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Ru(II)-Catalyzed N-Methylation of Amines Using Methanol as the C1 Source

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Cite This: *ACS Omega* 2023, 8, 36597−36603

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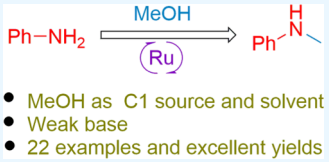
ABSTRACT: Four ruthenium complexes were used as catalysts for the N-methylation of amines using methanol as the C1 source under weak base conditions. The (DPEPhos)$RuCl_2PPh_3$(**1a**) catalyst showed the best catalytic performance (0.5 mol %, 12 h). The deuterium labeling and control experiments suggested the reaction via the Ru−H mechanism. This study provides a new ruthenium catalyst system for N-methylation with methanol under weak base conditions.



INTRODUCTION

Among various amine derivatives, N-methylated compounds are important building blocks in organic synthesis and drug discovery processes.[1] Generally, the synthesis of N-methylated compounds requires toxic halohydrocarbon reagents, which generate poor atom economy and pose environmental hazards.[2] Recently, transition-metal-catalyzed N-methylation of amines with MeOH via a borrowing hydrogen reaction has emerged as an efficient alternative.[3,4] This method has gained significant interest in organic synthesis because the only byproduct is H_2O.[5]

In 1981, Grigg developed the first N-methylation of amines with MeOH using an Rh catalyst.[6] Since then, various catalysts, including Ir,[7−12] Re,[13] Pd,[14,15] Ru,[16−26] Fe,[27,28] Co,[29] and Mn,[30−33] have been used for the N-methylation of amines with MeOH; however, for most catalysts, using a strong base (*t*-BuOK, *t*-BuOLi, KOH, or NaOH) is necessary for this borrowing hydrogen reaction. As shown in Scheme 1, Li et al. developed a bidentate cymene−Ru catalyst for the N-methylation of amines with MeOH under weak base conditions (1.0 equiv Cs_2CO_3).[18] Therefore, the development of an effective and easily synthesized Ru catalyst, especially using a weak base, is desirable. Herein, we present the facile synthesis of the Ru complex for the N-methylation of amines with MeOH under weak base conditions.

RESULTS AND DISCUSSION

Catalysis. As shown in Table 1, phenylamine in methanol was chosen for the model reaction. When the reaction was carried out at 140 °C for 12 h with 0.5 equiv of Cs_2CO_3, (DPEPhos)$RuCl_2PPh_3$ (**1a**) showed the best catalytic performance (entries 1−4). When the amount of the catalyst was reduced to 0.3 mol %, the conversion was 85% (entry 5). The reaction was also temperature-dependent. The conversion decreased when the temperature was reduced to 120 °C (entry 6). For other weak bases, such as K_2CO_3 and Na_2CO_3, the conversions were approximately 70−75% (entries 7 and 8). When Et_3N was used as the base, the product was *N*-ethylaniline (entry 9). Without a base or catalyst, the reaction did not proceed (entries 10 and 11).

To explore the substrate scope and functional group tolerance of this catalyst, a series of aniline derivatives were tested under the optimum conditions (0.5 mol % **1a**, 12 h). As shown in Table 2, the reactions of anilines bearing functional groups in the *para* position, such as halogen, methyl, methoxyl, and *N*-phenyl groups, afforded the corresponding N-methylated compounds in 95−97% yields (**3b**−**3g**). Aniline derivatives with functional groups in the *meta* position also produced the desired products in excellent yields (95−98%, **3h**−**3l**). Moreover, the yield did not depend on the electron-withdrawing or -donating nature of the functional groups. For 3,4-(methylenedioxy)aniline and 3,5-dimethoxyaniline, the yields were 95−97% (**3m**−**3n**). Owing to the steric effects of functional groups at the *meta* position, the conversion decreased to 77−84% (**3o**−**3q**). For other aniline derivatives such as naphthalene, pyridine, and quinoline, the yields were approximately 70−94% (**3r**−**3t**). For *p*-phenylenediamine, the yield of the product N^1,N^4-dimethylbenzene-1,4-diamine was 65% (**3u**) when 1 mol % of catalyst was used. For nitrobenzene, the yield of *N*-methylaniline was 58% (**3v**).

