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Tandem Transformation of Nitro Compounds to N-methylated Amines: Greener Strategy for the Utilization of Methanol as a Methylating Agent

Bhaskar Paul, Sujan Shee, Kaushik Chakrabarti and Sabuj Kundu*[a]

Abstract: A simple air and moisture stable, highly efficient NNN ruthenium catalyst is reported for the first time to catalyse the tandem transformation of various aromatic and aliphatic nitro compounds to the corresponding N-methylated amines up to 98% yields using methanol as a green and sustainable methylating agent. Gram scale reactions using challenging nitro substrates demonstrated the practical application aspects of this catalytic system. Importantly, N-methylamine group was smoothly introduced to various complex molecular setting without using any expensive Pd/phosphine/amine based cross coupling reaction.

N-methylated amines are important building blocks in synthesis of a range of valuable compounds including dyes, surfactants, medicines, preservatives and agrochemicals etc.[1] To synthesize them the most conventional approach require toxic and carcinogenic methyl halides or other strong reagents like MeOMs, MeOTs, Me_2SO_4, $OC(OMe)_2$ etc.[2] Generation of stoichiometric amount of waste and formation of over alkylated products are the major disadvantages of these methods.[2]

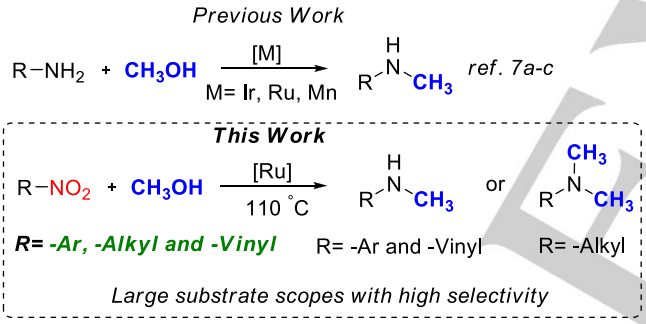
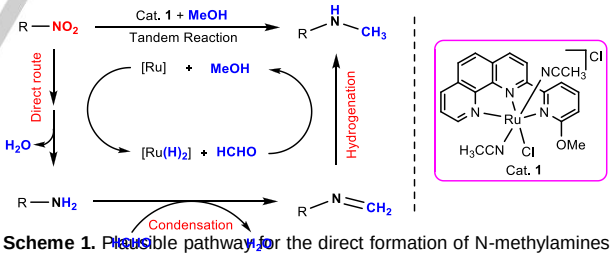


Figure 1. Synthesis of N-methylamines using methanol.

Low-cost methanol has great potential as a energy carrier and feedstock, is readily accessible from various abundant natural resource such as natural gas, biomass, and coal.[3] Therefore, utilization of easily available and less toxic methanol as a methylating agent is atom economical and highly attractive greener alternative. Although, several transition metal catalyzed N-alkylation of amines using higher alcohols following hydrogen autotransfer process were reported;[4] only few systems are known for the N-methylation of amines utilizing methanol.[5] Higher activation energy for the dehydrogenation of methanol compare to other higher alcohols makes this strategy challenging.[6] Recently, N-methylation of amines using methanol were reported by Li, Seayad and Beller groups.[7] Saito group also demonstrated similar transformation using Ag/TiO_2 photocatalyst.[8]

Reduction of inexpensive and readily available nitroarenes is one of the most conventional process to synthesize anilines.[9] So, one-pot synthesis of N-alkylated amines from nitroarenes and alcohols is attractive technique which recently has been explored.[10] However, tandem conversion of nitroarenes to N-methylated amines using methanol is rare, to the best of our knowledge only two reports are known. Li group reported Raney-Ni catalysed synthesis of N,N-dimethylaniline from nitrobenzene at 170 °C and 30 atmosphere of N_2 pressure.[11] Similar transformation using Pd (8 mol%)/TiO_2 nano-catalyst under UV-light was revealed by Shi group.[12] Remarkably, they also demonstrated N-methylation using $CuAlO_x$ catalyst and CO_2/H_2.[13] However, higher pressure (30- 70 bar) and temperature (170 °C) as well as longer reaction time (48 h) were essential. Expensive and tedious experimental setups, harsh reaction conditions, limited substrate scopes and poor selectivity are the major limitations in these protocols.[11-14] Therefore, development of a simple, versatile and effective system for the direct synthesis of N-methylated amines using methanol is indispensable.

We recently reported highly active *in situ* generated Ru(II) catalyzed chemoselective transfer hydrogenation (TH) of nitroarenes in 2-propanol.[15] As a part of our continuing interest in reduction of nitroarenes[16] and utilization of alcohols as alkylating agents,[17] herein we report air and moisture stable simple Ru(II) catalyzed environmentally benign, tandem and selective conversion of various nitro compounds to the corresponding N-methylated amines using methanol.



