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N-Monomethylation of Aromatic Amines with Methanol via PN^{H}P-Pincer Ru Catalysts

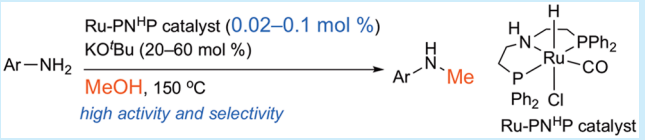
Osamu Ogata,*[,†] Hideki Nara,[†] Mitsuhiko Fujiwhara,[†] Kazuhiko Matsumura,[†] and Yoshihito Kayaki*[,‡]

[†]Corporate Research and Development Division, Takasago International Corporation, 1-4-11 Nishi-Yawata, Hiratsuka, Kanagawa 254-0073, Japan

[‡]Department of Chemical Science and Engineering, School of Materials and Chemical Technology, Tokyo Institute of Technology, 2-12-1-E4-1 O-okayama, Meguro-ku, Tokyo 152-8552, Japan

Supporting Information

ABSTRACT: The use of methanol for the selective methylation of aromatic amines with RuHCl(CO)(PN^{H}P) (PN^{H}P = bis(2-diphenylphosphinoethyl)amine) is reported. Various aromatic amines were transformed into their corresponding monomethylated secondary amines in high yields at 150 °C with a very low catalyst loading (0.02−0.1 mol %) in the presence of KO^{t}Bu (20−60 mol %). The catalyst precursor, RuHCl(CO)(PN^{H}P), was converted to [RuH(CO)$_2$(PN^{H}P)]$^+$ under the catalytic conditions and also serves as a highly effective catalyst. The robustness of this catalyst contributes to its outstanding catalytic activity, even under reaction conditions, in which CO is liberated from methanol.



N-Methylated aromatic amines are integral components in many fine chemicals, including pharmaceuticals, agrochemicals, and dyes.[1] In general, aniline derivatives are methylated via reactions with methyl electrophiles or carbene precursors. Common methylating reagents such as methyl iodide, dimethyl sulfate, and diazomethane[2] are operationally problematic because they are toxic, harmful, and hazardous. As a result, catalytic methylation by dimethyl carbonate over solid catalysts,[3] reductive amination of formaldehyde,[4] and reductive methylation with CO_2[5] or formic acid[6] have been studied as viable *N*-alkylation methods. Nevertheless, successive methylation often proceeds, inevitably leading to the formation of tertiary dimethylated amines as byproducts, because the monomethylated amines are more reactive than the starting primary amines.

Direct amine alkylation with alcohols is considered to be a desirable alternative method from an economical and environmental perspective.[7] Since the pioneering works by Grigg[8] and Watanabe,[9] amine alkylation based on hydrogen transfer (Figure 1) has been achieved with a variety of homogeneous Ir[10] and Ru[11,12] catalysts. Catalysts based on Os,[13] Pd,[14] Ni,[15] Cu,[16] Fe,[17] Co,[18] Mn,[19] Ge,[20] and nonmetal-based catalyst[21] have also emerged in the past decade. Besides heterogeneous catalytic systems using gaseous[22] or supercritical[23] methanol as well as photocatalysis,[24] selective *N*-monomethylation by a borrowing-hydrogen methodology that uses methanol as a renewable methylating agent remains a challenge.[25]

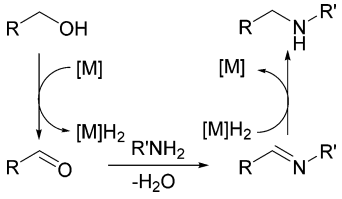


Figure 1. *N*-Alkylation of amines with alcohols via a borrowing-hydrogen mechanism.

The monoalkylation of aniline derivatives can be carried out by several Ru catalysts[26,27] such as a binary catalyst system of $RuCl_3 \cdot nH_2O$ with P^{n}Bu$_3$ and $[RuCl(PPh_3)_2(CH_3CN)_3]^+$-$[BPh_4]^-$; however, relatively high catalyst loadings (2 and 1 mol %) are required. Seayad reported the *N*-methylation of amines with 0.5 mol % of $[Cp^*RuCl_2]_2$ and 1.2 mol % of DPEPhos,[28] whereas $CpRuCl(PPh_3)_2$ was not effective for the *N*-methylation of anilines and promoted *N*,*N*-dimethylation of aliphatic amines.[29] Chen reported the first Ir-catalyzed *N*-monomethylation of aromatic primary amines using 0.1 mol % of $[IrCp^*Cl_2]_2$.[30,31] In line with the recent desire to utilize earth-abundant first-row transition metals in catalysis, Beller reported the *N*-methylation of aromatic amines with 1−2 mol % of manganese catalysts.[19] Most of these reactions required more than 1 mol % of metal, while precious Ir catalysts could be used in amounts as low as 0.1 mol %.[30,31a]

