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N-Methylation of Amines with Methanol in the Presence of Carbonate Salt Catalyzed by a Metal–Ligand Bifunctional Ruthenium Catalyst [(*p*-cymene)Ru(2,2′-bpyO)(H_2O)]

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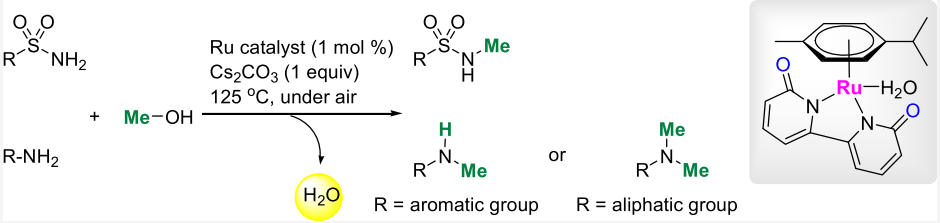

ABSTRACT: A ruthenium complex [(*p*-cymene)Ru(2,2′-bpyO)(H_2O)] was found to be a general and efficient catalyst for the *N*-methylation of amines with methanol in the presence of carbonate salt. Moreover, a series of sensitive substituents, such as nitro, ester, cyano, and vinyl groups, were tolerated under present conditions. It was confirmed that OH units in the ligand are crucial for the catalytic activity. Notably, this research exhibited the potential of metal–ligand bifunctional ruthenium catalysts for the hydrogen autotransfer process.

INTRODUCTION

N-methylated amines represent one of the important nitrogen-containing compounds, which display a wide range of biological properties and are also utilized as valuable synthetic building blocks for many natural products, pharmaceuticals, materials, and fine chemicals.[1] The *N*-methylation of amines provides one of the most direct and simplest methods for the synthesis of *N*-methylated amines and is typically performed with methyl iodide, dimehylasulphate, or diazomethane as methylating agents under basic conditions.[2] Despite being effective, these approaches involve the use of carcinogenic methylating and/or highly toxic reagents, low selectivity (overmethylated products were easily generated), and the formation of a large amount of waste. With the increasing requirement of environmental protection, considerable attention has been directed to transition metal-catalyzed *N*-methylation of amines with methanol as an alternative methylating agent based on a hydrogen-borrowing strategy or a hydrogen autotransfer process,[3] using iridium,[4] ruthenium,[5] manganese,[6] iron,[7] cobalt,[8] rhenium,[9] and palladium[10] catalysts. In this process, methanol is initially dehydrogenated to formaldehyde, followed by condensation between the resulting formaldehyde and amines, giving unsaturated imines, which goes through transfer hydrogenation by the metal hydride species to form *N*-methylated amines. This approach is attractive due to the utilization of a renewable and abundant C1 source,[11] high atom economy, and formation of water as the only side product. However, these procedures were usually performed in the presence of an inorganic strong base (KOtBu, LiOtBu, KOH, or NaOH) and thus the practical application is highly restricted.[12]

Recently, Fujita and co-workers synthesized a series of Cp*Ir complexes bearing a hydroxybipyridine or a bipyridonate ligand, which are efficient catalysts for acceptorless dehydrogenation of alcohols and N-heterocycles[13] and hydrogen production from an alcohol–water solution.[14] We also demonstrated that these complexes are highly effective metal–ligand bifunctional catalysts for the hydrogen autotransfer process,[15] acceptorless dehydrogenative coupling,[16] and transfer hydrogenation of aldehydes and ketones.[17] Chen and Ke group also independently developed two Cp*Ir complexes bearing a hydroxybipyridine ligand for the hydrogen autotransfer process.[18] As part of continuing interest in this field,[15−17] we turned our attention from iridium complexes to ruthenium ones because the latter are much cheaper than the former and the utilization of them as catalysts for the hydrogen autotransfer process remains unexplored.[19] Herein, we wish to describe our effort toward the *N*-methylation of a range of amines with methanol under a weak base catalyzed by a metal–ligand bifunctional ruthenium catalyst (Scheme 1).

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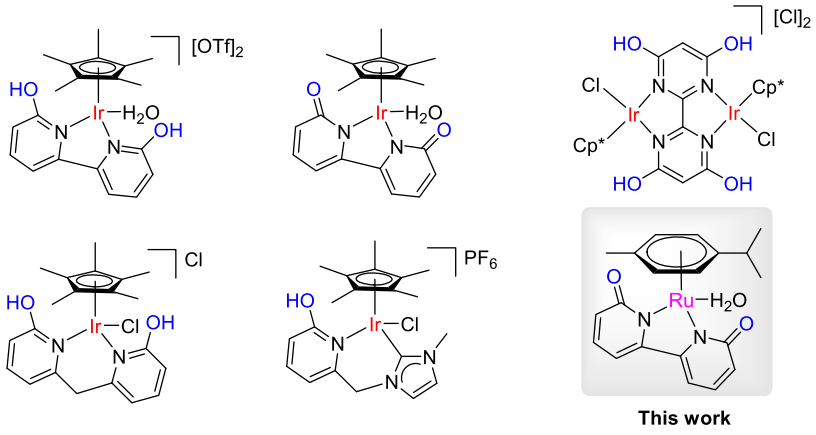
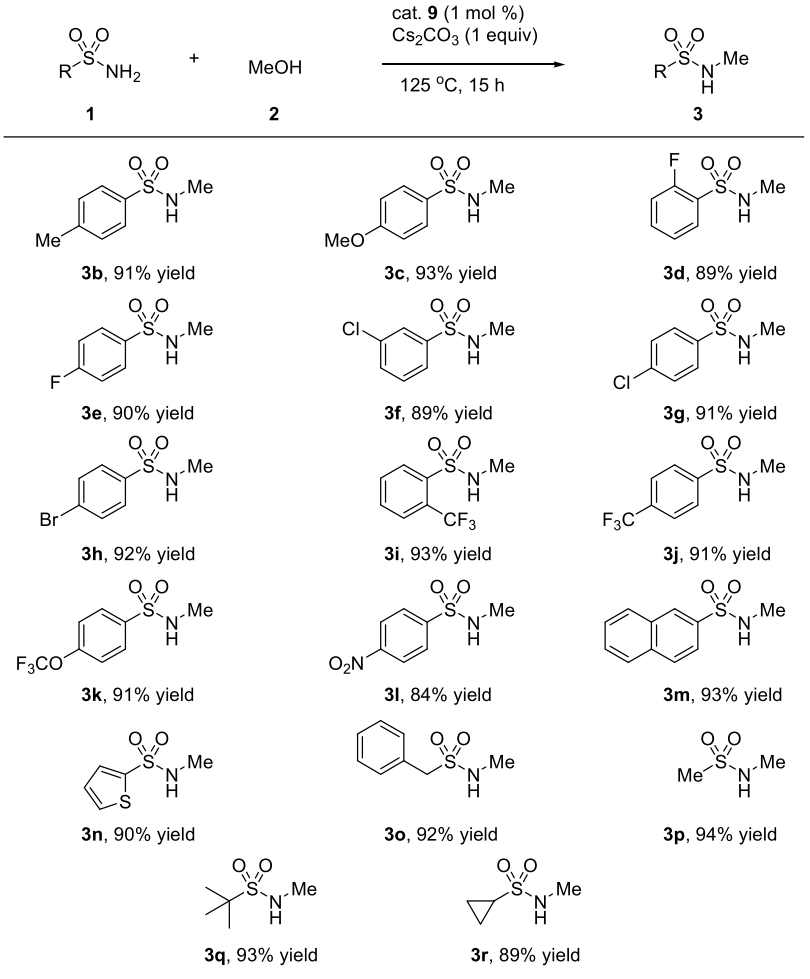
Scheme 1. Metal−Ligand Bifunctional Catalysts for the Hydrogen Autotransfer Process