Scheme 1. Plausible pathway for the direct formation of N-methylamines from nitro compounds.

Recently, we observed that in Ru(II) catalyzed TH of nitroarenes among the various ligands phenpy-OMe exhibited the highest catalytic activity.[15] Hence, we started this work with complex **1** to test its potential in N-methylation of amines using methanol and accordingly the reaction condition was optimized (see SI) and the substrate scope is outlined in table **1**. Various substituted anilines bearing -Cl, -Br, -Me, -OMe and -OPh groups were converted to the corresponding N-methylated anilines (**1a**-**1g**) in excellent yields. Heterocyclic pyridin-3-amine was also successfully N-methylated, although the reaction was bit slower (**1i**). Selective N,N-dimethylation was observed with benzylamine probably due to more nucleophilicity compare to the aromatic amines (**1j**). Similarly, hexyl amine and oleyl amine produced the corresponding N,N-dimethylated amines in 92% and 78% yields

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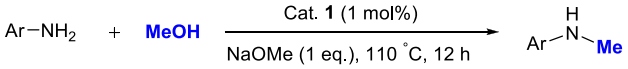
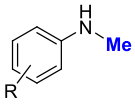
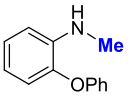
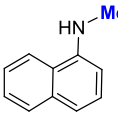
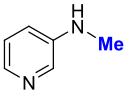
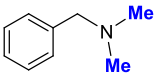
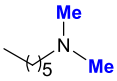
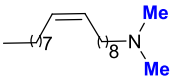
respectively (**1k, 1l**). Notably, C=C bond of the oleyl amine was unaffected during this transformation.

Table 1. Complex **1** catalysed N-methylation of amines using methanol.[a]



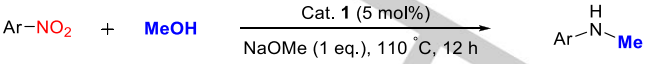
Entry	Product		Yield [%]
1	 R = H	**1a**	98
2	R = 3-Cl	**1b**	99
3	R = 4-Cl	**1c**	99
4	R = 4-Br	**1d**	80
	R = 4-Me	**1e**	89
6	R = 4-OMe	**1f**	100
7		**1g**	73[b]
8		**1h**	71[b]
9		**1i**	84[c]
10		**1j**	87
11		**1k**	92
12		**1l**	78[b]

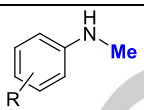
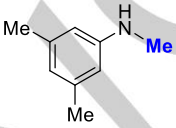
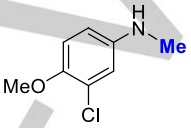
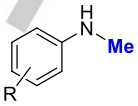
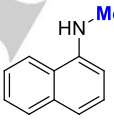
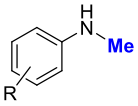
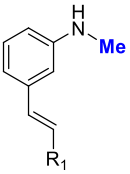
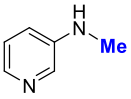
[a] Reaction conditions: amine (0.5 mmol), methanol (1.0 mL), Cat. **1** (1.0 mol%) and NaOMe (1 eq.) at 110 °C for 12 h; GC yield. [b] ^{1}H NMR yield. [c] 24 h.

Encouraged by the finding that complex **1** is efficient for N-methylation of amines using methanol, we investigated tandem transformation of nitrobenzene to N-methylaniline in methanol. Several Ru(II) complexes were screened and among all, complex **1** bearing phenpy-OMe ligand exhibited the maximum reactivity, which presented 100% conversion of nitrobenzene within 12 hours with 98% selectivity for N-methylaniline (see SI). Probably metal-ligand cooperative phenomenon was not significant in this reaction as phenpy-OH based Ru(II) complexes showed lower activity compare with the complexes having phenpy-OMe ligand.[18]

Next, TH of nitrobenzene in methanol was carried out with a series of bases and NaOMe was found to be the most suitable (see SI). Optimization of the amount of catalyst and oil bath temperature advocated 5 mol% complex **1** at 110 °C were ideal. Although, 2 mol% of complex **1** was also suitable for this transformation at 140 °C (yielded 91% of N-methylaniline), for operational simplicity we preferred relatively lower temperature (110 °C) (see SI).

