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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02141 • Publication Date (Web): 08 Nov 2019

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Commercial Pd/C-Catalyzed *N*-Methylation of Nitroarenes and Amines using Methanol as Both C1 and H_2 source

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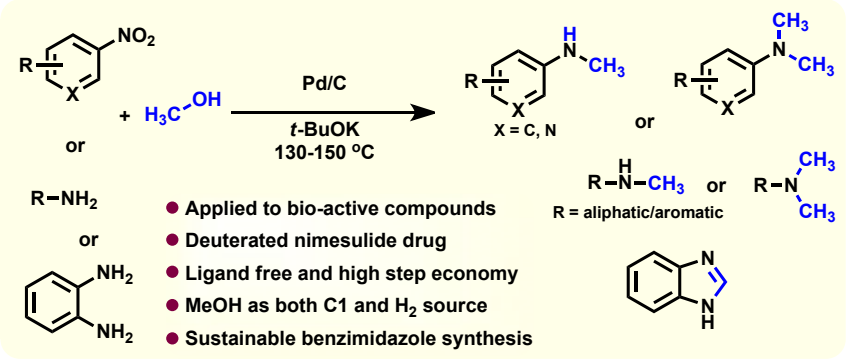
Supporting Information



ABSTRACT: Herein we report, commercially available carbon-supported palladium (Pd/C) catalyzed *N*-methylation of nitroarenes and amines using MeOH as both C1 and H_2 source. This transformation proceeds with high atom-economy and environmental-friendly way *via* borrowing hydrogen mechanism. A total of >30 structurally diverse *N*-methylamines, including bioactive compounds were selectively synthesized and isolated yields of up to 95%. Furthermore, selective *N*-methylation and deuteration of nimesulide, a nonsteroidal anti-inflammatory drug was realized through the late-stage functionalization.

INTRODUCTION

N-methylated amines are among the most essential bio-active compounds in drug discovery.[1] Of the top 200 small molecule drug retail sales in 2016, twenty-one compounds contain *N*-methyl moiety in their overall structure (Figure 1).[2] Besides these commercial drugs, *N*-methylated analogs also serve as key intermediates in organic synthesis, especially for the production of pharmaceuticals, agrochemicals, dyes, and surfactants.[3] Notably, *N*-methylation is one of the simplest chemical modification, but it is a powerful method to regulate the biological activity and physicochemical properties of peptide drug candidates by installing one or more methyl groups.[4] On the other hand, molecular and bio-imaging has become an indispensable tool in biomedical research. The direct deuteration of labeled compounds/drugs has also become one of the valuable organic transformation.[5] For all these reasons, the research on *N*-methylation is still intense and numerous important discoveries have been reported over the last few years.[6]

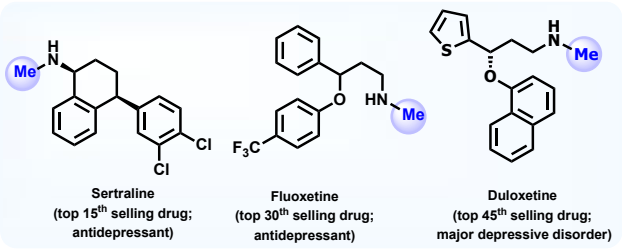
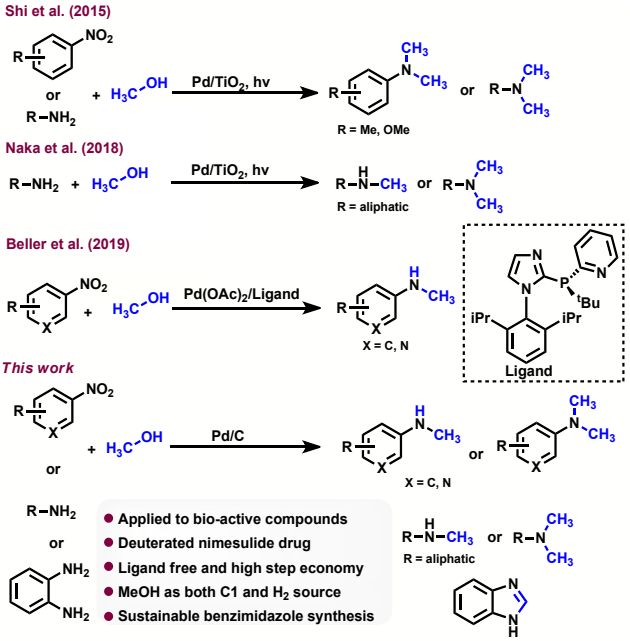