Scheme 2. *N*-Methylation of a Variety of Sulfonamides with Methanol Catalyzed by [(*p*-Cymene)Ru(2,2′-bpyO)(H_2O)]



[a]Reaction conditions: **1** (0.5 mmol), **2** (1 mL), cat. **9** (1 mol %), Cs_2CO_3 (1 equiv), 125 °C, 15 h. [b]Isolated yield.

RESULTS AND DISCUSSION

To explore the feasibility of the above proposal, the *N*-methylation of benzenesulfonamide (**1a**) with methanol (**2**) was chosen as a model reaction (Table 1). A series of ruthenium complexes, including [(*p*-cymene)$RuCl_2]_2$ (cat. **1**), [(*p*-cymene)$RuCl_2(PPh_3)$] (cat. **2**), [(*p*-cymene)$RuCl_2$(P-$(NMe_2)_3$)] (cat. **3**), [{$RuCl(\mu$-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] (cat. **4**), [$(terpy)_3RuCl_3$] (cat. **5**), [$RuCl_2(PPh_3)_3$] (cat. **6**), [(*p*-cymene)Ru{6,6′-$(OMe)_2$-2,2′-bpy(H_2O)}][OTf]$_2$ (cat. **7**), [(*p*-cymene)Ru(6,6′-$(OH)_2$bpy)(H_2O)][OTf]$_2$ (cat. **8**), and [(*p*-cymene)Ru(2,2′-bpyO)(H_2O)] (cat. **9**), were screened for their catalytic activities to the model reaction. In the presence of cat. **1**−**7** and Cs_2CO_3 (1 equiv), the reaction was carried out for 15 h to give the *N*-methylated product **3a** in less than 49% yield (Table 1, entries 1−7). To our delight, the yield of **3a** could be

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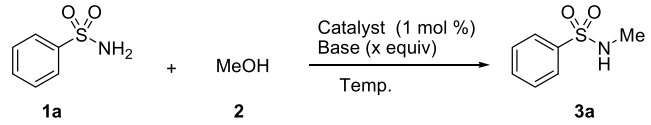
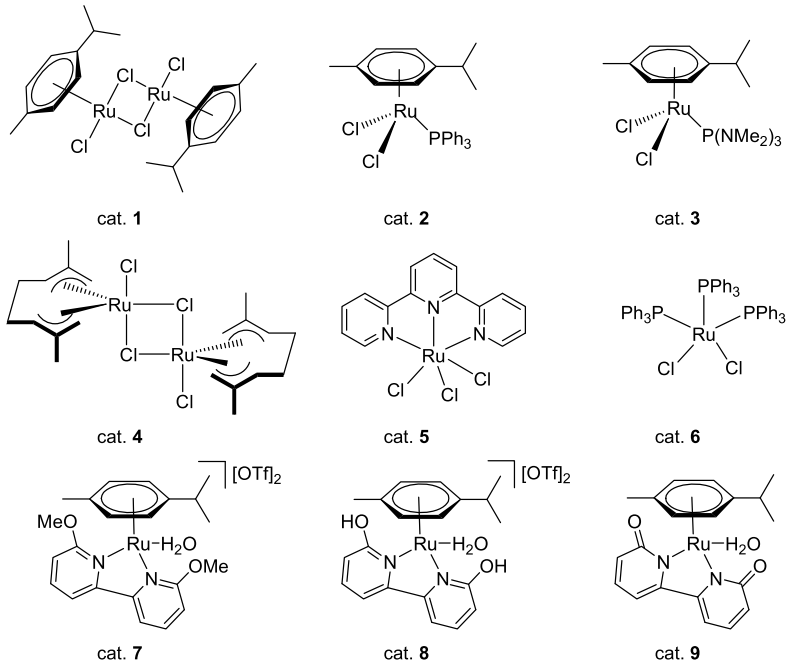
Table 1. *N*-Methylation of Aniline with Methanol under Various Conditions[a]



1a 2 3a

Entry	Catalyst	Base	Temp.	x	Yield (%)[b]
1	cat. **1**	Cs_2CO_3	125	1	27
2	cat. **2**	Cs_2CO_3	125	1	35
3	cat. **3**	Cs_2CO_3	125	1	31
4	cat. **4**	Cs_2CO_3	125	1	28
5	cat. **5**	Cs_2CO_3	125	1	<5
6	cat. **6**	Cs_2CO_3	125	1	<5
7	cat. **7**	Cs_2CO_3	125	1	49
8	cat. **8**	Cs_2CO_3	125	1	83
9	**cat. 9**	**Cs_2CO_3**	**125**	**1**	**95 (89[c])**
10	cat. **9**	Cs_2CO_3	115	1	70
11	cat. **9**	Cs_2CO_3	125	0.5	75
12	cat. **9**	K_2CO_3	125	1	81
13	cat. **9**	Na_2CO_3	125	1	77



[a]Reaction conditions: **1a** (0.5 mmol), **2** (1 mL), catalyst (1 mol %), base (*x* equiv), 15 h. [b]Yield was determined based on the ^{1}H NMR spectrum of the crude reaction mixture. [c]Isolated yield.

enhanced to 83 and 95%, respectively, when cat. **8** and cat. **9** were serviced (Table 1, entries 8 and 9). Obviously, functional groups in the bpy ligand are crucially important for the catalytic activities. To decrease the reaction temperature, use K_2CO_3 or Na_2CO_3 as an alternative base or reduce the amount of Cs_2CO_3, which results in relatively low yields (Table 1, entries 10−13).