Table 2. Tandem transformation of nitroarenes to N-methylamines using methanol.[a]



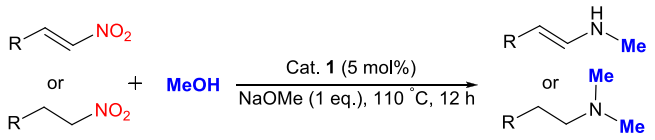
Entry	Product		Yield [%]
1	 R = H	**2a**	98
2	R = 2-Me	**2b**	85
3	R = 3-Me	**2c**	87
4	R = 4-Me	**2d**	92
5	R = 4-OMe	**2e**	95
6	R = 4-SMe	**2f**	94
7		**2g**	97
8		**2h**	84
9	 R = 3-Cl	**2i**	89
10	R = 4-Cl	**2j**	98
11	R = 4-Br	**2k**	92
12		**2l**	71[b]
13	 R = 4-NO_2	**2m**	85[b]
14	R = 3-CH_2OH	**2n**	82[b]
15	 R_1 = H	**2o**	98[b]
16	R_1 = Ph	**2p**	95[b]
17		**2q**	30(87[c])[b]

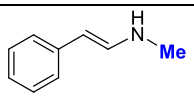
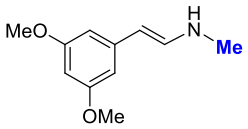
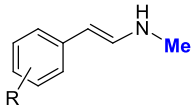
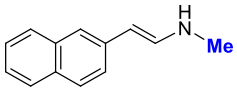
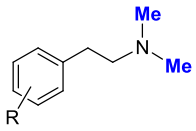
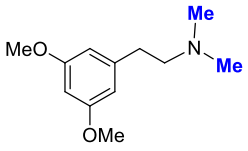
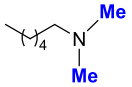
[a] Reaction conditions: nitroarene (0.5 mmol), methanol (2.5 mL), Cat. **1** (5.0 mol%) and NaOMe (1 eq.) at 110 °C for 12 h; GC yield. [b] ^{1}H NMR yield. [c] 48h.

After achieving the optimum conditions for the direct synthesis of N-methylaniline from nitrobenzene, next we explored the potential of this catalytic protocol for the N-methylation of a variety of nitroarenes bearing both the electron donating and electron withdrawing groups which showed excellent results (Table **2**, **2b-2k**). Furthermore, a good yield was achieved with reductive N-methylation of 1-nitronapthalene (**2l**). This catalytic system selectively transformed 1,4-dinitrobenzene to N-methyl-4-nitroaniline successfully (**2m**). This protocol was also tolerated the hydroxyl group at the benzylic position and afforded the desired

product in 82% yield (**2n**). Interestingly, selective N-methylation of nitro styrenes furnished the corresponding amines in excellent yields (**2o** and **2p**). In addition, N-methylation of heterocyclic nitroarenes such as 3-nitro pyridine was also achieved in moderate yield (**2q**).

Table 3. Direct formation of aliphatic N-methylamines from nitro compounds.[a]



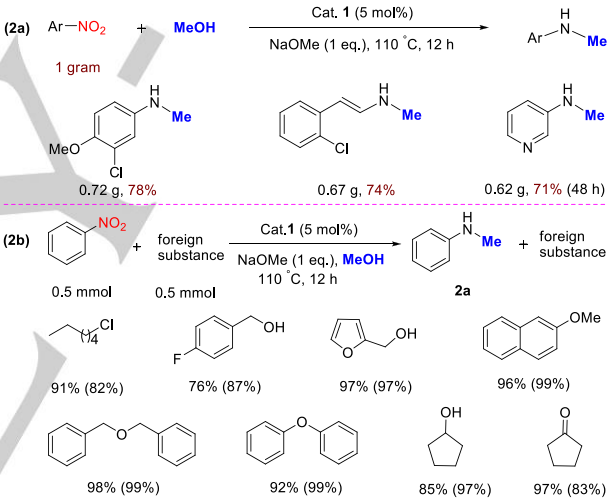
Entry	Product		Yield [%]
1		**3a**	84
2		**3b**	74
3		R = 2-Cl **3c**	81
4		R = 4-Br **3d**	85
5		**3e**	92
6		R = 2-OMe **3f**	78
7		R = 4-OMe **3g**	83
8		**3h**	87
9		**3i**	87

[a] Reaction conditions: nitro substrate (0.5 mmol), methanol (2.5 mL), Cat. **1** (5.0 mol%) and NaOMe (1 eq.) at 110 °C for 12 h; ^{1}H NMR yield.

Next, N-methylation of a range of challenging aliphatic nitro compounds in methanol were explored (Table **3**). Under the optimized conditions, α,β-unsaturated nitro compounds furnished the mono methylated amines whereas aliphatic nitro compounds yielded the N,N-dimethyl amines selectively as the intermediate aliphatic amines are more nucleophilic than the α,β-unsaturated amines. *Trans*-β-nitrostyrene derivatives containing both the electron donating and electron withdrawing groups at different position of aromatic ring produced the respective N-monomethylated secondary amines in a good to excellent yields (**3b-d**). In similar fashion, *trans*-2-(2-nitrovinyl)-naphthalene afforded mono methylated amine with 92% yield (**3e**). Furthermore, aliphatic nitro compounds selectively produced the corresponding N,N-dimethylamines in moderate to excellent yields (**3f-i**).

