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Cp*Rh(III)-Catalyzed Regioselective C(sp^3)−H Methylation of 8-Methylquinolines with Organoborons

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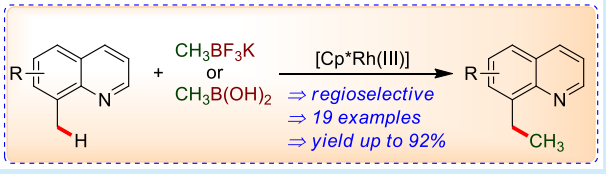
Supporting Information

ABSTRACT: Rh(III)-catalyzed highly regioselective methylation of the unactivated C(sp^3)−H bond of 8-methylquinolines with bench stable organoboron reagents is described. A variety of substituted 8-methylquinolines provided the highly regioselective monomethylated products with potassium methyltrifluoroborates/methylboronic acid through primary C(sp^3)−H bond activation. Complete chemoselectivity and regioselectivity were observed in all cases as methylation at the C2 position or dimethylation of the C(sp^3)−H bond of 8-methylquinoline was not detected. The mechanistic study uncovered the fact that the reaction may proceed through the five-membered rhodacycle intermediate.



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Transition metal-catalyzed C−H bond activation has been broadly utilized for the building of numerous organic molecules.[1] Among various transition metal catalysts, a rhodium(III) catalyst has been well explored for C(sp^2)−H bond functionalization reactions due to its high efficiency and selectivity,[2] whereas the functionalization of more challenging C(sp^3)−H bonds has not been explored much.[3] Recently, Rh(III)-catalyzed transformation has been reported for the functionalization of 8-methylquinoline through C(sp^3)−H bond activation;[4] however, the methylation/alkylation of 8-methylquinolines using a Rh(III) catalyst has not yet been explored.

Methylation is greatly important in pharmaceuticals as the substitution of the methyl group modifies the lipophilicity, solubility, and conformation of the molecules, which leads to the exceptional improvement in the biological activity of the molecules.[5] Among various bioactive molecules, the methyl-substituted molecules such as renexa and NIBR-0213 have shown much better activity as compared to their precursor. Similarly, simvastatin[6] has shown better results as compared to lovastatin; i.e., the methylation leads to a remarkable increase in the potency of these drug molecules (Figure 1). Therefore, various groups reported the transition metal-catalyzed methylation of organic molecules mainly through C(sp^2)−H bond activation.[7]

Significantly, there have been very few reports about the more challenging C(sp^3)−H methylation.[8] Although the Yu group reported the Pd-catalyzed methylation and alkylation of 8-methylquinolines with boroxine and boronic acid reagents (Scheme 1),[9] bench stable potassium methyltrifluoroborates have not yet been explored in this reaction. The organoborane reagents have been used for the C(sp^2)−H bond functionalization of various heterocyclic compounds,[10] and reports of the use of the organoboron reagents in Rh(III)-catalyzed construction of the C(sp^3)−C(sp^3) or C(sp^3)−C(sp^2) bonds are very limited.[11]

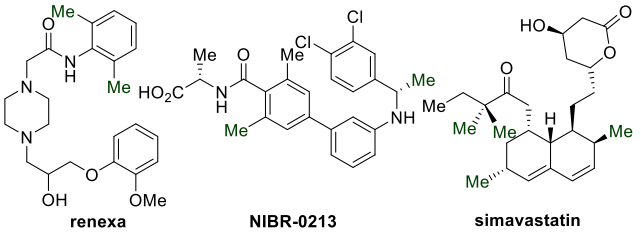
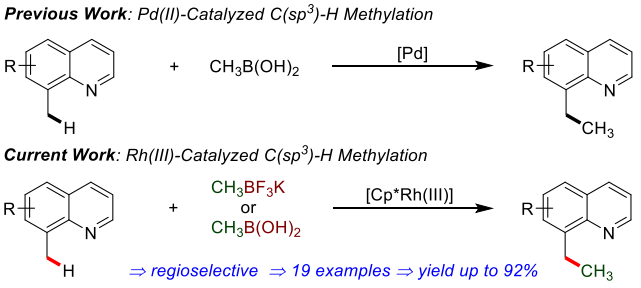


Figure 1. Important methyl-substituted molecules.