Furthermore, the proposed mechanism was supported by additional deuterium labeling and control experiments (Scheme 2). When CH_3OD was used as the solvent under the standard condition, phenylamine was transformed into *N*-methylaniline, and the D-levels of the NH and CH_3 groups were 85 and 2%, respectively (Scheme 2, entry 1). When CD_3OD was used under this standard condition, the NH and CH_3 groups were deuterated, and their D-levels were 84 and 97% (Scheme 2, entry 2). Generally, the D/H exchange between CH_3OD and the NH group can occur under this condition. Therefore, *N*-

Received: August 23, 2023
Accepted: September 8, 2023
Published: September 20, 2023

Scheme 1. Ru-Catalyzed N-Methylation of Amines under Weak Base Conditions

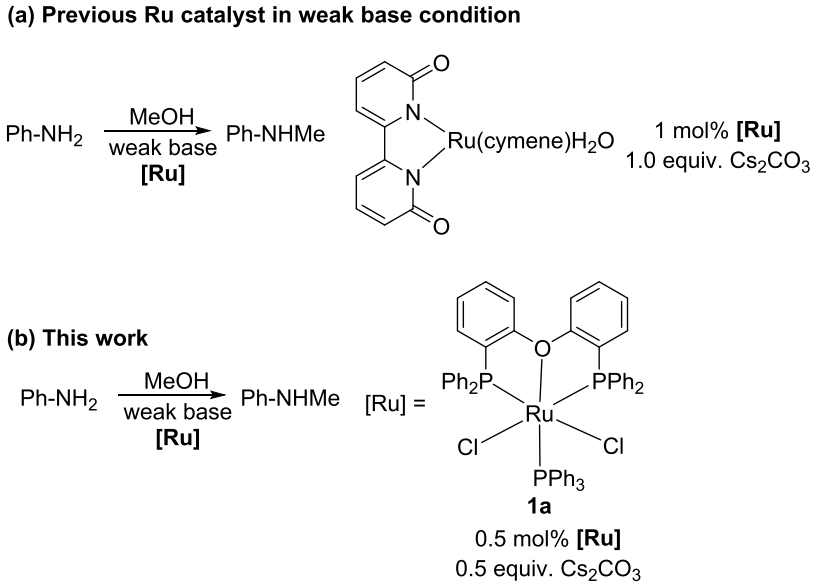
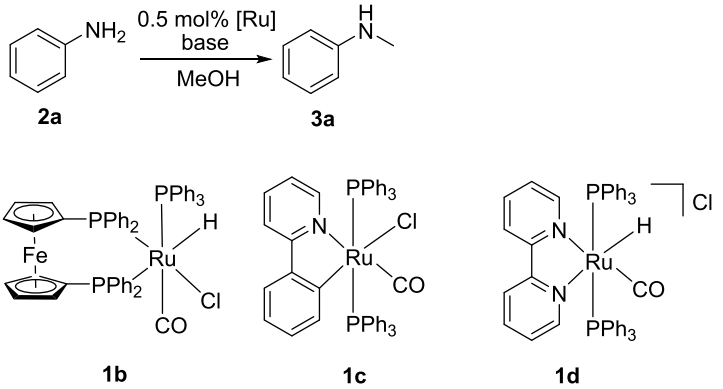


