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Simple $RuCl_3$-catalyzed *N*-Methylation of Amines and Transfer Hydrogenation of Nitroarenes using Methanol

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Methanol is a potential hydrogen source and C_1 synthon, which finds interesting applications in both chemical synthesis and energy technologies. The effective utilization of this simple alcohol in organic synthesis is of central importance and attracts scientific interest. Herein, we report a clean and cost-competitive method with the use of methanol as both C_1 synthon and H_2 source for selective *N*-methylation of amines by employing relatively cheap $RuCl_3.xH_2O$ as a ligand-free catalyst. This readily available catalyst tolerates various amines comprising electron-deficient and electron-donating groups and allows them to transform into corresponding *N*-methylated products in moderate to excellent yields. In addition, few marketed pharmaceutical agents (e.g., venlafaxine and imipramine) were also successfully synthesized *via* late-stage functionalization from readily available feedstock chemicals, highlighting synthetic value of this advanced *N*-methylation reaction. Using this platform, we also attempted tandem reactions with selected nitroarenes to convert them into corresponding *N*-methylated amines using MeOH under H_2-free conditions including transfer hydrogenation of nitroarenes-to-anilines and prepared drug molecules (e.g., benzocaine and butamben) as well as key pharmaceutical intermediates. We further enable one-shot selective and green syntheses of 1-methylbenzimidazole using *ortho*-phenylenediamine (OPDA) and methanol as coupling partners.

Introduction

The development of practical and eco-compatible reactions for the production of sustainable amines from readily available feedstock chemicals by employing cheap, abundant and renewable reagents is one of the key research goals in advanced industrial organic synthesis.[1] In particular, the development of operationally simple processes predicted on easily accessible catalysts for the economical formation of carbon-nitrogen bonds through a hydrogen-borrowing strategy is rather appealing.[2] Such one-pot reaction procedures offer ease of handling and enable cost-efficient pathways for different kinds of amines by releasing water as the only by-product.[2a–d] Within this context, the reaction of amines or nitroarenes with biodegradable methanol is highly attractive because it generally satisfies most of the twelve principles of green chemistry.[3]

Many pharmaceutical agents contain at least one and sometimes multiple *N*-methyl subunits in their core structures. In general, the installation of methyl groups leads to a dramatic change in the pharmacological properties of the drug candidate.[4] Hence, *N*-methylated molecules are popular in drug discovery. Also, *N*-methylated amines play significant roles as building blocks in the synthesis of industrial chemicals, pharmaceuticals, agrochemicals, and life science materials.[5] Regarding their synthesis, a hydrogen-borrowing approach represents a waste-free process to generate diverse *N*-methylated molecules.[1f,3a–r] In addition, reductive amination of amines using CO_2 also constitutes a green methodology to produce *N*-methyl amines.[6] Apart from these approaches, reagents such as (para)formaldehyde,[7] formic acid,[8] dimethyl carbonate,[8f,9] DMSO,[10] Me-NO_2,[11] dimethylamines,[12] Me_3N-BH_3[13] and methoxy unit of lignin[14] have been successfully employed to achieve useful *N*-methylamines or *N*, *N*-dimethylanilines. Traditionally, industrial *N*-methylation reactions are mainly performed using toxic reagents like methyl halides, dimethyl sulfate, dimethyl phosphite and diazomethane.[15] However, most of these activated reagents involve exothermic work-up and release large amounts of harmful waste along with product formation, which in general are environmentally non-compatible and show poor atom-economy. Thus, the search for more sustainable reagents to minimize environmental impact and to improve green credentials is gaining momentum in both chemical and pharmaceutical industries.[15d,16]

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Among the variety of C_1 building blocks, methanol is a cheap and abundant industrial raw material for a large number of high-quality basic chemicals.[17] Methanol can be produced from both fossil and renewable sources.[18] Therefore, simple and high yielding methodologies for efficient utilization of methanol by selective organic transformations under controlled conditions are highly desirable.[17a] However, there exists a challenge for the activation of methanol, because of its relatively high energetic demand for dehydrogenation to active formaldehyde (for methanol $\Delta H = 84\ kJ\,mol^{-1}$ *vs* $68\ kJ\,mol^{-1}$ for ethanol).[17b] Despite these limitations, the last five years have witnessed an increasing interest in the area of methanol utilization as a single-carbon building block for *C*-methylation[2c,17b,19] and *N*-methylation reactions.[3]

