e]KO*t*Bu (0.5 mmol) and 18-*crown*-6-ether (0.5 mmol) were used.

Scheme 3. Scope of Alcohols for C-Alkylation of 4-Methyl Pyridine (1b)[a]



[a]Reaction was carried out with **1b** (1.0 mmol), primary alcohol (1.0 mmol), $[Cp^*IrCl_2]_2$ (0.5 mol %), KO*t*Bu (0.5 mmol), 18-*crown*-6-ether (0.5 mmol), and THF (1.0 mL) at 120 °C for 20 h. Isolated yields are shown.

Scheme 4. Scope of *N*-Heteroaromatic Compounds for C-Alkylation with Benzyl Alcohol (2a)[a]



[a]Reaction was carried out with *N*-heteroaromatic compounds (1.0 mmol), **2a** (1.0 mmol), $[Cp^*IrCl_2]_2$ (0.5 mol %), KO*t*Bu (0.5 mmol), 18-*crown*-6-ether (0.5 mmol), and THF (1.0 mL) at 120 °C for 20 h. Isolated yields are shown. [b]Reaction was carried out at 140 °C.

high yields. These results would be a good example of the improvement for the C-alkylation of **1b** with alcohols.

We next investigated the range of applicable *N*-heteroaromatic compounds to the present catalytic system (Scheme 4). The reactions of quinoline derivatives having a methyl substituent at the two- or four-position with **2a** gave the corresponding products (**5a** and **5b**) in good yields of 81 and 80%, respectively. The reactions of 2-methylquinoxaline and 4-methylpyrimidine with **2a** gave the target products (**5c** and **5d**) in yields of 93 and 70%, respectively. It should be noted that the reaction of 3,4-dimethylpyridine resulted in selective C-alkylation at the four-position to give **5e** in 79% yield. Additionally, the C-alkylation of 1-methylisoquinoline with **2a** was also possible by the present catalytic system, giving **5f** in high yield (83%). Furthermore, double C-alkylation starting with 2,5-dimethylpyrazine and 2 equiv of **2a** proceeded by the present catalytic system to give **6a** in 60% yield (Scheme 5). This reaction proceeded without undesired side reactions.

A possible reaction mechanism for the C-alkylation of methylated *N*-heteroaromatic compounds with primary alcohols based on a hydrogen-borrowing process is shown in Scheme 6.[17] This reaction proceeds through three steps: (i) Hydrogen transfer from a primary alcohol to an iridium catalyst occurs to form an aldehyde and an iridium hydride species. (ii) Cross-aldol-type condensation between an aldehyde and a methyl-substituted *N*-heteroaromatic compound under basic conditions occurs, giving an alkenyl *N*-heteroaromatic intermediate. (iii) Transfer hydrogenation of an alkenyl *N*-heteroaromatic intermediate with an iridium hydride species

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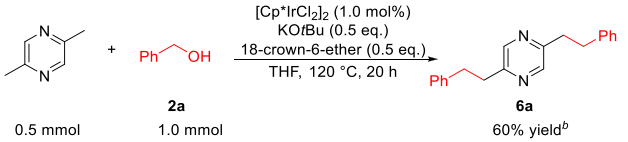
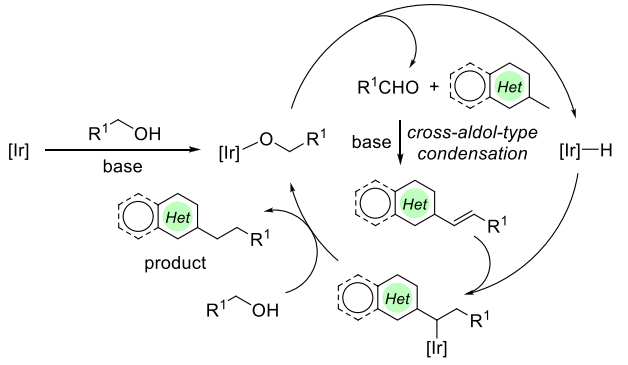
Scheme 5. Double C-Alkylation of 2,5-Dimethylpyrazine with Benzyl Alcohol (2a)



[a]Reaction was carried out with 2,5-dimethylpyrazine (0.5 mmol), **2a** (1.0 mmol), $[Cp^*IrCl_2]_2$ (1.0 mol %), KO*t*Bu (0.5 mmol), 18-*crown*-6-ether (0.5 mmol), and THF (1.0 mL) at 120 °C for 20 h. [b]Isolated yield.

Scheme 6. Reaction Mechanism for the C-Alkylation of Methylated *N*-Heteroaromatic Compounds with Primary Alcohols Based on the Hydrogen-Borrowing Process



and the primary alcohol occurs, giving an alkylated *N*-heteroaromatic product and an iridium alkoxide species.

In summary, we have developed a new and versatile catalytic system for the C-alkylation of *N*-heteroaromatic compounds using primary alcohols. A variety of methylated *N*-heteroaromatic compounds were alkylated with primary alcohols in the presence of a simple iridium catalyst, $[Cp^*IrCl_2]_2$, combined with a base and a crown ether. We believe that this new catalytic system will contribute to the synthesis of useful pharmaceuticals and functional materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02635.

General experimental procedures and spectroscopic data for the corresponding products, characterization data, and NMR spectra (PDF)

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Author Contributions

M.O. established the reaction system and drafted the original manuscript. K.F. conceptualized, supervised, financed, reviewed, and edited the manuscript.

Notes

The authors declare no competing financial interest.

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(13) In each of the previously reported catalytic systems (refs 7−12), only a few kinds of substrates among 4-methylpyrimidine, 2-

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methylpyrazine, 2-methylquinoline, 2-methylquinoquinoxaline, 4-methylquinoline, and 1-methylisoquinoline were applicable. However, with our catalytic system reported in this Letter, the C-alkylation reaction of all of these substrates with primary alcohols was achieved.

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(16) The acidities of methyl groups on various heterocycles would affect the reactivity in C-alkylation with alcohols. On the basis of a previous publication, the methyl group in 4-methylpyridine (**1b**) would have a lower acidity than the methyl group in 2-methylpyrazine (**1a**), 2-methylquinoline, or 2-methylquinoxaline: Zoltewicz, J. A.; Helmick, L. S. *J. Org. Chem.* **1973**, *38*, 658. Therefore, the C-alkylation of **1b** would be difficult, and there were no previous examples that realized such a transformation with high efficiency. In the present catalytic system, the combination of a strong base (KO*t*Bu) with 18-*crown*-6-ether was employed in an aprotic solvent, making the highly strong basic conditions compared with the previous catalytic systems for the C-alkylation of a methyl group on *N*-heterocyclic compounds. This would be a key point for the successful C-alkylation of a variety of substrates in this study.

(17) A similar catalytic mechanism based on the hydrogen-transfer process has been proposed for C−N and C−C bond-forming reactions using alcohols as alkylating reagents. See refs 3−6.

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