Figure 1. Top three selected commercial *N*-methylated drugs

Initiated by the groundbreaking work of Eschweiler and Clarke, the reductive amination of amine and formaldehyde has emerged as one of most widely applied and established tool for the creation of high-value *N*-methylamines not only in pharmaceutical and chemical industries but also in modern organic synthesis.[7] Application of this methodology to the methylation of amines or natural amino acids, including peptides would be of significant value.[4c, 8] In recent years, much attention has been devoted by researchers to the development of new methylating agents such as formic acid,[9] DMSO,[10] dimethyl carbonate,[11] (para)formaldehyde,[12] CO_2,[6, 13] methoxy group of lignin,[14] which has been successfully applied in transition metal-catalyzed methylation of amines

and nitroarenes. These C1 reagents shown to be a viable and powerful alternative to the use of standard and toxic reagents like methyl iodide, diazomethane, and methyl sulfate, etc.[15]

Methanol is a cheap, abundant, and renewable feedstock and has shown a great promise as a sustainable C1 reactant in methylation reactions.[16] Also, methanol plays an important role in chemical industries as a raw material for the production of various other useful chemicals.[17] Moreover, methanol can be produced from renewable sources,[18a] thereby offering more opportunities to utilize this biodegradable liquid as cheapest C1 source into value-added chemicals. Nonetheless, the conversion of methanol to transient active formaldehyde *via* dehydrogenation is challenging due to its low reactivity and high dehydrogenation energy (ΔH = +84 kJmol^{-1}) than its related alcohols (for example, ΔH of ethanol is +68 kJmol^{-1}).[18b] In the last five years, chemists have achieved impressive developments for *N*-methylation of amines or nitroarenes by employing methanol as a sustainable methylating agent in presence of homogenous complexes (Ir,[19] Ru,[21] Mn,[22] Re,[23] Co,[24] and Fe[25]), heterogeneous materials[20, 26] and photo-catalysis.[27]



Scheme 1. Palladium-catalyzed *N*-methylation reactions using methanol as both C1 and hydrogen source.

Palladium-based catalysts have also attracted much attention for *N*-methylation of amines/amino acids using methanol as C1 source under atmospheric hydrogen pressure[28] and few nice methodologies using Pd/TiO_2 under mild reaction conditions without using additional molecular hydrogen are also reported.[29] Quite recently, for the first time, Beller demonstrated an elegant protocol for the selective mono-*N*-methylation of nitroaromatics with methanol over homogeneous palladium complex (scheme 1).[30] Nevertheless, this reaction procedure requires the use of air sensitive phosphine ligands. To the best of our knowledge, commercial Pd/C has remained unexplored for *N*-methylation of nitroarenes and amines using MeOH as both C1 and H_2 source. This Pd/C has lot of benefits such as, (1) it is cheap, air stable, easy to handle and readily available, (2) it shows excellent catalytic activity even in the absence of ligand, and (3) it can be easily separated from the reaction medium by simple filtration and reused.[31] Inspired by the above-mentioned developments on *N*-methylation and based on the attractive catalytic features of Pd/C, we describe here an efficient tandem reaction of nitroarenes to *N*-methylanilines utilizing methanol as a key feedstock. Here, methanol has a dual function: it serves as a hydrogen donor for the reduction of nitroarenes to primary aniline derivatives and then as a methyl source for *N*-methylation reactions. Especially, this one-pot reaction of *N*-methylation from nitroaromatics in place of anilines as starting materials is highly advantageous from the standpoint of cost and step-economy. In addition to the nitro compounds, few amines were also tested for mono-*N*-methylation using MeOH as a methylating reagent without requiring external hydrogen.

RESULTS AND DISCUSSION

All reactions in this study were performed in sealed ACE® pressure tubes. In the initial optimization of reactions (Table 1), nitrobenzene (1a) was selected as a model substrate using methanol (2 ml) as both carbon and hydrogen source in the presence of 4.7 mol% Pd/C (10% w/w) and base at 130 °C for 20 h. Interestingly, the desired product 1aa was obtained in a lower yield of 28%. After evaluating the effect of various bases (entries1-5) potassium *tert*-butoxide (*t*-BuOK) was found to be the best base providing an excellent isolated yield of 1aa in 92% (entry 5). Inspired by this result, a set of other commercially available catalysts[40] that are known to mediate transfer hydrogenation reactions of nitroarenes were screened (entries 9-12), but the yields are <10% of the desired product with Ru/C and Rh/C (entries 11 & 12). Conversely, Co/C and Raney-Ni have shown large amounts of azobenzene and azoxybenzene along with small amounts of 1ab (entries 9 & 10). Thus the Pd is found to be a vital metal to gain high activity in this selective *N*-methylation reaction. Further optimizations using either activated carbon, absence of a base or Pd/C catalyst did not provide 1aa (entries 6-8). Few control experiments showed that the lowering of Pd/C loading to 2.35 mol% or decreasing the reaction time to 16 h, the yield of 1aa was dropped (entries 13-14). Decreasing the temperature or amount of base resulted in diminished yield (entries 15-16). Accordingly, 4.7 mol% of 10% Pd/C, 4 equivalents of *t*-BuOK, 2 ml of methanol at 130 °C and 20 h were considered as optimal reaction conditions for selective mono-*N*-methylation of nitroarenes.