Ruthenium is the most active catalyst for variety of organic reactions,[20] particularly for activation of alcohols *via* a borrowing hydrogen mechanism.[21] In 1981, Grigg et al.[22] initiated the breakthrough *N*-methylation of amines using methanol as a single-carbon reagent in presence of various transition metals (Rh, Ir, and Ru). Later, Watanabe and co-workers[23] used $RuCl_3.nH_2O/P(OBu)_3$ catalytic system for *N*-methylation of amines with methanol at 180 °C, but the substrate scope is very narrow. After their seminal work, many groups have extended the state of selective *N*-methylation of amines or nitroarenes with methanol in presence of noble[3a–e,h,l-q,s,u-z,aa, ac-ae,24] and non-noble metals.[3f,g,i–k,r,t, ab, af-ag] Regarding ruthenium catalysis, to date only five homogeneous catalytic systems are reported (Figure 1). For instance, Seayad group[3e] reported a $[RuCp^*Cl_2]_2$/dpePhos catalyst system for selective *N*-methylation of amines and sulfonamides using MeOH as a C_1 synthon. Following this report, Kundu et al.[3d] developed air and moisture stable [Ru(phenpy-OMe)-$(MeCN)_2$Cl]Cl (NNN-pincer complex) as an efficient catalyst for *N*-methylation of various aromatic and aliphatic nitro compounds using MeOH. Next, PNHP pincer Ru complex was also found to be active for selective *N*-methylation of amines with MeOH.[3n] Remarkably, Hong and associates[3ae] applied Ru-MACHO-BH as a catalyst for selective *N*-methylation of primary aliphatic amines using methanol as C_1 reagent under 40 bar H_2 pressure. Yang and co-workers,[3p] very recently demonstrated the use of $[RuCl_2(p\text{-cymene})_2]_2$ as the catalyst and an NNN pincer ligand (amine-pyridine-imine, API) for selective *N*-monomethylation of nitro compounds with MeOH as both C_1 and H_2 source. However, all these Ru-based catalysts are homogeneous and require external ligand. Hence, the use of simple and efficient catalysts including easy reaction work-ups for the preparation of valuable *N*-methylated amines is highly desirable both at academic and industrial level.

On the other hand catalytic transfer hydrogenation is one of the attractive transformation in organic synthesis, due to the ready availability of hydrogen donors and ease of handling.[25] Among various hydrogen donors, methanol serves as an excellent liquid organic hydrogen carrier (LOHC) for fuel cell applications.[26] Very recently, there are a few interesting reports available with methanol as H_2 source for selected organic reactions (Figure 2).[27] However, transfer hydrogenation of aromatic nitro derivatives using methanol is scarcely reported.[28] In this contribution, we also report the application of methanol as a hydrogen source for transfer hydrogenation of nitroarenes leading to anilines and prepared pharmaceuticals as well as key pharma intermediates by using $RuCl_3.xH_2O$ as a catalyst.

Most of the homogeneous catalysts employed for challenging reactions in chemical industries are mainly dependent on organic ligands or metal complexes, which may require Schlenk-line or glove box and sometimes that leading to expensive procedures. Hence, catalysts which are simple, versatile, and readily accessible are highly beneficial from cost-competitive and practical point of view. In this sense, $RuCl_3.xH_2O$ is simple, relatively cheap, and readily available in sufficient quantities. Interestingly, $RuCl_3.xH_2O$ is used as a catalyst for various organic transformations[29] including reductive *N*-alkylation of nitroarenes using glycerol as hydrogen source.[30] Inspiring from these aforementioned reports and our interest in *N*-methylation[3b] and hydrogenation reactions,[31] we

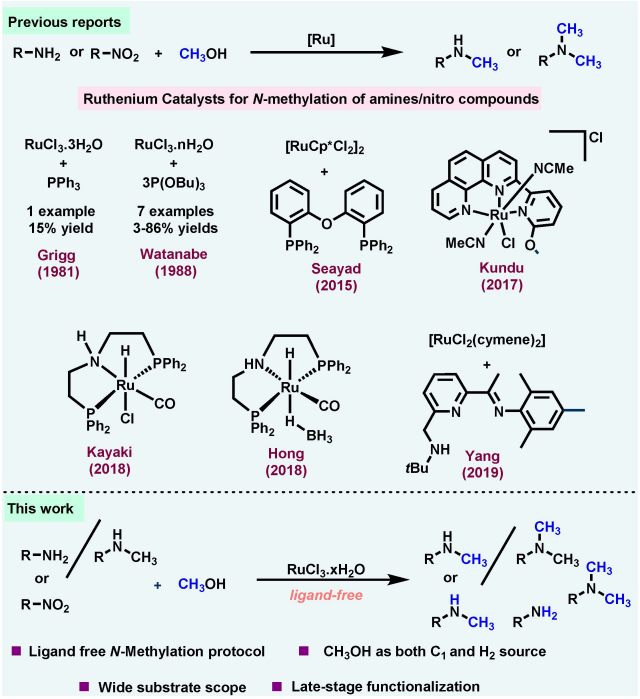


Figure 1. Overview of Ru-catalyzed *N*-methylation of amines/with methanol.