It is noteworthy to mention that the -NO_2 group in the starting unsaturated and aliphatic substrates was readily introduced by reacting the corresponding aldehydes with CH_3NO_2 or alkyl halides with $NaNO_2$ respectively.[19] Hence, following this greener protocol N-methylamine group can be ingeniously incorporated without using any expensive Pd/phosphine/amine based cross coupling reaction.[20]

To demonstrate the practical aspects of this catalytic system, gram scale reactions of different challenging substrates were carried out which furnished the respective N-methylated amines up to 78% yields (Scheme **2a**). Efficiency and functional group tolerance of this protocol was further examined by adding an equimolecular quantity of external substances such as ethers, aryl and aliphatic alcohols, alkyl chloride and cyclic ketone. In all these circumstances, N-methylaniline was achieved in good to excellent yields (76-98%), which implied that these impurities did not have substantial impact and after the reaction they were recovered up to 99% yields (Scheme **2b**).

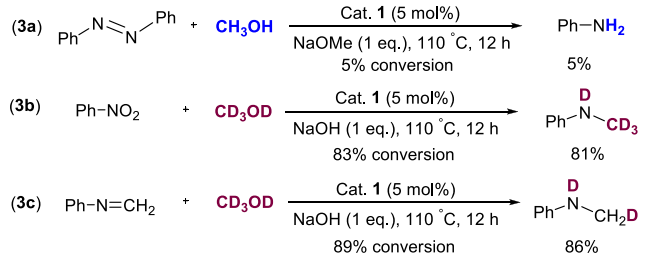


Numbers outside and inside of parenthesis refer to GC yield of **2a** and recovery of foreign substance respectively

Scheme 2. (a) Synthetic application: gram scale reaction (b) Impact of the various functional groups.

To shed some light on the mechanism of this tandem transformation, several experiments were carried out. We previously reported that complex **1** followed the direct route in transfer hydrogenation of nitrobenzene to aniline.[15] During the course of this direct transformation of nitroarenes to N-methylamines, corresponding azoarenes or azoxyarenes were not detected indicating preference for the direct route.[21] To further prove this, azobenzene was reacted under the optimized conditions which showed only 5% conversion (Scheme **3**, **3a**). Time dependent product distribution during the reductive N-methylation of nitrobenzene disclosed that throughout the reaction period concentration of the aniline remained significantly low. Notably, intermediate N-methylene aniline was not observed by GC (see SI). This result specified that the coupling reaction of aniline with *in situ* generated HCHO as well as the hydrogenation of N-methylene aniline were much faster compare to other steps. The use of CD_3OD as solvent led to clean formation of fully

deuterated N-methylaniline whereas partially deuterated N-methylaniline was observed with N-methylene aniline (Scheme **3**, **3b** and **3c**). On the basis of these observations we postulated a schematic pathway of this catalytic protocol as shown in Scheme **1** in which methanol act as a solvent, hydrogen source as well as a methylating agent.[11] Details mechanistic investigation of this tandem process is currently underway in our laboratory.



Scheme 3. Mechanistic studies with possible intermediates.

In summary, a practical, efficient and sustainable methodology for the tandem reductive N-methylation of nitroarenes using methanol as a greener methylating reagent was developed. Functional groups such as -Me, -OMe, -SMe, -X (X=Cl, Br, OH), etc. and C=C bonds were well tolerated during this transformation which provided the corresponding N-methylated amines in good to excellent yields. Furthermore, this system selectively transformed the α,β-unsaturated nitro compounds and aliphatic nitro compounds to the N-monomethylamines and N,N-dimethylamines respectively. Importantly, absence of any expensive and sensitive phosphine ligands and easy to synthesize air and moisture stable NNN Ru(II) catalyst make this an appealing methodology for accessing variety of N-methylated amines under mild reaction conditions.

Acknowledgements

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Keywords: tandem process • methanol • N-methylated amines • nitro compounds • ruthenium

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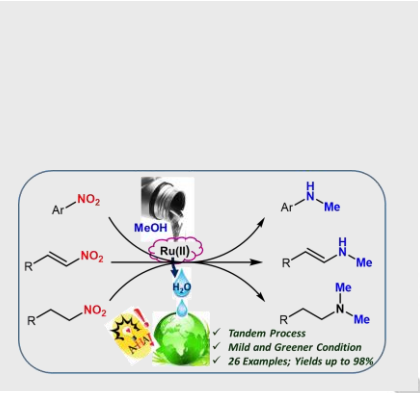
For the first time tandem transformation of various aromatic and aliphatic nitro compounds to the corresponding N-methylated amines using methanol as a green and sustainable methylating agent is reported.



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Tandem Transformation of Nitro Compounds to N-methylated Amines: Greener Strategy for the Utilization of Methanol as a Methylating Agent