Inspired by the promising result (Table 1, entry 9), the *N*-methylation of a series of sulfonamides with methanol was conducted and these results are outlined in Scheme 2. The reactions of sulfonamides bearing an electron-donating substituent, such as methyl and methoxy groups, gave corresponding products **3b** and **3c** in 91 and 93% yields, respectively. For sulfonamides bearing a halogen atom, such as fluoride, chloride, and bromide, desired products **3d−h** were obtained in 89−92% yields. More serious electron-withdrawing substituents, including trifluoromethyl, trifluoromethoxy, and nitro groups, were tolerated as well and transformations gave corresponding products **3i−l** in 84−93% yields. When naphthyl- and thienyl-substituted substrates were used, *N*-methylated products **3m** and **3n** were isolated in 93 and 90% yields, respectively. The catalytic system was also proven to be suitable for aliphatic sulfonamides, such as benzenemethanesulfonamide, methanesulfonamide, *tert*-butylsulfonamide, and cyclopropanesulfonamide, affording desired products **3o−r** in 89−94% yields.

To further expand the scope of the reaction, the *N*-methylation of a variety of aromatic and aliphatic amines with methanol was evaluated (Scheme 3). Transformations of aniline

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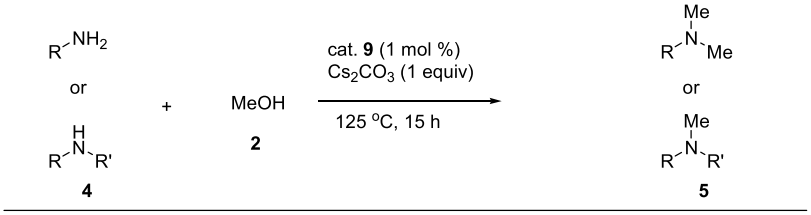
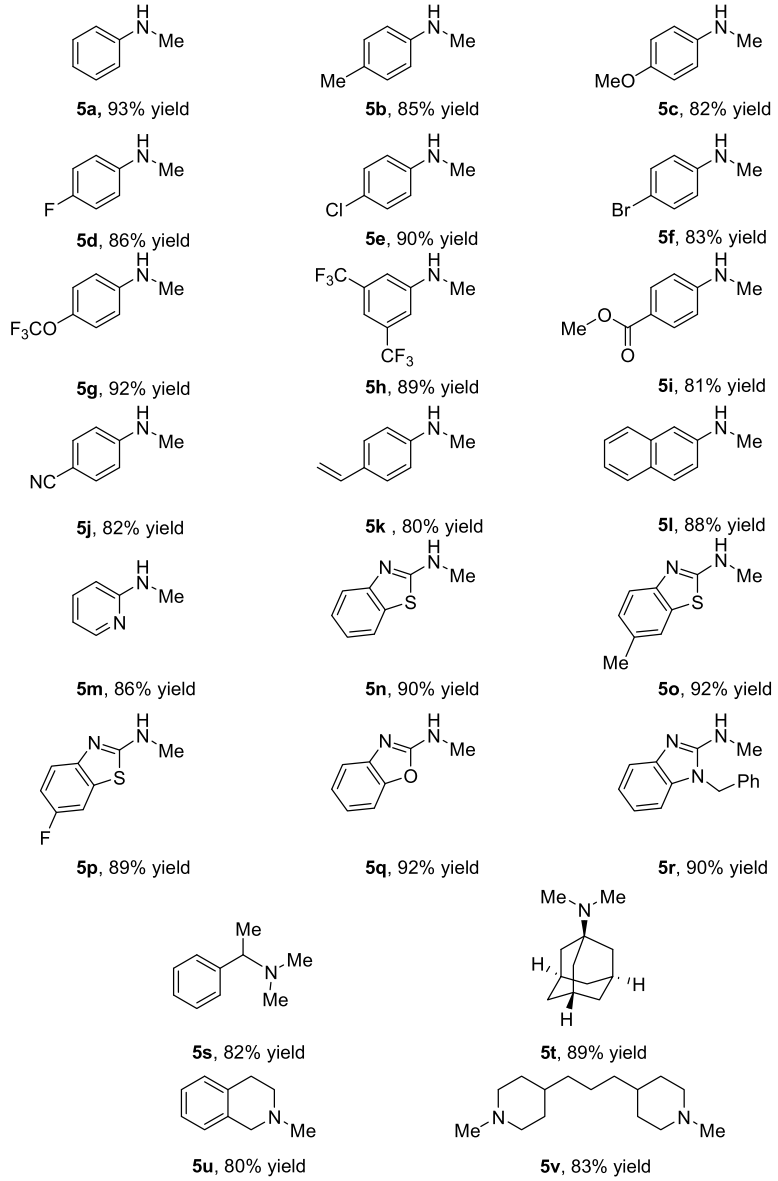
Scheme 3. *N*-Methylation of a Series of Aromatic and Aliphatic Amines with Methanol Catalyzed by [(*p*-Cymene)Ru(2,2′-bpyO)(H_2O)]





[a]Reaction conditions: **4** (0.5 mmol), **2** (1 mL), cat. **9** (1 mol %), Cs_2CO_3 (1 equiv), 125 °C, 15 h.
[b]Isolated yield.

afforded the desired product **5a** in 93% yield. As anilines bearing both electron-donating and electron-withdrawing substituents were utilized as substrates, corresponding products **5b**–**h** were obtained in 82–92% yields. Furthermore, sensitive functional groups, such as ester, cyano, and vinyl groups, were tolerated and the reactions afforded desired products **5i**–**k** in 80–82% yields. Naphthylamine and aminopyridine are also compatible with this system, giving corresponding products **5l** and **5m** in 88 and 86% yields, respectively. The *N*-methylation of 2-amino-azole derivatives, such as 2-amino-thiazoles, 2-amino-oxazole, and 2-amino-imidazole, exhibited complete regioselectivities and only N-exo-substituted products **5n**–**r** were obtained. When aliphatic amines, such as α-methylbenzylamine and amantadine, were used, the reactions proceeded smoothly to afford *N*,*N*-dimethylated products **5s** and **5t** in 82 and 89% yields, respectively. For secondary amines, such as 1,2,3,4-tetrahydroisoquinoline and 4-(3-(piperidin-4-yl)propyl)piperidine,

