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Letter

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Rhodium(III)-Catalyzed Site-Selective C−H Alkylation and Arylation of Pyridones Using Organoboron Reagents

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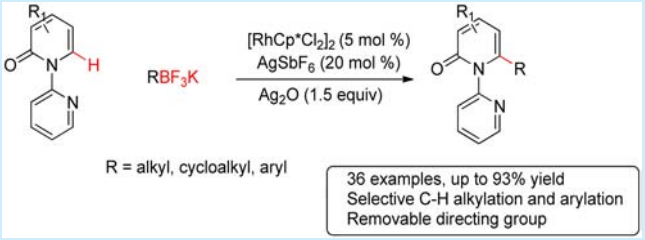
Supporting Information

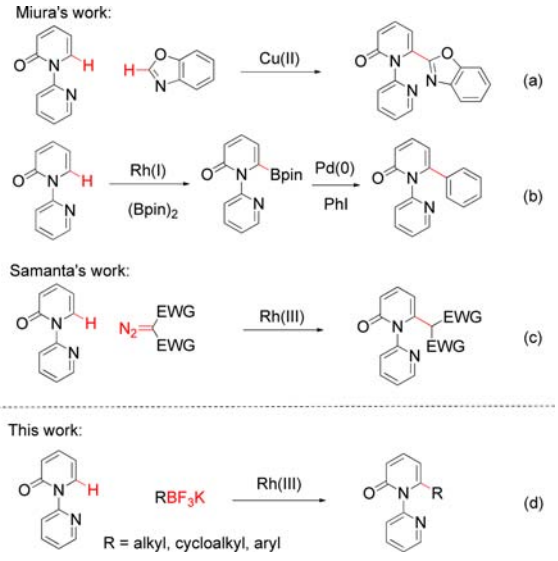
ABSTRACT: In this study we developed a method for the pyridine-directed, rhodium-catalyzed, site-selective C−H alkylation and arylation of pyridones using commercially available trifluoroborate reagents. This simple and versatile transformation proceeded smoothly under relatively mild conditions with perfect site selectivity. The coupling groups in the boron reagents can be extended to primary alkyl, benzyl, and cycloalkyl. Moreover, direct C−H arylation products could also be obtained under similar conditions.



The pyridone motif is a prevalent heterocyclic structure in many biologically active compounds.[1] Therefore, the development of protocols for the functionalization of pyridone-containing rings has received significant attention. Traditionally, the alkylation of pyridones was often performed using halogenated pyridones as the starting material.[1a,e,f] In recent decades, the direct C−H functionalization strategy represents a more effective synthetic route to the formation of C−C and C−heteroatom bonds.[2] Although transition-metal-promoted, site-selective C−H functionalization of relatively electron-rich C3[3] and C5[4] positions of 2-pyridones have been well investigated, access to the more electron-deficient C6-selective position is still underdeveloped.[5] Nakao, Hiyama, and co-workers demonstrated C6-selective alkenylation and alkylation using nickel/aluminum catalysis.[5a,b] Cramer and co-workers developed the synthesis of 1,6-annulated 2-pyridones by intramolecular nickel/aluminum catalyzed cyclization.[5c] Recently, Miura and co-workers discovered the synthesis of C6-selective heteroarylated 2-pyridones by copper-mediated, pyridine-directed dehydrogenation (Scheme 1a).[5d] Since then, some research groups have reported transition-metal-mediated C−H functionalization at the C6 position.[6] Among them, Miura and co-workers further developed rhodium-catalyzed, site-selective C−H borylation of 2-pyridones with bis(pinacolato)diboron. Thus, palladium-catalyzed Suzuki−Miyaura cross-coupling could be achieved (Scheme 1b).[6e] Samanta and co-workers reported rhodium catalyzed C6-alkylation of 2-pyridones with α-diazocarbonyl compounds (Scheme 1c).[6b] Despite the above-mentioned progress, direct and efficient C6-selective C−H alkylation and arylation of 2-pyridones remain undeveloped.

Organoboron reagents have been extensively employed in C−H functionalization.[7] Recently, rhodium-catalyzed C−H activation of arenes leading to efficient cross-couplings has attracted increasing attention.[8] Although rhodium-catalyzed direct C−H arylation has been achieved,[9] related alkylation of arene remains unexplored.[7g] In this letter, we report the rhodium-catalyzed, site-selective C−H alkylation and arylation of pyridones using potassium trifluoroborates (Scheme 1d).