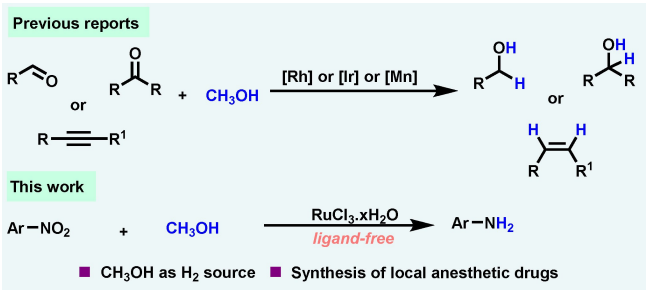


Figure 2. Overview of methanol as a transfer hydrogen source in organic syntheses.

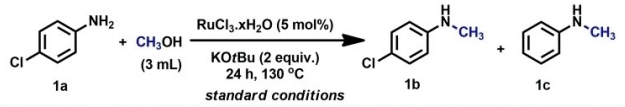
demonstrate the use of $RuCl_3.xH_2O$ as a ligand-free catalyst for selective *N*-methylation of amines using methanol and without external added hydrogen. This simple catalyst tolerates various amines bearing electron-deficient and electron-donating groups and allows them to transform into their corresponding *N*-methylated products in moderate to excellent yields. In addition, two pharmaceutical agents and one alkaloid were successfully synthesized *via* late-stage functionalization from readily available starting materials. Moreover, tandem reactions with selected nitroarenes to convert them into corresponding *N*-methylated amines using methanol as both single-carbon and H_2 source were also attempted, including sustainable synthesis of 1-methylbenzimidazole.

Results and Discussion

We began our investigation by selecting 4-chloroaniline (**1 a**) as a benchmark reaction because it allows the smooth reaction monitoring of both reactivity and selectivity for *N*-methylation over carbon-chloride (C–Cl) dehalogenation. In the beginning, we executed the reaction with **1 a** and MeOH as both reductant and one-carbon source using commercially available $RuCl_3.xH_2O$ (5 mol%) as a catalyst, 2.0 equiv. KO*t*Bu as base at 130 °C and 24 h; these conditions enabled the desired product formation in 92% isolated yield (Table 1, entry 1). Among, various surveyed bases (entries 2–5), K_3PO_4 and NaOH gave moderate to good yields of **1 b** (entries 4–5). Substitution of $RuCl_3.xH_2O$ with alternative ruthenium sources, for instance, $RuCl_2(PPh_3)_3$, $[Ru(COD)Cl_2]_n$ and Ru/C led to decline in the yields (entries 6–8). Other carbon supported catalysts, such as Pd/C, Rh/C and homogeneous $Pd(OAc)_2$ catalysts were found to be non-selective and gave low yields of **1b** along with by-product (**1 c**) in high quantities (entries 9–11). Either no reaction or poor yields were observed when cobalt, iron, zinc, and zirconium pre-catalysts were used as catalysts (entries 12–15). Control experiments revealed that conversion of **1 a** to **1 b** is not possible without the employment of base and catalyst (entries 16–17). When 1 equiv. of KO*t*Bu was used, only 67% of **1 b** was obtained as major product (entry 18).

After identifying this suitable catalytic system, the effect of time (A) and temperature (B) was systematically investigated. As shown in figure 3, within the first 5 h of the reaction, 4-chloroaniline (**1 a**) started reacting with MeOH and the conversion of **1 a** reaches to ~20%, while the selectivity of **1 b** is >99%. Then, the conversion of **1 a** gradually increased with time and at 24 h, >99% conversion of **1 a** and ~95% selectivity of **1 b** was observed. During the course of the reaction, very low amounts (<5%) of **1 c** and traces of 4-chloro-*N,N*-dimethylaniline (Figure 3A) were detected, indicating high selectivity of this *N*-methylation reaction with simple $RuCl_3.xH_2O$ catalyst. Nevertheless, 59% of 4-chloro-*N,N*-dimethylaniline was obtained at 48 h. These results clearly indicate the effect of time is

Table 1. Reaction optimization for *N*-Methylation of 4-chloroaniline using MeOH as C_1 synthon and a H_2 Source.[a]



entry	deviation from standard conditions	yield of 1b (%)	yield of 1c (%)
1	none	95(92)	5
2	K_2CO_3, instead of KO*t*Bu	59	9
3	Na_2CO_3, instead of KO*t*Bu	76	7
4	K_3PO_4, instead of KO*t*Bu	88	9
5	NaOH, instead of KO*t*Bu	89	10
6	$RuCl_2(PPh_3)_3$, instead of $RuCl_3.xH_2O$	33	3
7	$[Ru(COD)Cl_2]_n$, instead of $RuCl_3.xH_2O$	26	12
8	Ru/C, instead of $RuCl_3.xH_2O$	41	16
9	Pd/C, instead of $RuCl_3.xH_2O$	55	45
10	Rh/C, instead of $RuCl_3.xH_2O$	24	75
11	$Pd(OAc)_2$, instead of $RuCl_3.xH_2O$	26	73
12	$Co(NO_3)_2{\cdot}6H_2O$, instead of $RuCl_3.xH_2O$	02	-
13	$Fe(NO_3)_3.9H_2O$, instead of $RuCl_3.xH_2O$	-	-
14	$Zn(NO_3)_2.6H_2O$, instead of $RuCl_3.xH_2O$	-	-
15	$Zr(C_5H_7O_2)_4$, instead of $RuCl_3.xH_2O$	-	-
16	without base	-	-
17	without catalyst	-	-
18	1 equiv. of KO*t*Bu, instead 2 equiv. of KO*t*Bu	67	2