To understand the conversion and reaction profile of this tandem reaction, time course experiments were conducted (all these reactions were monitored by GC-MS (see supplementary information, Figure S2 and S3). The results show that, within 4 h almost all the nitrobenzene (1a) was consumed and the possible products were only aniline (1ab) and *N*-methylaniline (1aa) with 45% and 55% yields, respectively. By increasing the reaction time, 1ab is consumed completely, suggesting that it acts as an intermediate in this overall reaction process. After 20 h, 100% selectivity of 1aa was observed. Interestingly, we did not observed azobenzene or azoxybenzene, indicating that these are not the intermediates in our Pd/C *N*-methylation using MeOH (see SI, Figure S3).

Table 1. Reaction condition optimization for *N*-methylation of nitrobenzene using MeOH as both C1 and H_2 source[a]

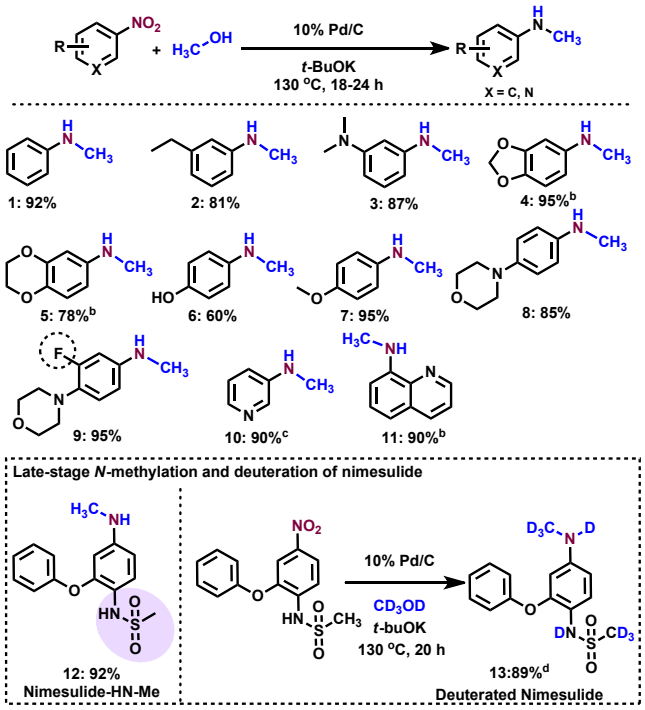
1a 1aa 1ab

Entry	Catalyst	Base	1aa[b] [%]	1ab[b] [%]
1	Pd/C	KOH	28	70
2	Pd/C	NaOH	35	64
3	Pd/C	Na_2CO_3	16	83
4	Pd/C	K_2CO_3	10	25
5	Pd/C	*t*-BuOK	>99(92)	0
6	Pd/C	none	0	0
7	none	*t*-BuOK	0	0
8	activated carbon	*t*-BuOK	0	0
9	Co/C	*t*-BuOK	0	8
10	Raney Ni	*t*-BuOK	0	28
11	Ru/C	*t*-BuOK	11	89
12	Rh/C	*t*-BuOK	6	84
13[c]	Pd/C	*t*-BuOK	79	21
14[d]	Pd/C	*t*-BuOK	85	15
15[e]	Pd/C	*t*-BuOK	83	17
16[f]	Pd/C	*t*-BuOK	67	33

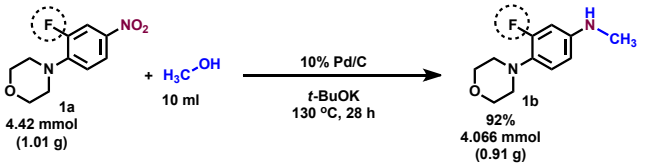
[a]Reaction conditions: 1a (0.5 mmol), 2 ml of MeOH as a reagent and solvent, catalyst (25 mg), base (2 mmol, 4 equiv.), 130 °C, 20 h. [b] Determined by GC-MS, isolated yields shown in parentheses. [C] Pd/C (12.5 mg). [d] reaction time is 16 h. [e]reaction temperature is 110 °C. [f]amount of base is (1mmol, 2 equiv.)