Table 1. Optimization of Reaction Conditions[a]



entry	cat. (mol %)	T (°C)	base (equiv)	t (h)	conversion (%)[b]
1	**1a** (0.5)	140	Cs_2CO_3 (0.50)	12	>99
2	**1b** (0.5)	140	Cs_2CO_3 (0.50)	12	73
3	**1c** (0.5)	140	Cs_2CO_3 (0.50)	12	47
4	**1d** (0.5)	140	Cs_2CO_3 (0.50)	12	51
5	**1a** (0.3)	140	Cs_2CO_3 (0.50)	12	85
6	**1a** (0.5)	120	Cs_2CO_3 (0.50)	12	64
7	**1a** (0.5)	140	K_2CO_3 (0.50)	12	77
8	**1a** (0.5)	140	Na_2CO_3 (0.50)	12	70
9[c]	**1a** (0.5)	140	Et_3N (1.00)	12	n.r.
10[c]	**1a** (0.5)	140		12	n.r.
11[c]		140	Cs_2CO_3 (0.50)	12	n.r.

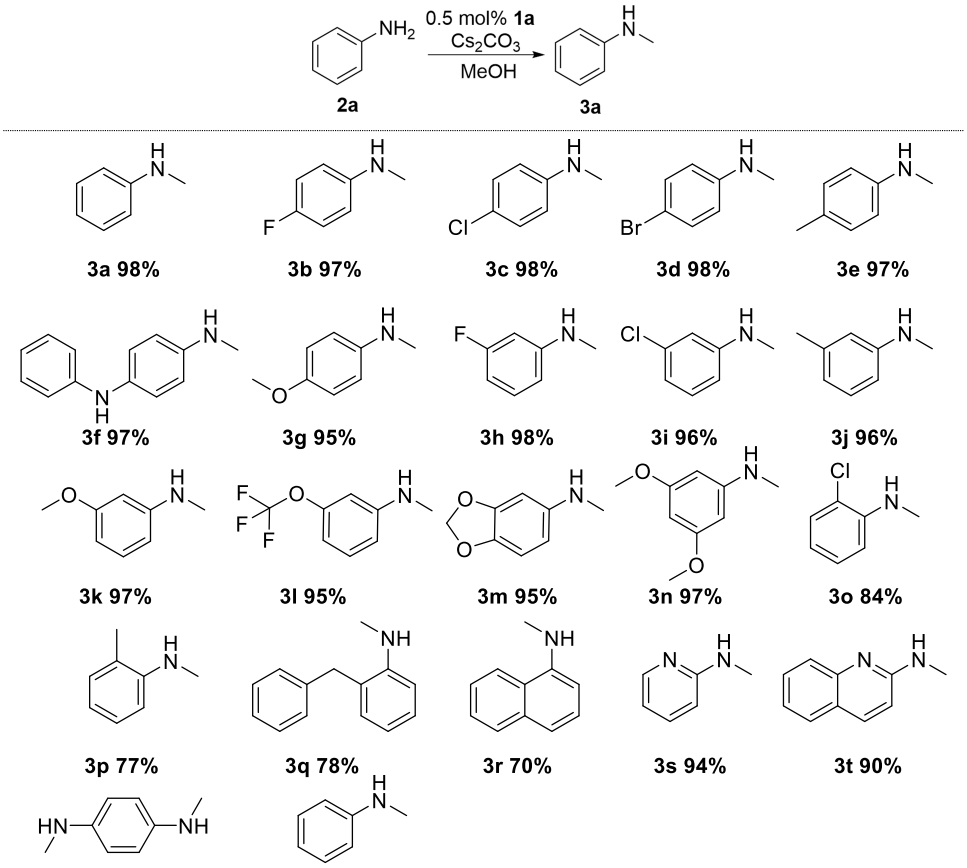
[a]Reaction conditions: **2a** (1 mmol), base, MeOH (1 mL), Ru catalyst 0.5 mol %, Ar. [b]Conversion was determined by GC using xylene as the internal standard. [c]n.r., no reaction.

methylaniline was also tested to obtain more experimental details. As shown in entry 3, after reaction with CH_3OD at 140 °C for 12 h, only the NH group was deuterated, and its D-level was nearly 100% (Scheme 2, entry 3). To further investigate the mechanism, controlled experiments were conducted. As shown in entry 4, when 0.25 mmol of **1a** was reacted with phenylamine and MeOH under the standard condition, the Ru−H bond could be observed by ^{1}H NMR (−4.83 ppm, − 6.45 to −6.95 ppm). These results agree with the Ru−H mechanism via a borrowing hydrogen process.