Scheme 1. C6-Selective Functionalization of 2-Pyridones



During our studies on the C6-selective C−H functionalization of 2-pyridones,[6d] we initially attempted the catalytic direct C6 alkylation of 1-(2-pyridyl)-2-pyridone (**1a**) (Table 1). We found the coupling reagents potassium alkyltrifluoroborates are crucial. Using $MeBF_3K$ (3.0 equiv) as the coupling reagent and $[RhCp^*Cl_2]_2$ (5 mol %) as the catalyst, a desired coupling

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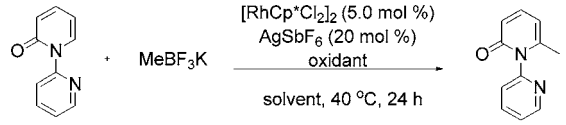
Table 1. Optimization Studies[a]



1a 2a 3a

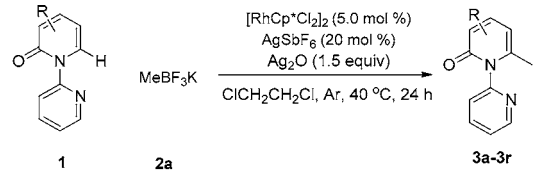
entry	Oxidant (equiv)	solvent	yield[b] (%)
1	AgOAc (3.0)	$ClCH_2CH_2Cl$	11
2	Ag_2CO_3 (1.5)	$ClCH_2CH_2Cl$	10
3	$AgBF_4$ (3.0)	$ClCH_2CH_2Cl$	15
4	AgF (3.0)	$ClCH_2CH_2Cl$	89
5	Ag_2O (1.5)	$ClCH_2CH_2Cl$	91
6	$Cu(OAc)_2$ (3.0)	$ClCH_2CH_2Cl$	trace
7	Ag_2O (1.5)	MeOH	trace
8	Ag_2O (1.5)	MeCN	7
9	Ag_2O (1.5)	1,4-dioxane	62
10	Ag_2O (1.5)	toluene	31
11[c]	Ag_2O (1.5)	$ClCH_2CH_2Cl$	7
12[d]	Ag_2O (1.5)	$ClCH_2CH_2Cl$	6
13[e]	Ag_2O (1.5)	$ClCH_2CH_2Cl$	73
14[f]	Ag_2O (1.5)	$ClCH_2CH_2Cl$	65
15[g]	Ag_2O (1.5)	$ClCH_2CH_2Cl$	81
16[h]	Ag_2O (1.5)	$ClCH_2CH_2Cl$	n.d.
17[i]	Ag_2O (1.5)	$ClCH_2CH_2Cl$	trace

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $[RhCp^*Cl_2]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %), and oxidant in solvent (2.0 mL) under argon at 40 °C for 24 h. [b]Isolated yield. [c]Methylboronic acid (0.6 mmol) was used. [d]2-Methyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.6 mmol) was used. [e]Reaction was performed using **2a** (0.4 mmol). [f]Ag_2O (0.2 mmol) was used. [g]Reaction was performed at 25 °C. [h]No $[RhCp^*Cl_2]_2$ was used. [i]No $AgSbF_6$ was used. n.d. = not detected.

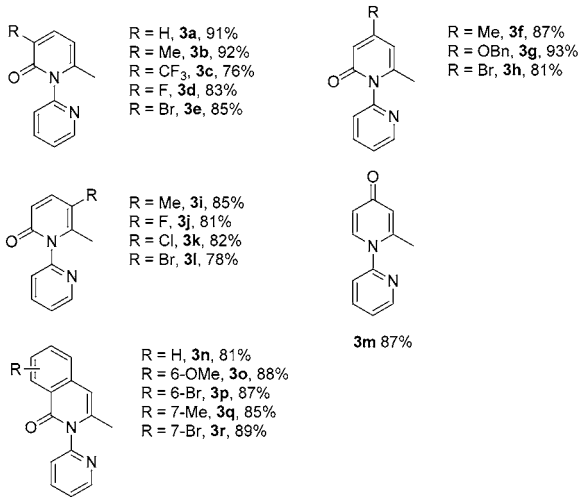
product **3a** was produced in the presence of $AgSbF_6$ (20 mol %) and AgOAc (3.0 equiv) in $ClCH_2CH_2Cl$, albeit with an 11% isolated yield (entry 1). Screening of the oxidant indicated that Ag_2O is crucial (entry 5), AgF showed almost the same efficiency (entry 4), and other oxidants afforded inferior results (entries 2, 3, 6). Optimization of the solvent indicated that $ClCH_2CH_2Cl$ is optimal (entries 7−10). The reaction proceeded inefficiently when the alkylating reagent was replaced by methylboronic acid or 2-methyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (entries 11 and 12). The stated amount of $MeBF_3K$ and Ag_2O seems necessary, because lower yields were obtained when the equivalents were reduced (entries 13 and 14). Lowering the temperature to 25 °C resulted in a slightly diminished yield (entry 15). By contrast, the reaction gave poor or no conversion when $AgSbF_6$ or $[RhCp^*Cl_2]_2$ was omitted (entries 16 and 17).