Our study expanded the utility of RuHCl(CO)(PN^{H}P) (**1**, Ru-MACHO), which was originally developed as an ester hydrogenation catalyst,[32] for the reverse acceptorless dehydrogenation of 1,4-butanediol to give γ-butyrolactone in the presence of 0.01 mol % of **1** in neat conditions (Scheme 1).[33] Dong and Guan reported that the same catalyst yielded carboxamides by the dehydrogenative coupling of primary alcohols and amines, as well as *N*-benzylimines via the dehydrative dehydrogenation of secondary alcohols and

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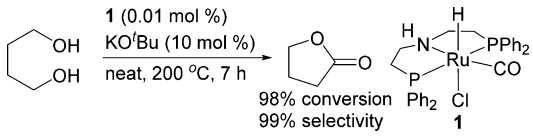
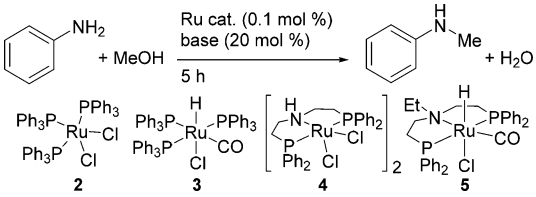
Scheme 1. Dehydrogenation of γ-Butyrolactone with 1



benzylamine.[34] The dehydrogenation activity of **1** also allowed methanol transformations, including the oxidative coupling of amines and methanol to give urea,[35] and hydrogen generation from aqueous methanol.[36] The potential of **1** for the dehydrogenation of methanol encouraged us to explore its efficient *N*-methylation of aromatic amines.[37]

The initial investigation was performed using aniline as a benchmark substrate, and the results are summarized in Table 1. A mixture of aniline (2.0 mmol), **1** (0.002 mmol), base (0.4 mmol), and methanol (3.6 mL) was added to a 100 mL autoclave and stirred at a bath temperature of 150 °C for 5 h. In each case, the desired monomethylated product, *N*-methylaniline, was selectively obtained without formation of formanilide as the dehydrogenative coupling product.[38] Notably, the choice of base was crucial to the catalytic function. As shown in entries 1−7, the yield of *N*-methylaniline increased with the base selection in the order $OH^- < OMe^- < O^tBu^-$ and $Li^+ < Na^+ < K^+$, which implies that the basicity and solubility of the additive base in the reaction mixture strongly affect the catalytic performance. In fact, reducing the amount of base by half led to a lower yield (entry 8). The reaction was accelerated with increased temperature, and the optimal yield (96%) was obtained at 150 °C (entries 7, 9, and 10).

Table 1. Ru-Catalyzed *N*-Methylation of Aniline Using Methanol as the Methylating Agent[a]



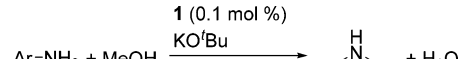
entry	Ru cat.	base	temp (°C)	yield (%)[b]
1	**1**	NaOH	150	14
2	**1**	LiOMe	150	34
3	**1**	NaOMe	150	52
4	**1**	KOMe	150	54
5	**1**	LiO^{t}Bu	150	35
6	**1**	NaO^{t}Bu	150	89
7	**1**	KO^{t}Bu	150	96 (93[c])
8	**1**	KO^{t}Bu[d]	150	78
9	**1**	KO^{t}Bu	140	77
10	**1**	KO^{t}Bu	130	44
11	**2**	KO^{t}Bu	150	<1
12	**3**	KO^{t}Bu	150	<1
13[e]	**4**	KO^{t}Bu	150	48
14	**5**	KO^{t}Bu	150	52

[a]Standard conditions: Aniline (2.0 mmol), Ru cat. (0.002 mmol), base (0.4 mmol), MeOH (3.6 mL), 5 h. [b]Yields were determined by GC. [c]Isolated yield. [d]The amount of KO^{t}Bu was halved (0.2 mmol). [e]**4** (0.001 mmol, aniline/Ru = 1000/1).