A possible mechanism based on the above results and according to the related literature is presented in Scheme 3.[15] Initially, **1a** reacts with Cs_2CO_3 and MeOH to form intermediate **R1**. After β-H elimination, **R1** transforms into the Ru−H intermediate **R2** and formaldehyde. Subsequently, formaldehyde reacts with the amine to form imine and H_2O and then reacts with the Ru−H intermediate **R2** to form intermediate **R3**. Finally, **R3** reacts with another molecule of MeOH to form intermediate **R2** and *N*-methylaniline, and the catalytic cycle ends.

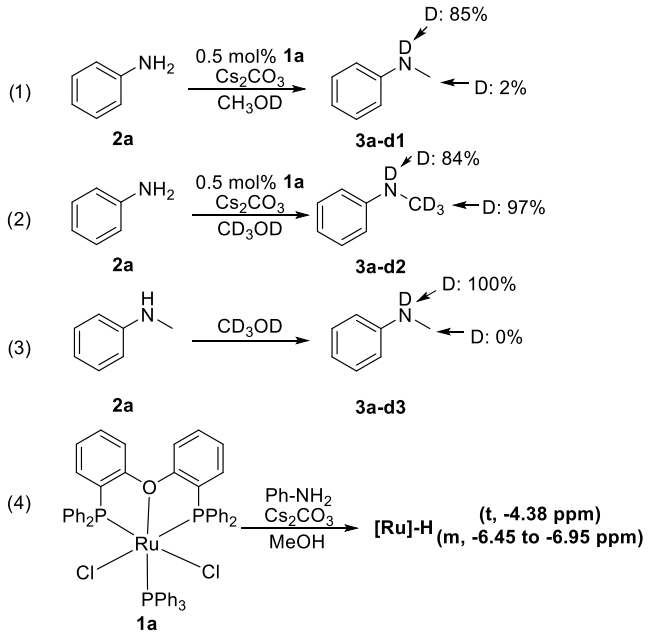
https://doi.org/10.1021/acsomega.3c06260
ACS Omega 2023, 8, 36597−36603

Table 2. Substrate Scope for Semihydrogenation of Alkynes Using Precatalyst 1a[a]



[a]Reaction conditions: Amines (1 mmol), Cs_2CO_3 (0.50 equiv), MeOH (1 mL), **1a** (0.5 mol %), Ar, 12 h; isolated yields. [b]1 mol % **1a**. [c]Nitrobenzene instead of amine.

Scheme 2. Deuterium-Labeling and Control Experiments



CONCLUSIONS

We have established the (DPEPhos)$RuCl_2PPh_3$(**1a**)-catalyzed N-methylation of amines using methanol as the C1 source. With a low weak base loading (0.5 equiv of Cs_2CO_3), 21 *N*-methylaniline derivatives were prepared under this borrowing hydrogen condition. The deuterium labeling and control experiments suggested the reaction via a Ru−H borrowing hydrogen mechanism. This study provides a new weak base system for the N-methylation of amines using an easily synthesized Ru catalyst.

EXPERIMENTAL SECTION

General Considerations. All manipulations were carried out under an inert nitrogen atmosphere using a Schlenk line. MeOH and all reagents were purchased from Adamas and used as received. **1b−1d** were prepared as previously described.[35,36] The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer.