With the optimized conditions identified, we investigated the scope and limitation of pyridones (Scheme 2). Satisfyingly, the C3 position of 2-pyridones bears either electron-donating or -withdrawing groups (**3b**−**3e**). It should be mentioned that the electron-rich 3-methyl substituted **1b** showed better reactivity. Similarly, in the cases of the C4-substituted 2-pyridones both electron-donating and -withdrawing groups were accommodated, providing the methylation products in excellent yields (**3f**−**3h**). Remarkably, in spite of steric factors, substituents at the C5 position were feasible (**3i**−**3l**). Electron-donating and -withdrawing substituents, such as methyl (**1i**), fluoro (**1j**), chloro (**1k**), and bromo (**1l**), worked efficiently to provide the desired products in high yields. Meanwhile, 4-pyridone **1m**

Scheme 2. Scope of Pyridones[a,b]



1 2a 3a-3r



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), $[RhCp^*Cl_2]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %), and Ag_2O (0.3 mmol) in $ClCH_2CH_2Cl$ (2.0 mL) under argon at 40 °C for 24 h. [b]Isolated yield.

could be methylated monoselectively at the C2 position (**3m**), suggesting that site selectivity is controlled by pyridine coordination rather than the innate nature of pyridones.[5d] Moreover, substituted benzene-fused isoquinolinone could also be used for this transformation, forming the corresponding products in high yields (**3n**−**3r**).

We evaluated the scope of potassium alkyltrifluoroborates (Scheme 3). Generally, alkylation of 2-pyridone **1a** with *n*-butyl, cyclopropanemethyl, and benzyl groups proceeded efficiently to produce **4a**−**4c** in good to high yields. Importantly, alkyl chains bearing phenyl, alkenyl, ester, and amide were compatible with the reaction conditions (**4e**−**4g**), which allowed further transformation. Besides the 1° alkyl groups, 2° alkyl trifluoroborates with much more hindrance afford relatively acceptable yields when AgF was used as the oxidant at higher temperature (**4h** and **4j**). In addition, the more reactive potassium cyclopropyltrifluoroborate afforded an acceptable yield (**4i**).

For broad utility, we explored the possibility of extending this catalytic system to C6-selective arylation of 2-pyridones (Scheme 4).[6e] Indeed, the 6-phenyl-2*H*-[1,2′-bipyridin]-2-one (**6a**) was obtained in high yield (81%) when using the rhodium(III) catalytic system under higher temperature. Arylation of **1a** bearing either electron-donating or -withdrawing functional groups in the *para*-position resulted in the exclusive formation of the C6-arylated products **6d**−**6h** in high yields, which allowed further transformation. However, substituents at the *ortho*-position of the trifluoroborates was detrimental, probably as a result of steric factors (**6b**). Substituents at the less sterically hindered *meta*-position of the trifluoroborates were feasible, which gave the C6-arylated product (**6c**) in moderate yield (56%).

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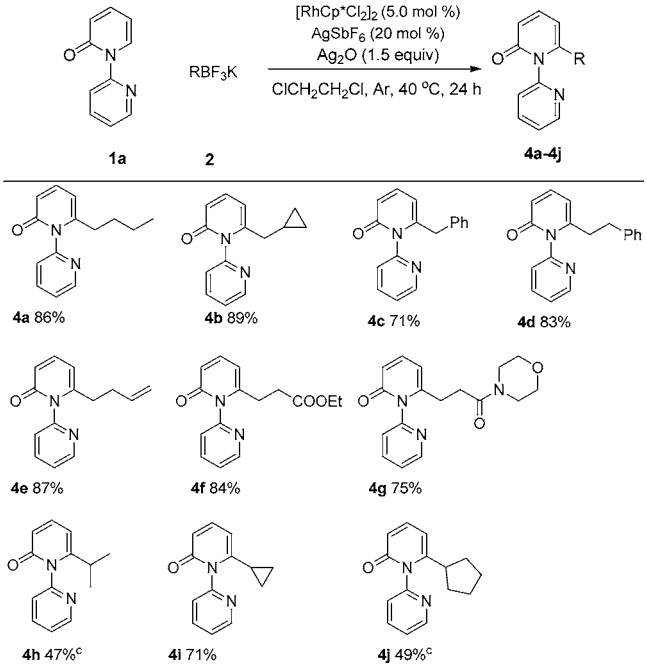
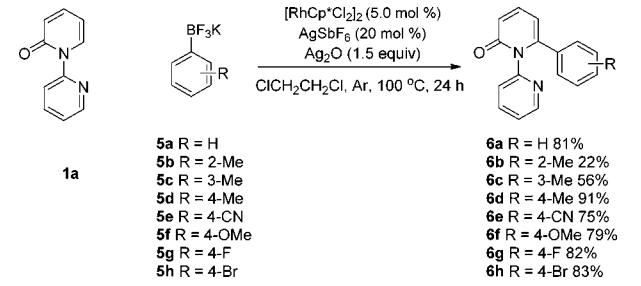
Scheme 3. Scope of Potassium Alkyltrifluoroborates[a,b]