[a] **Reaction conditions**: 4-chloroaniline **1 a** (0.5 mmol), $RuCl_3.xH_2O$ (5 mol%), base (2 equiv.), MeOH (3 mL), 130 °C, 24 h. Conversion and yield were determined using GCMS analysis. Isolated yields shown in parentheses.

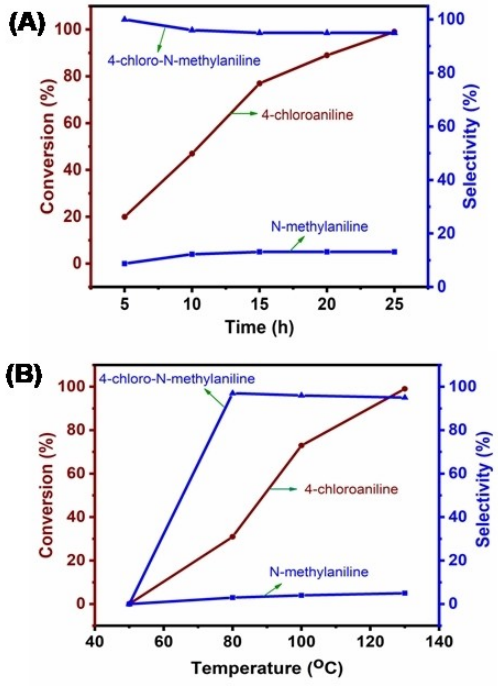
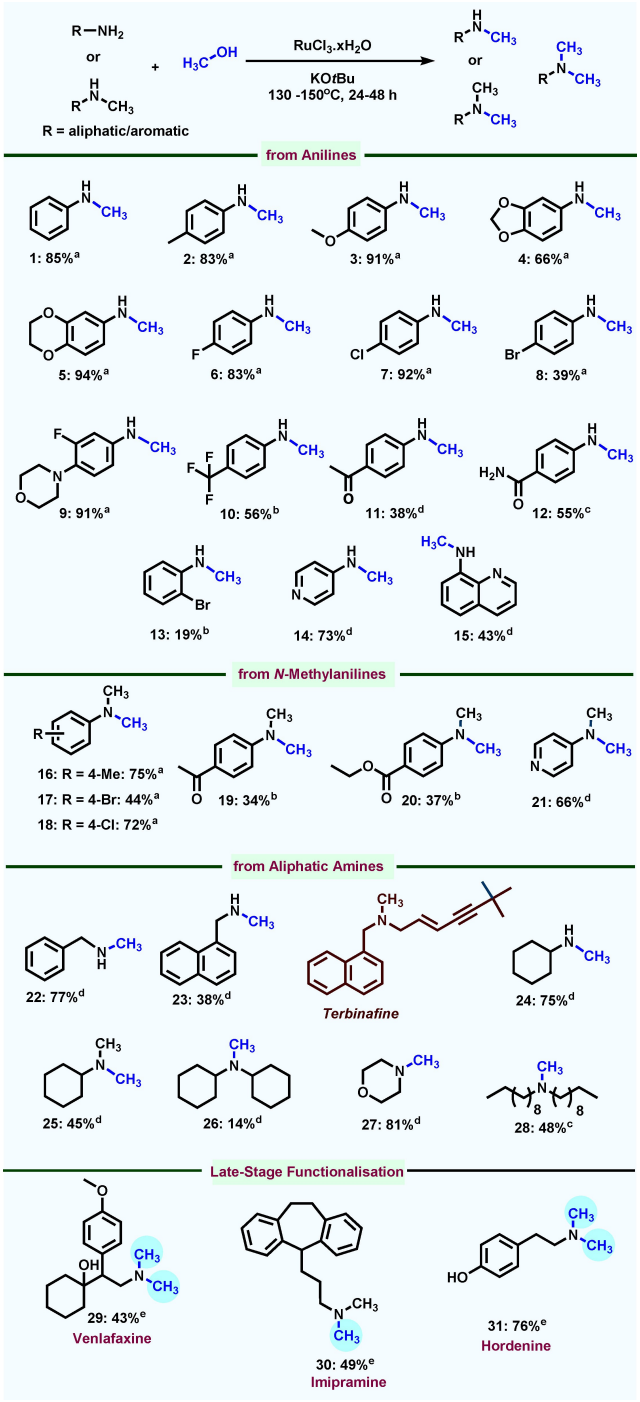