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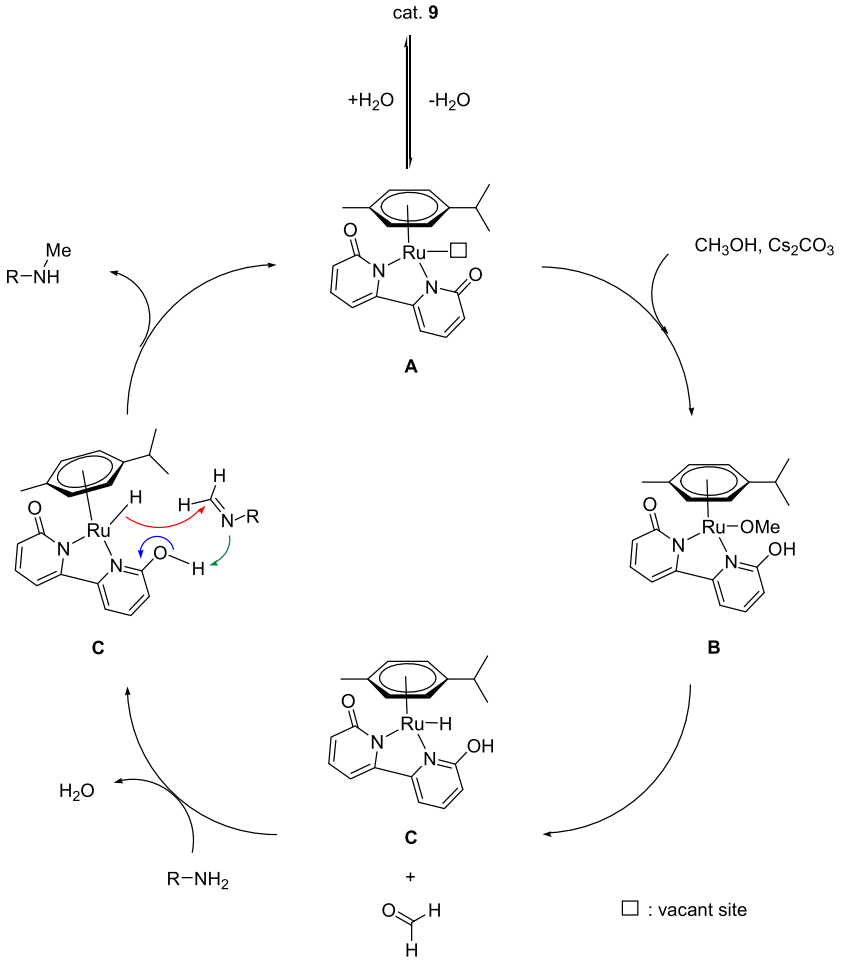
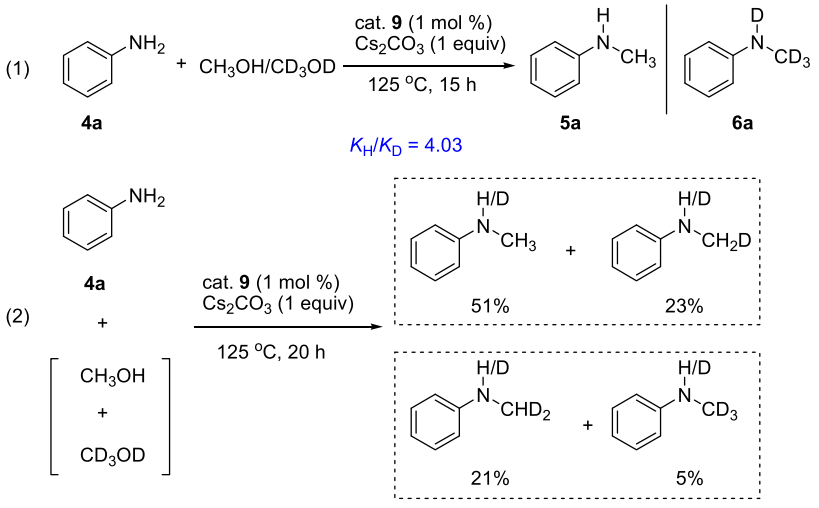
Scheme 4. Proposed Reaction Mechanism



Scheme 5. Labeling Experiments with Deuterated Methanol



desired products **5u** and **5v** were obtained in 80 and 83% yields, respectively.

On the basis of the experimental results, a plausible mechanism for the present ruthenium-catalyzed *N*-methylation of amines with methanol was proposed (Scheme 4). The initial step of the reaction involved the elimination of H_2O from cat. **9** to afford unsaturated ruthenium species **A** bearing a 2,2′-bipyridonate ligand. In the step of base-promoted activation of methanol,[20] the ligand accepted a proton and methoxy ruthenium species **B** was formed, which was further converted to ruthenium hydride **C** and formaldehyde by *β*-hydrogen elimination.[21] The condensation between amines and the resulting formaldehyde gave unsaturated imines. Subsequently, the ligand promoted the simultaneous delivery of the hydroxy proton on the bpy ligand and the hydride on ruthenium to the carbon−nitrogen double bond of imines,[22] resulting in the

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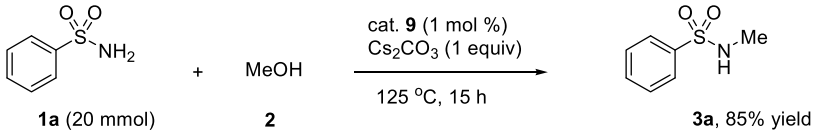
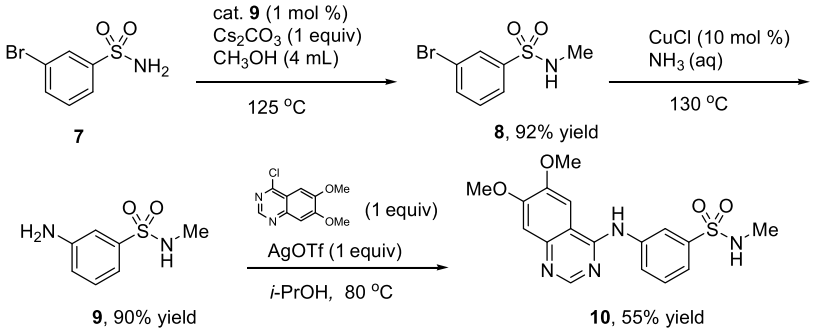
Scheme 6. Gram-Scale *N*-Methylation of 1a with Methanol



Scheme 7. Preparation of a Biologically Active Molecule



regeneration of catalytic ruthenium species **A** and the liberation of *N*-methylated amines as desirable products.