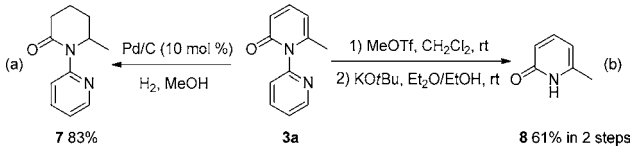
[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), $[RhCp^*Cl_2]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %), and Ag_2O (0.3 mmol) in $ClCH_2CH_2Cl$ (2.0 mL) under argon at 40 °C for 24 h. [b]Isolated yield. [c]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), $[RhCp^*Cl_2]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %), and AgF (0.6 mmol) in $ClCH_2CH_2Cl$ (2.0 mL) under argon at 90 °C for 24 h.

Scheme 4. Preliminary Study of C6 Arylation Reaction



To demonstrate the applicability of this reaction in the synthesis of C6-alkylated piperidin-2-one derivatives[10] which show a wide range of biological activities, further transformation was explored (Scheme 5a). Hydrogenation of **3a**

Scheme 5. Synthetic Transformations of 3a

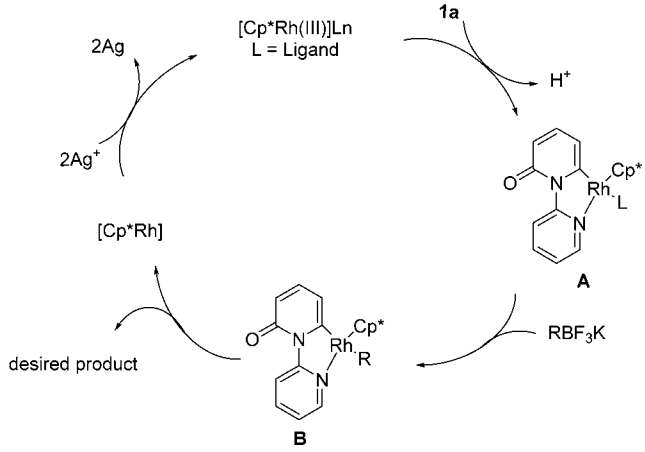


gave the corresponding piperidin-2-one **7** in 83% yield. Furthermore, the directing group could be removed efficiently by the "quaternization and alcoholysis" strategy.[5d,6,11] The corresponding 6-methylpyridin-2(1*H*)-one **8** was obtained easily from **3a** through a mild, two-step sequence in 61% yield (Scheme 5b).

A series of control experiments were performed to explore the possible reaction pathway. First, radical scavenger experiments were implemented (Scheme S1). Separate reactions were conducted by the addition of a stoichiometric amount of a radical inhibitor (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) or an electron-transfer scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT). The alkylated product **3a** was isolated without significantly affecting the efficiency, suggesting that a radical process is not involved in the reaction. Subsequently, to gain insight into the C−H cleavage step, the hydrogen−deuterium (H/D) exchange experiments were carried out (Scheme S2). H/D exchange of **1a** was observed at the C6-position (52% D) under Rh(III) catalysis and using CD_3COOD as the deuterium source, indicating the relevancy of C−H activation. Next, to probe the electronic preference, intermolecular competition experiments were carried out using an equimolar mixture of **1b** and **1c**. The results indicated that the more electron-rich substrate **1b** reacted at a higher rate (Scheme S3).

Based on the preliminary results and literature precedents,[6,7g,9] a plausible alkylation pathway is proposed (Scheme 6). First, a cationic Cp*Rh(III) species, which was generated by

Scheme 6. Proposed Mechanism



the aid of Ag salt, coordinates to the directing group and undergoes electrophilic C−H bond cleavage to form rhodacyclic intermediate **A**. Then, the coupling most likely involves transmetalation between the organoboron reagent to form rhodacyclic intermediate **B**. Next, reductive elimination of intermediate **B** gives rise to the desired product and the Rh(I) species. Finally, the Cp*Rh(III) species is regenerated when the Rh(I) is reoxidized by Ag(I).

In conclusion, we developed a simple, efficient Rh(III)-catalyzed direct site-selective C−H alkylation and arylation of pyridones using potassium trifluoroborates under mild conditions. The reaction proceeded with excellent regioselectivity and functional group tolerance. Furthermore, the directing group can be removed smoothly. This concise protocol to access an important scaffold may have important application in the synthesis of biologically active products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02755.

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Detailed experimental procedures, characterization data, derivatization reactions, mechanistic studies, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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