Figure 3. Kinetic investigations on the $RuCl_3$-catalyzed *N*-methylation of 4-chloroaniline with methanol. A) Effect of time. Reaction conditions: 4-chloroaniline (0.5 mmol), $RuCl_3.xH_2O$ (5 mol%), KO*t*Bu (2 equiv.), MeOH (3 mL), 130 °C, 0 to 24 h; B) Effect of temperature. Reaction conditions: 4-chloroaniline (0.5 mmol), $RuCl_3.xH_2O$ (5 mol%), KO*t*Bu (2 equiv.), MeOH (3 mL), 40 to 130 °C, 24 h.

an important parameter concerning the selectivity of *N*-methylation and *N*, *N*-dimethylation of amines. Next, when examining the reaction with the effect of temperature (Figure 3B), no product formation (**1 b**) was seen at 50 °C. The reaction started slowly at 80 °C and upon further increasing the temperature, the conversion of **1 a** sharply increased and led to the formation of **1 b** with high selectivity at 130 °C (Figure 3B).

Under optimal reaction conditions, the substrate scope and limitations of structurally diverse anilines including aliphatic amines were systematically assessed, and relevant results are shown in Scheme 1. Simple aniline underwent full conversion and gave corresponding *N*-methylaniline in 85% isolated yield. Anilines bearing electron-donating groups such as -Me, -OCH_3, 1,3-benzodioxole, and 1,4-benzodioxole furnished desired *N*-methylated products in 66–94% yield (entries 2–5). Halogenated anilines (-F, -Cl, and -Br) are converted into their desired *N*-methylated products with moderate to excellent yields by keeping halides intact (entries 6–9), thereby offering opportunities of these molecules in cross-coupling chemistry.[32] Arylamines bearing electron-withdrawing groups such as trifluoromethyl, ketone, and amide moieties were also compatible, but under high catalyst loadings and longer reaction times (entries 10–12). The *N*-methylation of *ortho*-substituted 2-bromoaniline resulted very low conversion and yield despite varying the reaction conditions (entry 13). This could be due to the steric repulsion/hinderance. Heterocyclic amines such as 4-(methylamino)pyridine and 8-aminoquinoline were also exploited under the optimal reaction conditions and the corresponding *N*-methylated products were furnished in 73% and 43% yields, respectively (entries 14–15). Subsequently, with substituents at various positions, *N,N*-dimethylation of mono-*N*-methylamines was also tested: the corresponding *N,N*-dimethylated products afforded in moderate to high yields (entries 16–21).

Moreover, aliphatic amines are also used as substrates to react with methanol under standard conditions to afford corresponding *N*-methylamines. However, it should be noted that, when primary aliphatic amines were employed as starting materials, along with *N*-methylation, relatively low yields of *N,N*-dimethylated product was observed as by-product. Initially, using benzylamine as a starting material under the standard conditions, 77% of *N*-benzylmethylamine was obtained (entry 22). Remarkably, 1-naphthylmethylamine was also converted to the corresponding *N*-methyl-1-naphthylmethylamine in 38% yield (entry 23), which is an important precursor for the synthesis of terbinafine[33] and naftifine.[3e] Similarly, *N*-methylcyclohexylamine (entry 24), a key precursor for the synthesis of bromhexine,[3b] was also afforded in 75% yield. Other secondary amines were also examined under standard conditions. Although *N*-methylcyclohexylamine reacted moderately well with methanol to afford *N,N*-dimethylcyclohexylamine in 45% yield (entry 25), use of dicyclohexylamine resulted in very low yield, possibly due to steric hinderance (entry 26). Excitingly, morpholine and didecylamine furnished corresponding *N*-methylated products in 81% and 48% yields, respectively (entry 27 & 28). Unfortunately, few amines bearing sensitive functional groups at various positions were unsuited for *N*-methylation with the standard reaction conditions (see Supporting Information, Scheme S1).



Scheme 1. Reaction conditions: [a] substrate (0.5 mmol), $RuCl_3.xH_2O$ (5 mol%), KO*t*Bu (2 equiv.), MeOH (3 mL), 130 °C, 24 h, isolated yields; [b] substrate (0.5 mmol), $RuCl_3.xH_2O$ (10 mol%), KO*t*Bu (2.5 equiv.), MeOH (3 mL), 150 °C, 48 h, isolated yields; [c] same as [b] but 15 mol% of $RuCl_3.xH_2O$; [d] same as [b] but reaction temperature is 130 °C; [e] same as [a] but $RuCl_3.xH_2O$ (20 mol%), KO*t*Bu (3 equiv.), 150 °C, 60 h.