To understand the reaction mechanism, labeling experiments with deuterated methanol were investigated (Scheme 5). A significant kinetic isotope effect (KIE) (K_H/K_D = 4.03) was found when parallel reactions of **4a** with CD_3OD and CH_3OH proceeded under standard reaction conditions (Scheme 5, eq 1). Furthermore, competitive reactions with a mixture of CD_3OD and CH_3OH (v/v = 1/1) were also undertaken (Scheme 5, eq 2). It could be speculated that PhN = CH_2 (74%) and PhN = CD_2 (26%) were generated in the step of condensation. These results indicate that the C−H bond cleavage of methanol may be a rate-determining step.[23]

To assess the practical application of this catalytic system, the gram-scale *N*-methylation of **1a** (20 mmol) was carried out under standard conditions (Scheme 6). The expected product **2a** could be obtained in 85% yield, which is slightly lower than the yield on the submillimolar scale.

As shown in Scheme 7, the present catalytic system was also utilized for the preparation of a biologically active molecule (an inhibitor of troponin I-interacting kinase).[24] Under standard conditions, the *N*-methylation of 3-bromobenzenesulfonamide **7** with methanol proceeded for 15 h to give the key intermediate **8** in 92% yield. Then, Cu-catalyzed Ullmann-type ammoniation of **8** afforded the product **9** in 90% yield, which further underwent the SNAr reaction to afford the final product **10** in 55% yield.

CONCLUSIONS

In summary, we demonstrated the first example of ruthenium-catalyzed *N*-methylation of amines with methanol in the presence of carbonate salt. Under environmentally benign conditions, a variety of *N*-methylated amines could be obtained in high yields with complete selectivities. Moreover, a series of sensitive functional substituents, such as nitro, ester, cyano, and vinyl groups, were tolerated. It was confirmed that OH units in the ligand are crucial for catalytic activity. Notably, this study exhibited the potential of metal−ligand bifunctional ruthenium catalysts for the hydrogen autotransfer process.

EXPERIMENTAL SECTION

General Experimental Details. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were measured on a 500 MHz spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C), using $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constant J is given in hertz. Melting points were measured on an X-6 micro melting apparatus.

[(*p*-Cymene)$RuCl_2$]$_2$ (cat. **1**),[25] [(*p*-cymene)$RuCl_2(PPh_3)$] (cat. **2**),[26] {(*p*-cymene)$RuCl_2[P(NMe_2)_3]$} (cat. **3**),[27] [{$RuCl(\mu\text{-}Cl)(\eta^3{:}\eta^3\text{-}C_{10}H_{16})$}$_2$] (cat. **4**),[28] [(terpy)$_3$]$RuCl_3$ (cat. **5**),[29] [$RuCl_2(PPh_3)_3$] (cat. **6**),[30] {(*p*-cymene)Ru[6,6′-$(OMe)_2$-2,2′-bpy(H_2O)]}[OTf]$_2$ (cat. **7**),[19c] [(*p*-cymene)Ru(6,6′-$(OH)_2$bpy)(H_2O)][OTf]$_2$ (cat. **8**),[19c] and [(*p*-cymene)Ru(2,2′-bpyO)(H_2O)] (cat. **9**)[19c] were synthesized according the previous reports.

General Procedure for the *N*-methylation of Amines with Methanol Catalyzed by [(*p*-Cymene)Ru(2,2′-bpyO)(H_2O)] (cat. 9) (Schemes 2−3). In a 25 mL Schlenk tube, amines **1** or **4** (0.5 mmol), Cs_2CO_3 (163 mg, 0.5 mmol, 1 equiv), [(*p*-cymene)Ru(2,2′-bpyO)(H_2O)] (2.3 mg, 0.005 mmol, 1 mol %), and methanol **2** (1 mL) were added. The mixture was heated in an oil bath at 125 °C for 15 h and allowed to cool to ambient temperature. The mixture was concentrated in vacuo and purified by flash column chromatography to give corresponding products **3a−r** and **5a−v**.

*N-Methylbenzenesulfonamide (**3a**).*[31] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 89% yield (76 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 7.3 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 5.15 (br s, 1H), 2.63 (d, J = 4.1 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 138.5, 132.6, 129.0, 127.0, 29.1.

*N,4-Dimethylbenzenesulfonamide (**3b**).*[32] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 91% yield (84 mg); mp 73−74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 2.62 (d, J = 5.2 Hz, 3H), 2.42 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 143.3, 135.5, 129.6, 127.1, 29.1, 21.4.

*4-Methoxy-N-methylbenzenesulfonamide (**3c**).*[31] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 93% yield (94 mg); mp 94−95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.6 Hz, 2H), 3.87 (s, 3H), 2.63 (d, J = 5.3 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.8, 130.2, 129.3, 114.1, 55.5, 29.1.

*2-Fluoro-N-methylbenzenesulfonamide (**3d**).*[33] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 89% yield (84 mg); mp 68−69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (t, J = 7.7 Hz, 1H), 7.60 (q, J = 7.6 Hz, 1H), 7.30 (t, J =

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7.7 Hz, 1H), 7.22 (t, J = 9.8 Hz, 1H), 5.03 (br s, 1H), 2.69 (d, J = 4.8 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.7 (C−F, $^{1}J_{C-F}$ = 253.9 Hz), 134.9 (C−F, $^{3}J_{C-F}$ = 8.6 Hz), 130.6, 126.6 (C−F, $^{3}J_{C-F}$ = 13.1 Hz), 124.4 (C−F, $^{4}J_{C-F}$ = 3.7 Hz), 116.8 (C−F, $^{2}J_{C-F}$ = 21.5 Hz), 29.1.