Synthesis of (DPEPhos)$RuCl_2PPh_3$ (1a). A solution of DPEPhos (0.23 g, 1.0 mmol, 1.0 equiv) and $RuCl_2(PPh_3)_3$ (0.95 g, 1 mmol, 1.0 equiv) was reacted in refluxing EtOH (20 mL) under N_2 overnight. The mixture was cooled to room temperature and filtered to obtain 880 mg of (DPEPhos)-$RuCl_2PPh_3$ (**1a**) (90%) as a red powder. **1a**:[37] ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.51 (d, J = 8.0 Hz, 2H), 7.34−6.98 (m, 35H), 6.87−6.83 (m, 6H), ^{13}C NMR (100 MHz, $CDCl_3$): 159.2, 136.9, 136.4, 134.8, 134.7, 130.6, 130.4, 129.2, 128.7, 127.5, 127.4, 127.4, 126.8, 126.7, 123.8, 117.8. ^{31}P NMR (162 MHz, $CDCl_3$, ppm): 55.8 (t, J = 29.2 Hz), 29.9 (d, J = 29.2 Hz).

General Procedure for N-Methylation of Amines. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with Ru catalyst (0.5 mol %, 0.005 equiv), amines (1.0 mmol, 1.0

https://doi.org/10.1021/acsomega.3c06260
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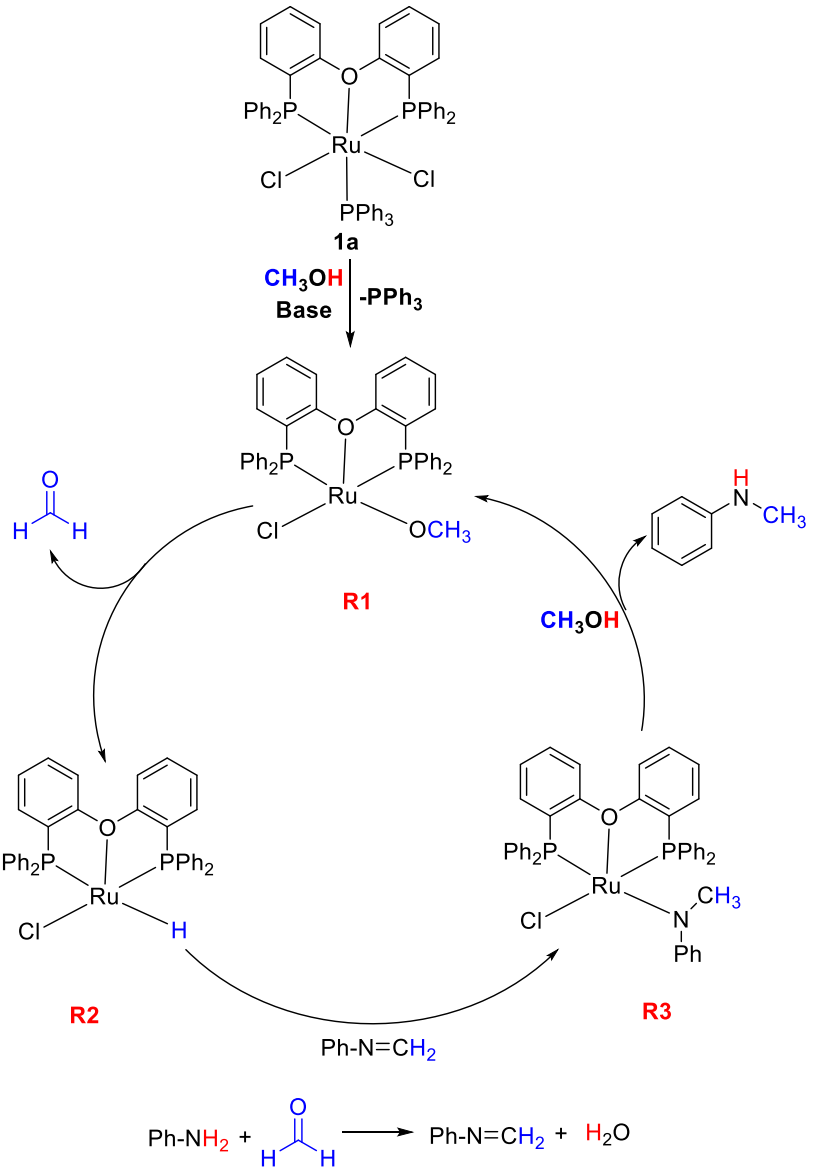
Scheme 3. Proposed Reaction Mechanism



equiv), base, and anhydrous MeOH (1 mL). The mixture was reacted at 140 °C for 12 h. After reducing in vacuo, the residue was purified by chromatography on silica gel to give the *N*-methylaniline products.