Next, we showcase the late-stage *N*-methylation of amines to afford drug molecules and natural products. Such *N*-methylation in structurally diverse molecules at late-stages will

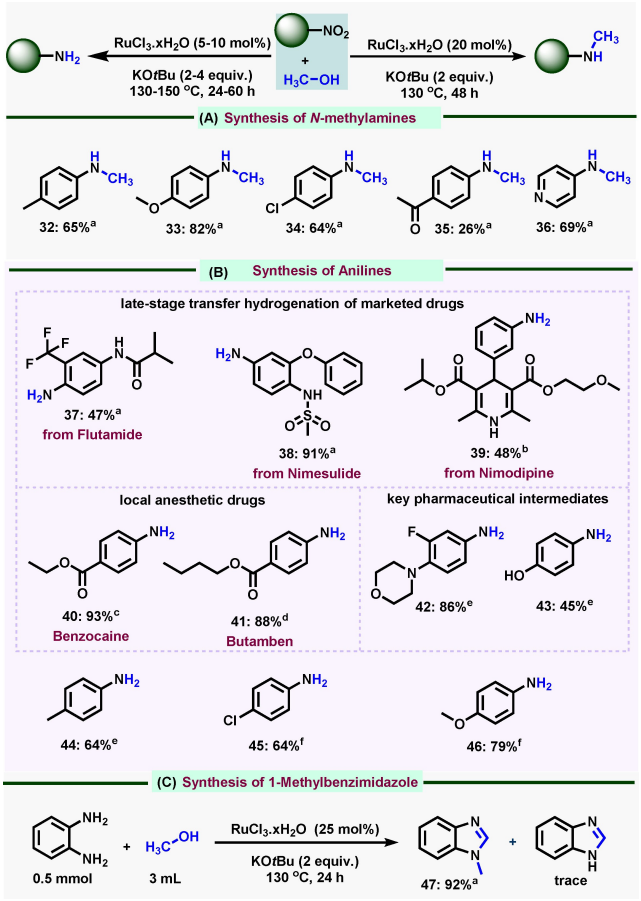
eliminate the need for additional synthetic steps and provide straight-forward access to key pharmaceutical agents. In this respect, antidepressant drug molecules venlafaxine and imipramine were directly synthesized from their corresponding precursors in 43% and 49% yield, respectively, albeit under high catalyst loadings and longer reaction times (entries 29 and 30). Eventually, hordenine was also synthesized in 76% yield from tyramine as a precursor (entry 31).

The successful execution of *N*-methylation from amines prompted us to further explore the feasibility of tandem reaction with selected nitroarenes and methanol under exogenous H_2-free conditions. Compared to anilines, nitroarenes as starting materials are hugely beneficial from the viewpoint of step-efficiency. Delightfully, 4-methyl nitrobenzene, 4-methoxy nitrobenzene, 4-chloro nitrobenzene, 1-acetyl-4-nitrobenzene and 4-nitropyridine were successfully transformed into their corresponding *N*-methylamines in moderate to good yields (Scheme 2, entries 32–36).

Next, the reduction of nitroarenes is one of the most widely used reaction in chemical industries; the resulting anilines are often found in fragrances, dyestuff, and pharmaceuticals.[31b,34] During one-shot *N*-methylation of nitroarenes with methanol, the formation of low amounts of anilines was noticed. This result encouraged us to employ methanol as a reductant for nitro-to-aniline reduction. Recently, there are a few reports with methanol as H_2 source for selected organic reactions.[27] However, transfer hydrogenation of aromatic nitro derivatives using methanol is scarcely reported.[28] In this sense, we slightly tuned the amount of $RuCl_3.xH_2O$ and reaction time and applied our approach for the synthesis of various anilines including drug-like molecules. In this sense, nitro-based drug compounds like flutamide, nimesulide and nimodipine were selectively converted into their respective anilines in good to excellent yields (Scheme 2, 37–39), without disturbing the other functional groups. We then applied the present methodology for the preparation of local anesthetic drugs such as benzocaine and butamben. These two pharmaceutical agents were conveniently synthesized and isolated in excellent yields (entries 40–41). Next, highly demanded pharmaceutical intermediates which are extremely useful for further production of commercial drugs such as Linezolid[35] and Paracetamol[1e] were isolated in good to high yields (entries 42–43). In addition, methyl, chloro and methoxy substituents at *para* position of aromatic nitro compounds have also been tolerated and gave corresponding arylamines in good yields (entries 44–46). The results indicate the robustness of $RuCl_3.xH_2O$ as catalyst and methanol as a reductant to access functional anilines that are often useful in biomedical sciences.