*4-Fluoro-N-methylbenzenesulphonamide (**3e**).*[34] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 90% yield (85 mg); mp 68−69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92−7.88 (m, 2H), 7.21 (t, J = 8.5 Hz, 2H), 4.83 (br s, 1H), 2.66 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.0 (C−F, $^{1}J_{C-F}$ = 254.7 Hz), 134.7, 129.8 (C−F, $^{3}J_{C-F}$ = 9.2 Hz), 116.2 (C−F, $^{2}J_{C-F}$ = 22.6 Hz), 29.1.

*3-Chloro-N-methylbenzenesulfonamide (**3f**).*[35] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 89% yield (92 mg); mp 44−45 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 5.06-4.98 (br s, 1H), 2.68 (d, J = 5.1 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 140.4, 135.2, 132.7, 130.4, 127.1, 125.2, 29.2.

*4-Chloro-N-methylbenzenesulfonamide (**3g**).*[34] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 91% yield (94 mg); mp 44−45 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 4.98−4.88 (br s, 1H), 2.66 (d, J = 5.3 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 139.1, 137.1, 129.3, 128.6, 29.1.

*4-Bromo-N-methylbenzenesulfonamide (**3h**).*[32] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow solid; 92% yield (115 mg); mp 74−76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.6 Hz, 2H), 7.66 (d, J = 8.6 Hz, 2H), 5.17 (br s, 1H), 2.64 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 137.6, 132.3, 128.7, 127.6, 29.1.

*N-Methyl-2-(trifluoromethyl)benzenesulfonamide (**3i**).*[33] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 93% yield (111 mg); mp 96−97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25-8.22 (m, 1H), 7.93-7.90 (m, 1H), 7.78−7.74 (m, 2H), 4.88 (br s, 1H), 2.71 (d, J = 4.8 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 137.3, 132.7, 132.3, 131.7, 128.4 (C−F, $^{3}J_{C-F}$ = 6.3 Hz), 127.3 (C−F, $^{2}J_{C-F}$ = 33.1 Hz), 122.8 (C−F, $^{1}J_{C-F}$ = 273.7 Hz), 29.2.

*N-Methyl-4-(trifluoromethyl)benzenesulfonamide (**3j**).*[4d] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 91% yield (109 mg); mp 77−78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 5.26 (br s, 1H), 2.69 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 142.2, 134.2 (C−F, $^{2}J_{C-F}$ = 33.0 Hz), 127.6, 126.2 (C−F, $^{4}J_{C-F}$ = 3.7 Hz), 123.1 (C−F, $^{1}J_{C-F}$ = 273.0 Hz), 29.0.

*N-Methyl-4-(trifluoromethoxy)benzenesulfonamide (**3k**).*[4d] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 91% yield (116 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 2.66 (d, J = 5.2 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.0, 137.0, 129.2, 120.9, 120.1 (C−F, $^{1}J_{C-F}$ = 259.0 Hz), 29.0.

*N-Methyl-4-nitrobenzenesulfonamide (**3l**).*[36] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a light yellow solid; 84% yield (91 mg); mp 75−76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 9.2 Hz, 2H), 6.96 (d, J = 9.2 Hz, 2H), 3.91 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.5, 141.4, 125.8, 113.9, 55.8.

*N-Methylnaphthalene-2-sulfonamide (**3m**).*[33] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a purple solid; 93% yield (103 mg); mp 105−107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.98 (d, J = 7.3 Hz, 2H), 7.97-7.83 (m, 2H), 7.68−7.60 (m, 1H), 2.69 (d, J = 5.4 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 135.4, 134.7, 132.0, 129.4, 129.1, 128.7, 128.6, 127.8, 127.4, 122.2, 29.2.

*N-Methylthiophene-2-sulfonamide (**3n**).*[37] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a brown solid; 90% yield (80 mg); mp 78−81 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63−7.60 (m, 2H), 7.11 (t, J = 4.8 Hz, 1H), 4.70 (br s, 1H), 2.74 (d, J = 5.4 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 139.5, 132.2, 131.8, 127.3, 29.4.

*N-Methyl(phenyl)methanesulfonamide (**3o**).*[38] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 92% yield (85 mg); mp 110−111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 5H), 4.23 (s, 2H), 2.66 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 130.5, 129.2, 128.8, 128.6, 57.5, 29.6.

*N-Methylmethanesulfonamide (**3p**).*[4d] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 94% yield (51 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (s, 3H), 2.75 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 38.2, 29.2.

*N,2-Dimethyl-2-propanesulfonamide (**3q**).*[15c] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 93% yield (70 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.16 (br s, 1H), 2.80 (d, J = 5.6 Hz, 3H), 1.17 (s, 9H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 55.5, 31.4, 22.4.

*N-Methylcyclopropanesulfonamide (**3r**).*[15c] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 89% yield (60 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (br s, 1H), 2.77 (d, J = 5.3 Hz, 3H), 2.40−2.36 (m, 1H), 1.11−1.09 (m, 2H), 0.97−0.94 (m, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 29.3, 28.4, 4.7.

*N-Methylaniline (**5a**).*[39] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 93% yield (50 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, J = 7.9 Hz, 2H), 6.71 (t, J = 7.3 Hz, 1H), 6.61 (d, J = 7.9 Hz, 2H), 2.83 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 149.2, 129.1, 117.1, 112.3, 30.6.

*N,4-Dimethylbenzenamine (**5b**).*[40] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a brown oil; 85% yield (51 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, J = 8.3 Hz, 2H), 6.60 (d, J = 8.4 Hz, 2H), 2.85 (s, 3H), 2.30 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 147.0, 129.6, 126.4, 112.5, 31.0, 20.3.

*4-Methoxy-N-methylbenzenamine (**5c**).*[41] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 82% yield (56 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, J = 8.9 Hz, 2H), 6.61 (d, J = 8.9 Hz, 2H), 3.77 (s, 3H), 2.81 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 151.9, 143.6, 114.8, 113.5, 55.7, 31.5.

*4-Fluoro-N-methylbenzenamine (**5d**).*[42] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 86% yield (54 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (t, J = 8.8 Hz, 2H), 6.56-6.52 (m, 2H), 3.60 (br s, 1H), 2.80 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 155.9 (C−F, $^{1}J_{C-F}$ = 234.3 Hz), 145.8, 115.7 (C−F, $^{2}J_{C-F}$ = 22.3 Hz), 113.2 (C−F, $^{3}J_{C-F}$ = 6.2 Hz), 31.4.