*N-Methylaniline (**3a**).*[18] Colorless oil (105 mg 98%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.29−7.25 (m, 2H), 6.81−6.77 (m, 1H), 6.69 (d, J = 8.0 Hz, 2H), 3.72 (s, 1H), 2.89 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): 149.4, 129.3, 117.3, 112.5, 30.8.

*4-Fluoro-N-methylbenzenamine (**3b**).*[18] Colorless oil (121 mg 97%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 6.95−6.91 (m, 2H), 6.59−6.56 (m, 2H), 3.62 (s, 1H), 2.83 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$):155.9 (J = 234.3 Hz), 145.8,115.7 (J = 22.3 Hz), 113.2 (J = 6.2 Hz), 31.4.

*4-Chloro-N-methylaniline (**3c**).*[18] Colorless oil (139 mg 98%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.17 (d, J = 8.4 Hz, 2H), 6.55 (d, J = 8.8 Hz, 2H), 3.71 (s, 1H), 2.84 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): 147.9, 129.0, 121.8, 113.5, 30.8.

*4-Bromo-N-methylbenzenamine (**3d**).*[18] Colorless oil (182 mg 98%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.28 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 3.80 (s, 1H),2.83 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): 148.2, 131.9, 114.0, 108.9, 30.7.

*N,4-Dimethylaniline (**3e**).*[18] Colorless oil (117 mg 97%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.05 (d, J = 8.0 Hz, 2H), 6.60 (d, J = 7.6 Hz, 2H), 3.58 (s, 1H), 2.85 (s, 3H), 2.29 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): 147.1, 129.7, 126.6, 112.7, 31.2, 20.4.

*N^1-Methyl-N^4-phenylbenzene-1,4-diamine (**3f**).*[15] Colorless oil (192 mg 97%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.31−7.27 (m, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.94−6.87 (m, 3H), 6.69 (d, J = 8.4 Hz, 2H), 5.49 (s, 1H), 3.72 (s, 1H), 2.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 146.5, 145.8, 134.0, 129.4, 124.1, 118.8, 114.9, 113.4, 31.3.

*4-Methoxy-N-methylbenzenamine (**3g**).*[18] Colorless oil (130 mg 95%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 6.85 (d, J = 7.6 Hz, 2H), 6.63 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H), 3.45 (s, 1H), 2.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 152.7, 142.1, 115.3, 113.7, 59.2, 35.2.

*3-Fluoro-N-methylaniline (**3h**).*[38] Colorless oil (123 mg 98%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.18−7.12 (m, 1H), 6.46−6.32 (m, 3H), 3.83 (s, 1H), 2.85 (s, 3H). ^{13}C NMR (100

https://doi.org/10.1021/acsomega.3c06260
ACS Omega 2023, 8, 36597−36603

MHz, $CDCl_3$):164.3 (d, J = 42.9 Hz), 150.3 (d, J = 10.6 Hz), 130.3 (d, J = 10.2 Hz), 108.9 (d, J = 2.4 Hz), 104.3 (d, J = 21.6 Hz), 99.6 (d, J = 25.9 Hz), 31.1.

*3-Chloro-N-methylaniline (**3i**).*[16] Colorless oil (136 mg 96%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.13−7.09 (m, 1H), 6.70 (d, J = 7.2 Hz, 1H), 6.61 (s, 1H), 6.50 (d, J = 8.0 Hz, 1H), 3.81 (s, 1H), 2.84 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): 150.4, 135.0, 130.1, 117.0, 111.9, 110.9, 30.6.