Impressively, this protocol is also amenable for one-shot selective sustainable synthesis of 1-methylbenzimidazole in high yields by reacting with OPDA and methanol under relatively mild reaction conditions (Scheme 2, entry 47). Previous protocols largely rely on harsh conditions and have selectivity problems for synthesizing valuable 1-methylbenzimidazole in a one-pot manner.[3b,x,36]

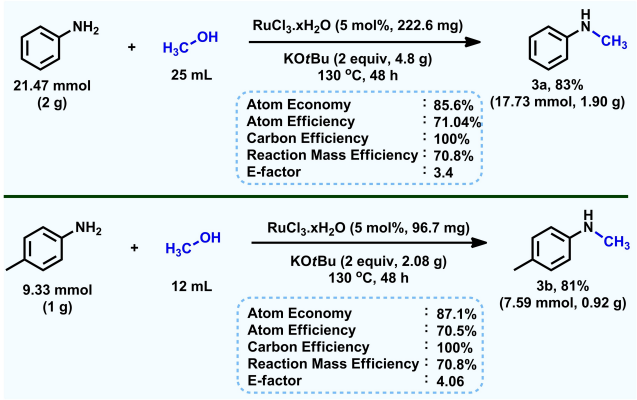
Gratifyingly, this concise protocol can also be applied for *N*-methylation of aniline and 4-methylaniline on gram-scale and



Scheme 2. (A) *N*-methylation of nitroarenes using methanol. Reaction conditions: [a] substrate (0.5 mmol), $RuCl_3.xH_2O$ (20 mol%), KO*t*Bu (2 equiv.), MeOH (3 mL), 130 °C, 48 h, isolated yields; (B) Transfer hydrogenation of nitroarenes using methanol. Reaction conditions: [a] substrate (0.5 mmol), $RuCl_3.xH_2O$ (10 mol%), KO*t*Bu (4 equiv.), MeOH (3 mL), 130 °C, 36 h, isolated yields; [b] same as [a] but substrate (0.25 mmol) and reaction time 48 h; [c] same as [a] but substrate (0.14 mmol) and reaction time 48 h; [d] same as [a] but reaction time 48 h; [e] same as [a] but reaction time 24 h; [f] substrate (0.5 mmol), $RuCl_3.xH_2O$ (5 mol%), KO*t*Bu (2 equiv.), MeOH (3 mL), 150 °C, 60 h, isolated yields; (C) Synthesis of 1-methylbenzimidazole. Reaction conditions: [a] substrate (0.5 mmol), $RuCl_3.xH_2O$ (25 mol%), KO*t*Bu (2 equiv.), MeOH (3 mL), 130 °C, 24 h, isolated yields.

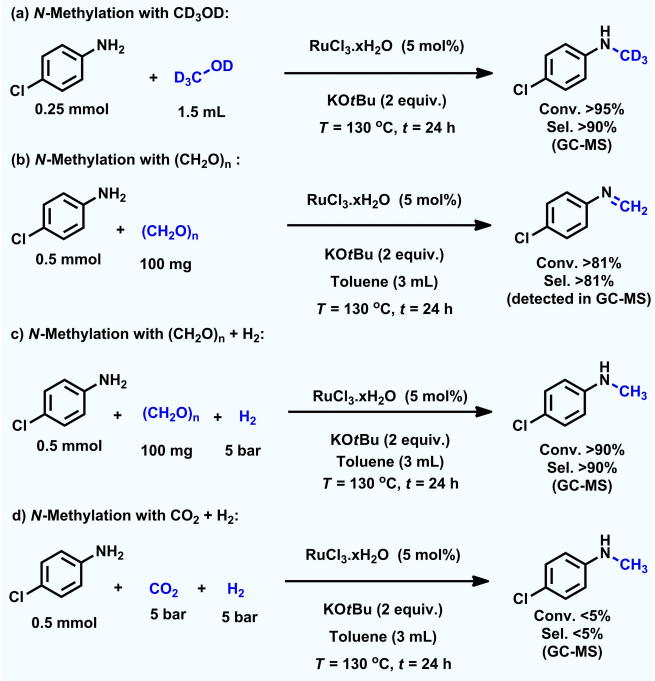
the obtained isolated yields are identical to its millimole-scale counterpart (Scheme 3). In addition, green chemistry metrics[37] were systematically evaluated for the selected g-scale reactions and the corresponding data was shown in Scheme 3. Atom economy is more than 85% for the synthesis of *N*-methylaniline (**3a**) and *N*-methyl-*p*-toluidine (**3b**). Atom efficiency is around 71% and carbon efficiency is 100% for both the products **3a** and **3b**. Other important parameter is reaction mass efficiency which is nearly 71% for both **3a** and **3b**. Lastly, the calculated *E*-factor for **3a** and **3b** is 3.4 and 4.06, respectively, which is quite low. The assessment of green metrics for gram-scale reactions (Scheme 3) indicates that the process is green and environmentally friendly.