Scheme 1. C(sp^3)−H Methylation of 8-Methylquinolines



In continuation of our interest in the C(sp^3)−H bond activation/functionalization,[12] herein we disclosed the first Rh(III)-catalyzed highly regioselective methylation of the primary C(sp^3)−H bonds of 8-methylquinolines with bench stable potassium methyltrifluoroborate.

We initiated our study with the reaction between 8-methylquinoline (**1a**) and potassium methyltrifluoroborate (**2a**) in the presence of $[RhCp^*Cl_2]_2/AgSbF_6$ as a catalyst, AgF as an additive, and DME as a solvent at 100 °C for 24 h. Pleasingly, under these conditions, we obtained a 45% yield of

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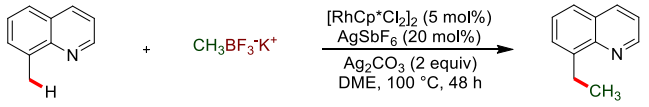
the expected methylated product (Table 1, entry 13). The methylated product was confirmed on the basis of one-

Table 1. Optimization Study[a]



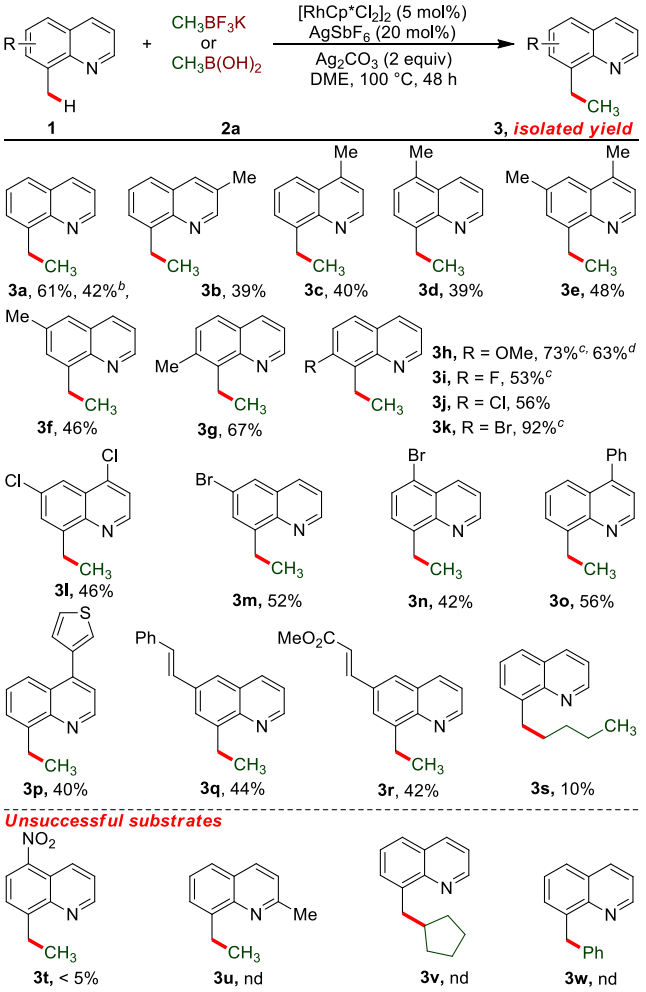
	variation from standard conditions	yield (%)[b]
1	–	66 (61)[c]
2	without Ag_2CO_3	38
3	without $[RhCp^*Cl_2]_2/AgSbF_6$	nd
4	24 h	56
5	36 h	60
6	72 h	–
7	EtOH, 24 h	53
8	H_2O, 24 h	40
9	DCE, 24 h	30
10	80 °C	50
11	under an Ar atmosphere	64
12	4 equiv of **2a**	61
13	AgF instead Ag_2CO_3, 24 h	45
14	under an O_2 atmosphere without Ag_2CO_3	<5