*4-Chloro-N-methylbenzenamine (**5e**).*[43] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 90% yield (64 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 8.8 Hz, 2H), 6.53 (d, J = 8.8 Hz, 2H), 3.58 (br s, 1H), 2.81 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 147.8, 128.8, 121.6, 113.3, 30.7.

*4-Bromo-N-methylbenzenamine (**5f**).*[15c] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 83% yield (77 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 8.8 Hz, 2H), 3.71 (br s, 1H), 2.77 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 148.2, 131.7, 113.8, 108.6, 30.6.

*N-Methyl-4-(trifluoromethoxy)benzenamine (**5g**).*[15c] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a pale yellow oil; 92% yield (88 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, J = 8.4 Hz, 2H), 6.58 (d, J = 8.6 Hz, 2H), 3.51 (br s, 1H), 2.83 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 147.7, 140.4, 122.2, 119.6 (C−F, $^{1}J_{C-F}$ = 254.3 Hz), 112.6, 30.8.

*3,5-Bis(trifluoromethyl)-N-methylaniline (**5h**).*[7a] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 89% yield (108 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.92 (s, 2H), 4.17 (br s, 1H), 2.89 (d, J = 4.5 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 149.5, 132.2 (C−F, $^{2}J_{C-F}$ = 21.7 Hz), 123.5 (C−F, $^{1}J_{C-F}$ = 275.0 Hz), 111.3 (C−F, $^{4}J_{C-F}$ = 3.3 Hz), 109.9−109.7 (m), 30.2.

*Methyl-4-(methylamino)benzoate (**5i**).*[4d] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 81% yield (67 mg); mp 94−95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.6 Hz, 2H), 6.55 (d, J = 8.6 Hz, 2H), 3.85 (s, 3H), 2.88 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 167.3, 152.8, 131.4, 118.0, 110.9, 51.4, 30.0.

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*4-(Methylamino)benzonitrile (**5j**).*[5a] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 82% yield (54 mg); mp 86−87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 8.7 Hz, 2H), 6.54 (d, J = 8.8 Hz, 2H), 4.45 (br s, 1H), 2.85 (d, J = 5.1 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.2, 133.5, 120.5, 111.7, 98.1, 29.8.

*N-Methyl-4-vinylaniline (**5k**).*[44] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 80% yield (53 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.5 Hz, 2H), 6.63 (dd, J = 10.9 and 17.6 Hz, 1H), 6.57 (d, J = 8.5 Hz, 2H), 5.54 (d, J = 17.6 Hz, 1H), 5.02 (d, J = 10.9 Hz, 1H), 3.77 (br s, 1H), 2.85(s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 149.0, 136.6, 127.2, 127.0, 112.1, 109.2, 30.6.

*N-Methylnaphthalen-2-amine (**5l**).*[43] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a brown oil; 88% yield (69 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76−7.66 (m, 3H), 7.44 (t, J = 7.6 Hz, 1H), 7.27 (t, J = 7.4 Hz, 1H), 6.92-6.88 (m, 1H), 6.85 (s, 1H), 3.87 (br s, 1H), 2.95 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 146.9, 135.2, 128.7, 127.6, 127.4, 126.2, 125.9, 121.8, 117.8, 103.6, 30.7.

*N-Methylpyridin-2-amine (**5m**).*[4d] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 86% yield (47 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 4.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 6.55 (t, J = 6.1 Hz, 1H), 6.37 (d, J = 8.4 Hz, 1H), 4.67 (br s, 1H), 2.89 (d, J = 4.3 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.5, 147.9, 137.3, 112.5, 106.0, 28.9.

*N-Methylbenzothiazol-2-amine (**5n**).*[45] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 90% yield (74 mg); mp 141-142 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 3.04 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.3, 152.3, 130.1, 125.9, 121.1, 120.8, 118.2, 31.5.

*N,6-Dimethylbenzo[d]thiazol-2-amine (**5o**).*[46] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 92% yield (82 mg); mp 151-152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 8.2 Hz, 1H), 7.39 (s, 1H), 7.10 (d, J = 8.1 Hz, 1H), 3.07 (s, 3H), 2.39 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.4, 150.2, 130.8, 130.2, 127.0, 120.8, 118.0, 31.5, 21.1.

*6-Fluoro-N-methylbenzo[d]thiazol-2-amine (**5p**).*[47] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100);a white solid; 89% yield (81 mg); mp 158−160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.8 Hz and 4.8 Hz, 1H), 7.30 (dd, J = 8.1 Hz and 2.6 Hz, 1H), 7.04−6.99 (m, 1H), 5.88 (br s, 1H), 3.09 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 167.9, 158.0 (C−F, $^1J_{C-F}$ = 240.0 Hz), 148.8, 131.0 (C−F, $^3J_{C-F}$ = 10.6 Hz), 118.9 (C−F, $^3J_{C-F}$ = 8.9 Hz), 113.4 (C−F, $^2J_{C-F}$ = 23.7 Hz), 107.5 (C−F, $^2J_{C-F}$ = 27.1 Hz), 31.5.

*N-Methyl-1,3-benzoxazol-2-amine (**5q**).*[48] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 92% yield (68 mg); mp 97−98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 7.02 (t, J = 7.8 Hz, 1H), 5.88 (br s, 1H), 3.10 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.8, 148.5, 142.8, 123.8, 120.6, 116.0, 108.6, 29.3.

*1-Benzyl-N-methyl-1H-benzo[d]imidazole-2-amine (**5r**).*[4d] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 90% yield (107 mg); mp 174-175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.9 Hz, 1H), 7.34−7.29 (m, 3H), 7.16−7.12 (m, 3H), 7.05 (d, J = 4.2 Hz, 2H), 5.06 (s, 2H), 3.06 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 155.0, 142.2, 135.4, 134.9, 129.0, 127.9, 126.2, 121.3, 119.6, 116.4, 107.1, 45.4, 29.9.

*N-Methyl-1-phenylethanamine (**5s**).*[49] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a pale yellow oil; 82% yield (61 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.27 (m, 4H), 7.26−7.21 (m, 1H), 3.23 (q, J = 6.7 Hz, 1H), 2.18 (s, 6H), 1.36 (d, J = 6.7 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 143.9, 128.1, 127.4, 126.8, 65.9, 43.1, 20.1.