The related tris(phosphine)−Ru complexes, $RuCl_2(PPh_3)_3$ (**2**) and $RuHCl(CO)(PPh_3)_3$ (**3**), did not promote *N*-methylation (entries 11 and 12), which corroborated the vital role of the tridentate PN^HP ligand. The carbonyl-free pincer complex $[RuCl_2(PN^HP)]_2$ (**4**) also catalyzed the reaction with a reasonable yield of 48% (entry 13). The importance of the metal/NH cooperation[39] for the catalysis was confirmed by the reduced activity of $RuHCl(CO)(PN^{Et}P)$ (**5**) which does not possess a protic amine moiety on the tridentate ligand (entry 14).

Under the optimized conditions at 150 °C using 0.1 mol % of **1** in the presence of KO^{t}Bu, the catalyst system was also successful for the monomethylation of a range of aromatic amines (Table 2). *o*-/*p*-Methylanilines were monomethylated at the amine nitrogen in excellent yields, whereas the reaction of sterically congested 2,4,6-trimethylaniline resulted in a 13% yield, and the unreacted substrate was mostly recovered (entries 2−4). Fluoro-, chloro-, and bromo-anilines yielded the corresponding monomethylated products without dehalogenation in 86−91% yields (entries 5−7). Cyano and olefinic substituents were also tolerated under the reaction conditions and afforded the desired products in yields greater than 80% (entries 8−10); however, *N*-methyl-4-vinylaniline was polymerized during purification. The reaction of aminopyridines, which are slightly less reactive than aniline, gave the monomethylated products in satisfactory yields with a higher concentration of KO^{t}Bu (entries 11 and 12). The selective *N*-monomethylations of 6-aminoquinoline and 1-aminonaphthalene were successfully carried out with 77% and 65% yields, respectively (entries 13 and 14).

Table 2. *N*-Monomethylation of Aromatic Amines[a]



entry	substrate	KO^{t}Bu (mol %)	time (h)	yield (%)[b]
1	aniline	20	5	93
2	4-methylaniline	20	5	100
3	2-methylaniline	40	8	91
4	2,4,6-trimethylaniline	60	16	13[c]
5	4-fluoroaniline	20	5	97
6	4-chroloaniline	40	5	86[c]
7	4-bromoaniline	40	5	87[c]
8	4-aminobenzonitrile	60	5	84
9	4-vinylaniline	40	5	83
10	3-vinylaniline	40	5	87[d]
11	3-aminopyridine	60	5	94
12	2-aminopyridine	100	5	95
13	6-aminoquinoline	20	5	77
14	1-naphthylamine	20	5	65

[a]Standard conditions: Substrate (2.0 mmol), **1** (0.002 mmol), KO^{t}Bu, MeOH (3.6 mL), 150 °C, 5 h. [b]Isolated yield. [c]Yields were determined by GC. [d]Yield was determined by ^{1}H NMR.

As shown in Table 3, the *N*-monomethylation of aniline with a reduced amount of catalyst (0.05 mol %) gave a slightly lower yield of 80% (entry 2). Further reduction of the catalyst loading to 0.02 mol % resulted in moderate activity (43%) (entry 3); however, *N*-methylation proceeded steadily to reach almost complete conversion when the reaction time was prolonged to 16 h with an increase in the amount of base (entries 4 and 5).

The PN^HP pincer complex **1** exhibits outstanding performance for *N*-methylation, although we anticipated that CO gas

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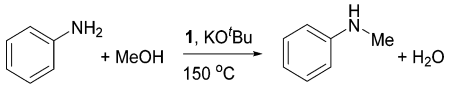
Table 3. *N*-Monomethylation of Aniline at Lower Catalyst Loadings[a]



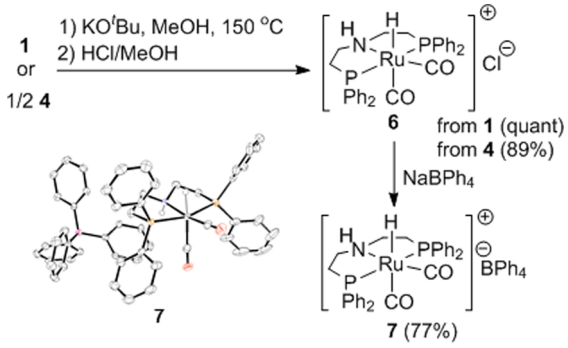
entry	cat. loading (mol %)	KO^{t}Bu (mol %)	time (h)	yield (%)[b]
1	0.1	20	5	96 (93[c])
2	0.05	20	5	80
3	0.02	20	5	43
4	0.02	40	5	72
5	0.02	40	16	98[c]

[a]Standard conditions: Substrate (2.0 mmol), **1**, KO^{t}Bu, MeOH (3.6 mL), 150 °C. [b]Yields were determined by GC. [c]Isolated yield.

generation during the dehydrogenation of methanol could deteriorate the catalytic activity. Notably, the reaction system became pressurized after the methylation was performed in a sealed reactor. When 2.0 mmol of aniline were methylated with 0.1 mol % of **1** under standard conditions, the formation of 0.93 mmol of CO gas was confirmed by a GASTEC Carbon Monoxide Detector Tube.