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (2 equiv), DME (0.5 mL), 100 °C, 48 h. [b]Yield based on NMR analysis of the crude reaction mixture using tetrachloroethane as an internal standard. [c]Isolated yield in parentheses.

dimensional and two-dimensional NMR and mass spectrometry.[13] When the reaction was carried out at 80 °C, a 50% yield of the desired product was observed (Table 1, entry 10). Control experiments without using a catalyst or an additive explained the necessity of both for the formation of the desired product (Table 1, entries 2 and 3). A variety of solvents were screened, and DME was found to be the solvent of choice (Table 1, entries 1 and 7–9). Increasing the reaction time to 48 h was found to be helpful, but beyond, 48 h diminution in the yield of **3a** was observed (Table 1, entries 1 and 4–6). An increase in the loading of **2a** (≤4 equiv) was not helpful (Table 1, entry 12). Using molecular O_2 as an oxidant instead of Ag_2CO_3 provided only traces of the desired alkylated product (Table 1, entry 14). The comparative yield was observed under an inert atmosphere (Table 1, entry 11). The reaction conditions using 0.1 mmol of **1a** and 0.3 mmol of **2a** in the presence of $[RhCp^*Cl_2]_2/AgSbF_6$ as a catalytic system and Ag_2CO_3 as an oxidant in the presence of DME at 100 °C for 48 h were finalized (Table 1, entry 1). The detailed optimization study has been included in the Supporting Information (Table S1).[13]

Next, substituted 8-methylquinolines (**1**) were reacted with potassium methyltrifluoroborate (**2a**) under the best developed reaction condition (Scheme 2). The methyl substituents at positions C3–C7 of 8-methylquinolines were well tolerated and afforded the methylated products in 39–67% yields with complete monoselectivity (**3b–g**). 8-Methylquinolines substituted with -OMe, -F, -Cl, and -Br at C7 and -Cl and -Br at C5 and C6 were also quite compatible under the developed reaction conditions and gave the desired monomethylated product in moderate to good yields (**3h–n**, 42–92%). 4-Phenyl- and 8-methyl-4-(thiophen-3-yl)quinoline also reacted

Scheme 2. Methylation/Alkylation of 8-Methylquinolines[a]



[a]Reaction conditions: **1** (0.30 mmol), **2** (0.90 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (2 equiv), DME (1.5 mL), 100 °C, 48 h. [b]Use of $MeB(OH)_2$ instead of **2a**. [c]Reaction time of 60 h. [d]In a 1.0 mmol scale reaction using $[RhCp^*Cl_2]_2$ (2.5 mol %) and $AgSbF_6$ (10 mol %).

smoothly (**3o** and **3p**). A sensitive functional group such as an olefin at C6 of 8-methylquinoline remains intact and provided the corresponding desired monomethylated products in moderate yield (**3q** and **3r**). The reaction of **1a** with potassium *n*-butyltrifluoroborate provided a very low yield of the desired alkylated product (**3s**) along with the formation of an uncharacterized side product. When 5-nitro-8-methylquinoline and 2,8-dimethylquinoline were reacted with **2a** under the optimal reaction conditions, no product formation was observed (Scheme 2, entries **3t** and **3u**, respectively). Unfortunately, in the case of potassium cyclopentyltrifluoroborate and phenyltrifluoroborate, no product was observed (**3v** and **3w**, respectively). Significantly, the reaction also proceeds with methylboronic acid affording the desired product **3a** in 42% yield.