*N,3-Dimethylaniline (**3j**).*[16] Colorless oil (116 mg 96%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.19−7.16 (m, 1H), 6.63 (d, J = 7.6 Hz, 1H), 6.52 (s, 2H), 3.66 (s, 1H), 2.89 (s, 3H), 2.38 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): 149.5, 139.0, 129.2, 118.3, 113.3, 109.7, 30.8, 21.7.

*3-Methoxy-N-methylaniline (**3k**).*[22] Colorless oil (133 mg 97%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.18−7.14 (m, 1H), 6.35 (d, J = 8.4 Hz, 1H), 6.30 (d, J = 7.6 Hz, 1H), 6.24 (s, 1H), 3.84 (s, 3H), 3.77 (s, 1H), 2.87(s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): 160.9, 150.9, 130.0, 105.7, 102.3, 98.4, 55.1, 30.7.

*N-Methyl-3-(trifluoromethoxy)aniline (**3l**).*[39] Colorless oil (181 mg 95%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.21−7.17 (m, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.45 (s, 1H), 3.86 (s, 1H), 2.86 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$):151.1 (q, J = 1 Hz), 139.9, 133.4, 123.2, 122.4, 121.8 (q, J = 256 Hz), 116.8, 37.9.

*N-Methyl-3,4-methylenedioxyaniline (**3m**).*[26] Colorless oil (143 mg 95%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 6.72 (d, J = 8.0 Hz, 1H), 6.28 (s, 1H), 6.07 (d, J = 8.0 Hz, 1H), 5.88 (s, 2H), 3.56 (s, 1H), 2.80 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): 148.4, 145.3, 139.5, 108.6, 103.8, 100.6, 95.6, 31.6.

*3,5-Dimethoxy-N-methylaniline (**3n**).*[40] Colorless oil (162 mg 97%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 5.93(s, 1H), 5.84 (s, 2H), 3.79(s, 6H), 2.83 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): 161.8, 151.4, 91.2, 89.5, 55.2, 30.7.

*2-Chloro-N-methylaniline (**3o**).*[26] Colorless oil (119 mg 84%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.29 (d, J = 7.6 Hz, 1H), 7.23−7.19 (m, 1H), 6.70−6.65 (m, 2H), 4.42 (s, 1H), 2.93 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): 145.0, 129.0, 127.9, 119.1, 117.1, 110.7, 30.4.

*N,2-Dimethylaniline (**3p**).*[16] Colorless oil (93 mg 77%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.24−7.20 (m, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.75−6.71 (m, 1H), 6.67 (d, J = 8.0 Hz, 1H), 3.64 (s, 1H), 2.95 (s, 3H), 2.19 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): 147.2, 130.0, 127.2, 122.0, 116.9, 109.2, 30.8, 17.5.

*N-Methyl-2-benzylaniline (**3q**).*[41] Colorless oil (154 mg 78%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.47−7.34 (m, 6H), 7.21 (d, J = 7.6 Hz, 1H), 6.93−6.89 (m, 1H), 6.83 (d, J = 8.0 Hz, 1H), 4.04 (s, 2H), 3.70 (s, 1H), 2.92 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): 147.4, 139.5, 130.6, 128.9, 128.7, 128.1, 126.6, 124.7, 117.2, 110.2, 38.1, 30.9.

*N-Methylnaphthalen-1-amine (**3r**).*[34] Colorless oil (110 mg 70%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.96 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.63−7.53 (m, 3H), 7.43 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 4.67 (s, 1H), 3.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 144.5, 134.4, 128.8, 126.9, 125.9, 124.9, 123.6, 120.1, 117.6, 104.2, 31.2.