To obtain deeper insights into this *N*-methylation reaction using methanol as both C_1 and H_2 source, *N*-trideuteromethylation of 4-chloroaniline was demonstrated with CD_3OD which



Scheme 3. Gram-scale reactions and their green metrics.

resulted the corresponding product in 90% selectivity (Scheme 4a). Notably, deuterated compounds play a key role in biomedical research.[2i] Next, we conducted the *N*-methylation using paraformaldehyde in presence and absence of hydrogen (Scheme 4b and 4c). When 4-chloroaniline is reacted with paraformaldehyde in absence of H_2, as expected 4-chloro-*N*-methylideneaniline was obtained in 81% yield (Scheme 4b, also see Supporting Information, Figure S1). However, by employing 5 bar of H_2, selective *N*-methylated product was observed (Scheme 4c, also Supporting Information, Figure S2). A very poor conversion and selectivity was noticed with the combination of $CO_2 + H_2$ to yield *N*-methylated product (Scheme 4d). In addition, *N*-methylation of aniline with CD_3OD and CH_3OH (1:1 ratio) under optimal conditions were executed and observed

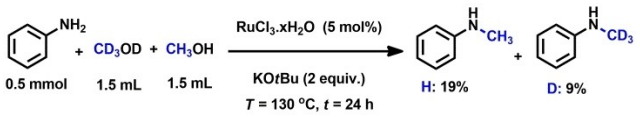


Scheme 4. The labelling and control experiments.

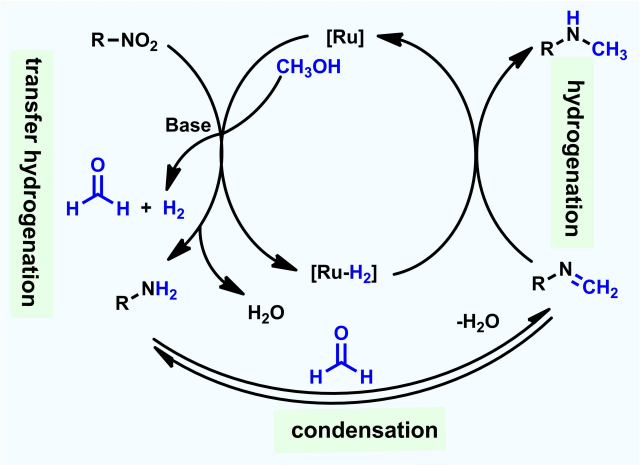
the incorporation of 19% H and 9% D (Scheme 5). Based on these observations and existing literature,[3a,b,f] we propose a plausible reaction mechanism (Scheme 6). In the first step methanol undergoes dehydrogenation in the presence of base to give dihydrogen (H_2) and formaldehyde ($-CH_2O$). The resulting H_2 reduces nitro-to-amine *via* transfer hydrogenation, which further reacts with $-CH_2O$ to produce an imine as an intermediate. Next, the imine undergoes hydrogenation with H_2 (generated from methanol) to yield desired *N*-methylated product (Scheme 6).

Conclusion

We have developed a $RuCl_3$-catalyzed *N*-methylation of amines by employing MeOH as both C_1 and H_2 source. This concise methodology features the use of relatively inexpensive $RuCl_3.xH_2O$ salt as a pre-catalyst and does not require the use of organic ligands. In addition, selected pharmaceuticals, and natural alkaloids (e.g., venlafaxine, imipramine and hordenine) were also successfully synthesized *via* late-stage functionalization from readily available starting materials. Furthermore, selected nitroarenes are directly converted to corresponding *N*-methylated amines with methanol under hydrogen-free conditions. Also, by slightly tuning the amount of $RuCl_3.xH_2O$, methanol serves as a hydrogen donor to reduce nitroarenes, exemplified by synthesis of local anesthetic drugs (e.g., benzocaine and butamben) and key pharma intermediates that are extremely useful in the manufacture of commercial drugs such as Linezolid and Paracetamol. Green chemistry metrics calculations for selected g-scale reactions reveal that the



Scheme 5. *N*-methylation of aniline with CD_3OD and CH_3OH.



Scheme 6. Plausible reaction mechanism.

reaction is green and environmentally friendly. This platform also enables one-shot selective and green syntheses of 1-methylbenzimidazole using *ortho*-phenylenediamine (OPDA) and methanol as coupling partners.

Experimental Section

General procedure for *N*-Methylation of amines. An oven dried 20 mL ACE® pressure tube was charged with $RuCl_3.xH_2O$ (5 mol%, 5.18 mg), KOtBu (2 equiv., 112 mg), amine (0.5 mmol), and MeOH (3 mL). The pressure tube was then sealed and allowed to stir at 130 °C in oil bath for 24 h. After completion of the reaction, the pressure tube was cooled to room temperature, and then the pressure build-up in the tube has been released slowly by losing the screw cap. The solid catalyst was separated from the reaction mixture by filtration through filter paper and washed with 3 mL of ethyl acetate. After evaporating the solvent through rotary evaporator, the crude mixture was purified by using 60–120 silica gel column chromatography (ethyl acetate: hexane) to obtain desired pure product, which was further submitted for NMR analysis.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Methanol · $RuCl_3.xH_2O$ · *N*-Methylation · Transfer hydrogenation · Pharmaceutical intermediates

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