Several control experiments were performed to gain insight into the reaction pathway (Schemes S1–S6).[13] A deuteration experiment in DME/CD_3OD revealed irreversible C–H bond cleavage with or without potassium methyl trifluoroborate (**2a**) (Scheme 3a). The kinetic isotope effect was analyzed by competition and parallel experiments that revealed that the C–

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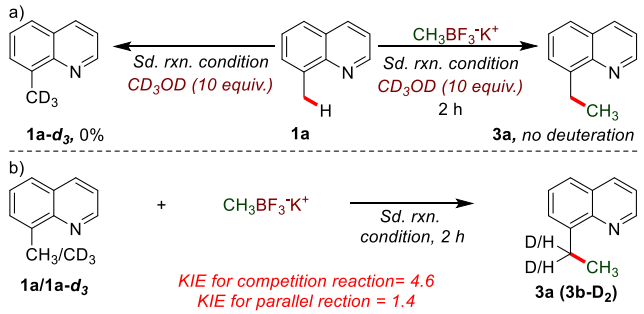
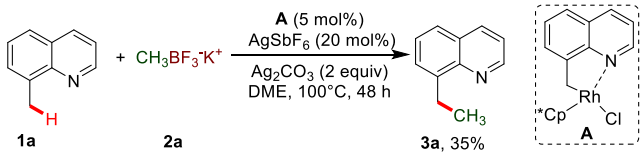
Scheme 3. Deuterium Labeling Experiments



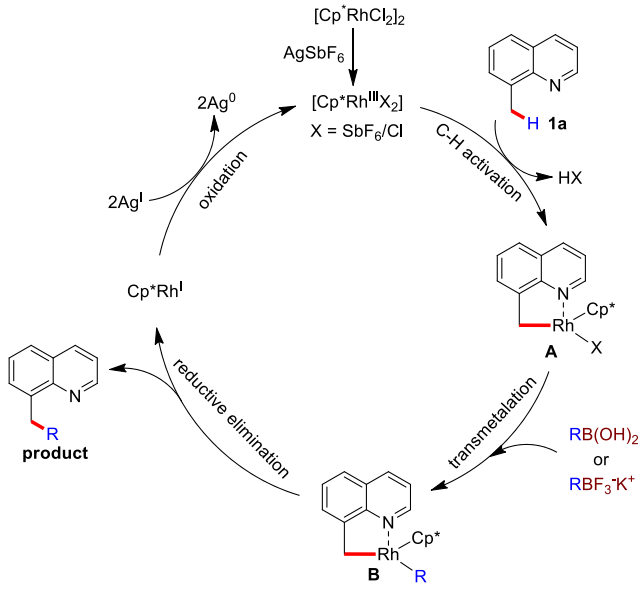
H bond cleavage step might be the rate-determining step (Scheme 3b). Subsequently, a five-membered rhodacycle (**A**) of 8-methylquinoline was synthesized by an earlier known method.[4b] Use of the rhodacycle (**A**) as a catalyst afforded 35% methylated product, confirming its intermediacy in the reaction (Scheme 4).

Scheme 4. Intermediate Study



On the basis of the experiments described above and literature reports,[11] a possible mechanism is proposed (Scheme 5). Initially, active Rh(III) species is formed in the presence of

Scheme 5. Plausible Mechanistic Cycle



$AgSbF_6$. This leads to the formation of a rhodacycle (**A**) with **1a**. This intermediate **A** in the presence of a methyl organoboron reagent gives **B** via ligand exchange. Finally, reductive elimination afforded the desired product **C** and Rh(I) species, which converted into active Rh(III) species in the presence of an oxidant to continue the catalytic cycle.

In summary, we have reported a Cp*Rh(III)-catalyzed regioselective C−H methylation of C(sp^3)−H of 8-methylquinolines with organoboron reagents. The developed method has a broad substrate scope with excellent regioselectivity and good to high yields. The preliminary mechanistic study revealed a five-membered rhodacycle as the key intermediate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04331.

General considerations, preparation of substituted 8-methylquinolines, reaction of 8-methylquinolines with potassium methyltrifluoroborate, mechanistic study, references, and ^1H and ^{13}C spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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