*N-Methylpyridin-2-amine (**3s**).*[34] Colorless oil (102 mg 94%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.09 (d, J = 6.0 Hz, 1H), 7.44−7.41 (m, 1H), 6.58−6.55 (m, 1H), 6.38 (d, J = 8.4 Hz, 1H), 4.75 (s, 1H), 2.91 (d, J = 4.4 Hz 3H).^{13}C NMR (100 MHz, $CDCl_3$): 159.6, 148.1, 137.4, 112.7, 106.2, 29.1.

*N-Methylquinolin-2-amine (**3t**).*[42] Colorless oil (142 mg 90%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.81 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.61−7.54 (m, 2H), 7.25−7.21 (m, 1H), 6.63 (d, J = 8.8 Hz, 1H), 5.00 (s, 1H), 3.10 (d, J = 4.8 Hz 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 157.7, 148.1, 137.2, 129.6, 127.5, 126.1, 123.4, 122.0, 111.3, 28.7.

*N^1,N^4-Dimethylbenzene-1,4-diamine (**3u**).*[43] Colorless oil (88 mg 65%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 6.63 (s, 4H), 3.39 (s, 2H), 2.83 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$): 141.9, 114.3, 32.0.

N-Methylation of Amine with CH_3OD. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with **1a** (4.89 mg, 0.5 mol %, 0.005 equiv), amines (93 mg, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (163 mg, 0.5 mmol, 0.5 equiv), and anhydrous CH_3OD (1 mL). The mixture was reacted at 140 °C for 12 h. After cooling to room temperature, the mixture was reduced and identified by ^{1}H NMR directly. **3a-d1**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.29−7.25 (m, 2H), 6.81−6.77 (m, 1H), 6.69 (d, J = 8.0 Hz, 2H), 3.77 (s, 0.15H), 2.80−2.89 (m, 2.95H).

N-Methylation of Amine with CD_3OD. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with **1a** (4.89 mg, 0.5 mol %, 0.005 equiv), amines (93 mg, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (163 mg, 0.5 mmol, 0.5 equiv), and anhydrous CD_3OD (1 mL). The mixture was reacted at 120 °C for 12 h. After cooling to room temperature, the mixture was reduced and identified by ^{1}H NMR directly. **3a-d2**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.29−7.25 (m, 2H), 6.81−6.77 (m, 1H), 6.69 (d, J = 8.0 Hz, 2H), 3.72 (s, 0.16H), 2.89 (s, 0.05H).

Reaction of *N*-Methylaniline with CH_3OD. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with *N*-methylaniline (95 mg, 1.0 mmol, 1.0 equiv) and anhydrous CD_3OD (1 mL). The mixture was reacted at 140 °C for 12 h. After cooling to room temperature, the mixture was reduced and identified by ^{1}H NMR directly. **3a-d3**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.29−7.25 (m, 2H), 6.81−6.77 (m, 1H), 6.69 (d, J = 8.0 Hz, 2H), 2.89 (s, 3H).

Control Experiment. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with **1a** (243 mg, 0.25 mmol, 1.0 equiv), amines (93 mg, 1.0 mmol, 4.0 equiv), Cs_2CO_3 (163 mg, 0.5 mmol, 2.0 equiv), and anhydrous MeOH (1 mL). The mixture was reacted at 140 °C for 12 h. After cooling to room temperature, the mixture was reduced and identified by ^{1}H NMR directly.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c06260.

Copies of NMR spectra (PDF)

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https://doi.org/10.1021/acsomega.3c06260
ACS Omega 2023, 8, 36597−36603

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of Jilin Province (Nos. YDZJ202201ZYTS615 and YDZJ202201ZYTS617) and the Education Department of Jilin Province, China (No. JJKH20220430KJ). The authors also thank the Foundation of Key Laboratory for Comprehensive Energy Saving of Cold Regions Architecture of the Ministry of Education, Jilin Jianzhu University (No. JLJZHDKF202205).

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https://doi.org/10.1021/acsomega.3c06260
ACS Omega 2023, 8, 36597−36603