*N,N-Dimethyl-1-adamantylamine (**5t**).*[50] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 89% yield (80 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.22 (s, 6H), 2.03 (s, 3H), 1.65−1.56 (m, 9H), 1.55-1.51 (m, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 53.5, 37.8, 36.8, 36.7, 29.4.

*2-Methyl-1,2,3,4-tetrahydroisoquinoline (**5u**).*[15c] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a white solid; 80% yield (59 mg); mp 122−123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14−7.09 (m, 3H), 7.04−7.01 (m, 1H), 3.58 (s, 2H), 2.93 (t, J = 6.0 Hz, 2H), 2.69 (t, J = 6.0 Hz, 2H), 2.47 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 134.6, 133.7, 128.5, 126.3, 126.0, 125.5, 57.8, 52.8, 46.0, 29.1.

*1-Methyl-4-(3-(1-methylpiperidin-4-yl)propyl)piperidine (**5v**).*[51] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; 83% yield (99 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.73 (d, J = 11.1 Hz, 4H), 2.15 (s, 6H), 1.79 (t, J = 10.7 Hz, 4H), 1.57 (d, J = 11.6 Hz, 4H), 1.21−1.10 (m, 12H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 55.8, 46.3, 36.6, 34.9, 32.2, 23.7.

Kinetic Isotope Effect (KIE) Studies (Scheme 5, eq 1). Parallel reactions for *N*-methylation were carried out using CH_3OH and CD_3OD under identical conditions following the general procedure, and the progress of the reaction was analyzed by ^{1}H NMR. All of the reactions were repeated twice and the average data were plotted as yield (%) versus time (h).

*PhNDCD$_3$ (**6a**).*[52] Purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100); a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, J = 7.6 Hz, 2H), 6.74 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 8.0 Hz, 2H), 2.85 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 149.2, 129.1, 117.1, 112.3, 29.7.

*Competitive for the N-Methylation of **4a** (Scheme 5, eq 2).* The reaction was carried out using CH_3OH/CD_3OD (v/v = 1/1, total volume: 1 mL) under identical conditions following the general procedure, and the progress of the reaction was analyzed by ^{1}H NMR. The incorporation of zero, one, two, or three deuterium on the methyl of the product was determined by the ^{1}H NMR spectrum of the crude mixture according to the previous report.

*Procedure for the Gram-Scale N-Methylation of **1a** with Methanol Catalyzed by [(p-Cymene)Ru(2,2′-bpyO)(H$_2$O)] (Scheme 6).* In a 250 mL Schlenk tube, benzenesulfonamide (**1a**) (3.14 g, 20 mmol), Cs_2CO_3 (6.52 g, 20 mmol, 1 equiv), cat. **9** (88 mg, 0.2 mmol, 1 mol %), and methanol **2** (40 mL) were added. The mixture was heated in an oil bath at 125 °C for 15 h and allowed to cool to ambient temperature. The mixture was concentrated in vacuo and purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 100/1) to give the corresponding product **3a** in 85% yield (2.89 g).

*Procedure for the Synthesis of 3-Bromo-N-methylbenzenesulfonamide (**8**) (Scheme 7).* In a 25 mL Schlenk tube, 3-bromobenzenesulfonamide **7** (236 mg, 2 mmol), Cs_2CO_3 (652 mg, 2 mmol, 1 equiv), cat. **9** (9.2 mg, 0.02 mmol, 1 mol %), and methanol **2** (4 mL) were added. The mixture was heated in an oil bath at 125 °C for 15 h and allowed to cool to ambient temperature. The mixture was concentrated in vacuo and purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/100, v/v) to give the corresponding product **8**.

*3-Bromo-N-methylbenzenesulfonamide (**8**).*[53] A yellow solid; 92% yield (460 mg); mp 209−210 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 5.6 Hz, 1H), 7.25−7.20 (m, 1H), 2.43 (d, J = 4.0 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 143.4, 134.1, 130.3, 129.6, 125.4, 122.6, 30.3.

*Procedure for the Synthesis of 3-Amino-N-methylbenzenesulfonamide (**9**) (Scheme 7).* To a 25 mL Schlenk tube were added 3-bromo-N-methylbenzenesulfonamide **8** (248 mg, 1 mmol), CuCl (10 mg, 0.1 mmol, 10 mol %), and NH_4OH (4 mL). The mixture was heated in an oil bath at 130 °C for 18 h and allowed to cool to ambient temperature. The mixture was concentrated in vacuo and purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/1) to give the corresponding product **9**.

*3-Amino-N-methylbenzenesulfonamide (**9**).*[54] A brown oil; 90% yield (168 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ7.22−7.18 (m, 2H), 6.95 (s, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 2.38 (d, J = 5.0 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6) δ 149.5, 139.8, 129.9, 117.7, 113.8, 111.6, 29.0.

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*Procedure for the Synthesis of 3-[(6,7-Dimethoxy-4-quinazolinyl)amino]-N-methylbenzenesulfonamide (**10**) (Scheme 7).* In a 5 mL microwave vial containing a stirrer bar, 4-chloro-6,7-dimethoxyquinazoline (112 mg, 0.5 mmol), 3-amino-N-methylbenzenesulfonamide **9** (120 mg, 0.65 mmol, 1.3 equiv), and AgOTf (128 mg, 0.5 mmol, 1 equiv) were dissolved in *i*-PrOH (2 mL) and subjected to microwave irradiation (150 °C) for 1.5 h. The mixture was concentrated in vacuo and purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1/1) to give the corresponding product **10**.

*3-[(6,7-Dimethoxy-4-quinazolinyl)amino]-N-methylbenzenesulfonamide (**10**).*[55] A brown solid; 55% yield (103 mg); mp 168−173 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.36 (s,1H), 8.82 (s, 1H), 8.26 (s, 1H), 8.16 (s, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.72−7.66 (m, 2H), 7.62−7.58 (m, 1H), 7.33 (s, 1H), 3.99 (d, J = 14.9 Hz, 6H), 2.48 (d, J = 4.9 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6) δ 158.5, 156.8, 150.6, 148.9, 140.1, 138.0, 136.1, 130.0, 128.6, 124.2, 122.9, 107.7, 104.2, 100.0, 57.3, 56.8, 29.0.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02685.

^{1}H NMR and ^{13}C NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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