The behavior of the catalyst precursor under the dehydrogenation conditions was investigated by treatment of **1** (0.33 mmol) with KO^{t}Bu (18.0 mmol) in methanol (20 mL) at 150 °C for 5 h. After the reaction mixture cooled, addition of a methanolic solution of hydrochloric acid quantitatively afforded a new bis(carbonyl)Ru complex (**6**) (Scheme 2).

Scheme 2. Formation of Dicarbonyl−Ru Complexes

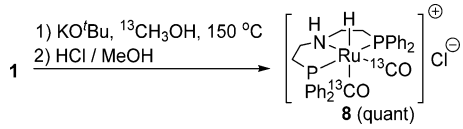


Anion exchange of **6** using sodium tetraphenylborate gave white crystals of the resulting cationic complex **7** in 77% yield. The crystal structure of **7** shows two CO ligands located *trans* to the protic amine moiety and the hydrido ligand.[40] Notably, the *N*-methylation of aniline using the isolated complex **6** or **7** as the catalyst showed comparable activity (95% and 93% yields, respectively) to **1**.

In a similar manner, the catalyst precursor **4** was also converted to **6** in 89% yield by the addition of KO^{t}Bu. Presumably, **4** was initially monocarbonylated with a methoxide anion to form **1**, followed by a second coordination of CO to afford **6**. These results are in agreement with the observation that *N*-methylation catalyzed by **4** (Table 1, entry 13) proceeded with a comparatively slow conversion, because catalytically active mono- or bis(carbonyl)ruthenium species such as **1** and **6** could be moderately generated during the reaction.

To further understand the transformation of methanol, isotope-labeling experiments were performed. When ^{13}C-labeled methanol (5 mL) was employed as the solvent in the reaction of **1** (0.082 mmol) with KO^{t}Bu (44.6 mmol) at 150 °C for 5 h, ^{13}C atoms were incorporated into the two CO ligands bound to the Ru center (Scheme 3), as supported by a

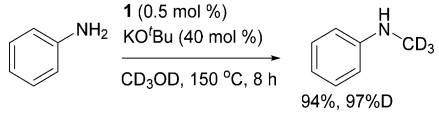
Scheme 3. Labeling Experiment Using Methanol-^{13}C



doublet of doublets at 57.7 ppm ($^2J_{CP}$ = 21.6 and 18.0 Hz) in the ^{31}P NMR spectrum in CD_2Cl_2. This complete incorporation verifies that the CO ligand is replaced with nonligated CO that originates from the methanol solvent during the methylation of amines.

When the catalytic reaction of aniline was performed with 0.5 mol % of **1** in methanol-d_3 at 150 °C, *N*-methylaniline-*d*3 was obtained in 94% yield after 8 h (Scheme 4). Deuterium

Scheme 4. Selective *N*-Methylation in CD_3OD



atoms were selectively located at the *N*-methyl group (97%) with no incorporation into the phenyl group. The catalytic activity decreased considerably compared to nondeuterated methanol, as broadly investigated in hydrogen-transfer catalyst systems.[41] These results agree with a borrowing-hydrogen mechanism involving the dehydrogenation of methanol to formaldehyde and subsequent condensation/reduction with the amine substrates, as shown in Figure 1, accompanied by the consecutive dehydrogenation of formaldehyde to CO.

In conclusion, the *N*-monomethylation of aromatic amines in methanol was accomplished with satisfactory selectivity using the PN^{H}P pincer Ru complex **1** and an appropriate amount of KO^{t}Bu. The catalyst loading could be lowered to 0.02 mol % by increasing the base concentration. These findings provide a practical method distinguished by an easily handled, environmentally benign transformation and a reliable, CO-tolerant catalyst.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01449.

Experimental section and characterization data, including X-ray data for **7** (PDF)

Accession Codes

CCDC 1841909 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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AUTHOR INFORMATION

Corresponding Authors

*E-mail: osamu_ogata@takasago.com.
*E-mail: ykayaki@o.cc.titech.ac.jp.

ORCID

Yoshihito Kayaki: 0000-0002-4685-8833

Notes

The authors declare no competing financial interest.

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