After identifying suitable reaction conditions for selective mono-*N*-methylation of nitrobenzene, we explored the scope and limitations with wide range of nitroaromatics using MeOH as C1 and H_2 source (scheme 2). Applying, ethyl-, dimethylamino, 1,3-benzodioxole, 1,4-benzodioxole, hydroxyl-, and methoxy substituted nitroarenes, mono-*N*-methylation with excellent selectivities (1-7, 60-95%) were observed. However, when halogenated and electron-withdrawing nitroarene substituents were applied, removal of functional group or undesired product formation has taken place (for more information see SI, Figure S5). These kinds of limitations were also observed with homogeneous palladium catalysis.[30] Further, 4-(2-Nitrophenyl)morpholine and its fluorinated analog underwent successful selective *N*-methylation in 85% and 95% yields respectively (scheme 2, 8-9). In addition, we performed the direct *N*-methylation of 4-(2-fluoro-4-nitrophenyl)morpholine, a starting material of linezolid[32] on a gram scale yielding 92% of desired product (scheme 3), representing the synthetic utility of this protocol. Moreover, heterocyclic *N*-methylamines, which are the core scaffolds in several biologically active molecules, were synthesized up to 90% yields, but with a higher concentration of Pd/C, *t*-BuOK and longer reaction times (10-11, 78-90%). Notably, the selective mono-*N*-methylation of nimesulide, nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties, has been realized with 92% yield (scheme 2, 12). Nimesulide, when reacted with deuterated methanol and Pd/C catalyst under the optimal reaction conditions established for mono-*N*-methylation of nitroarenes, deuteration occurred on nitro substituent, methyl protons of sulfonamide and the acidic proton of NH in nimesulide in a one-pot manner and furnished deuterated nimesulide in 89% yield representing the first example (scheme 2, 13).

We also investigated the recyclability and reusability of Pd/C-catalyzed *N*-methylation of nitrobenzene using MeOH under standard reaction conditions (see SI, Figure S1). However, we observed a loss in catalytic activity and the yield of desired product was dropped in second and third cycles (from 78% to 45%). This could be due to Pd-leaching from the Pd/C catalyst.[31e]

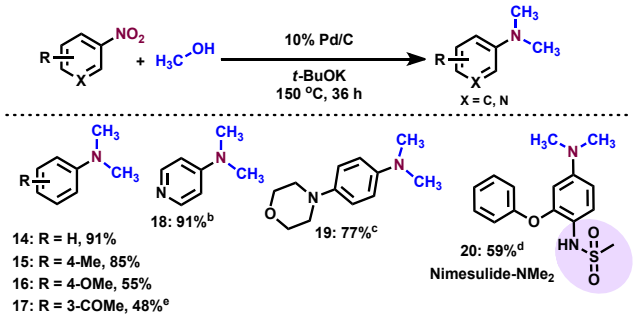


Scheme 2. Pd/C-catalyzed *N*-methylation of nitroaromatics with MeOH.[a] [a]Reaction conditions: 0.5 mmol of nitroarene, 10% Pd/C (4.7 mol% Pd, 25 mg), 2 ml of MeOH as a reagent and solvent, *t*-BuOK (2 mmol, 4 equiv.), 20 h, 130 °C, isolated yields. [b] Pd/C (50 mg), 48 h, 150 °C. [c] Pd/C (80 mg), *t*-BuOK (280 mg), 150 °C, 72 h. [d] 2 ml of CD_3OD as a reagent and solvent, *t*-BuOK (2 mmol, 4 equiv.), 20 h, 130 °C, isolated yield.



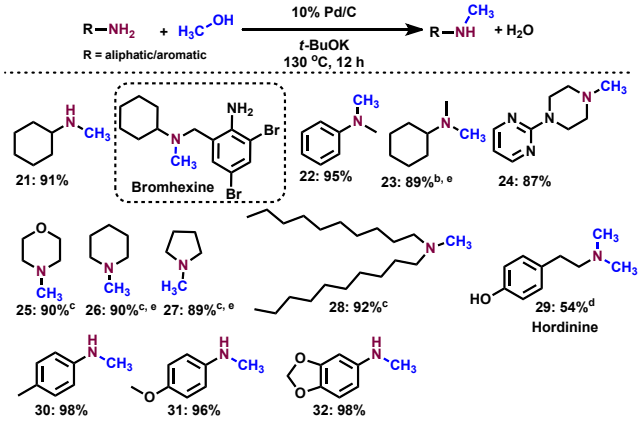
Scheme 3. Gram-Scale Reaction

Encouraged by the above results, we further applied commercial Pd/C for the synthesis of *N,N*-dimethylamines using MeOH as both C1 and H_2. Here, the reaction conditions developed for mono-*N*-methylation were used with slight modifications, i.e., reaction temperature and time. Six selected *N, N*-dimethylated anilines and nimesulide-*N*Me_2 were synthesized and isolated in moderate to excellent yields (scheme 4, 14-20, 48-91%).



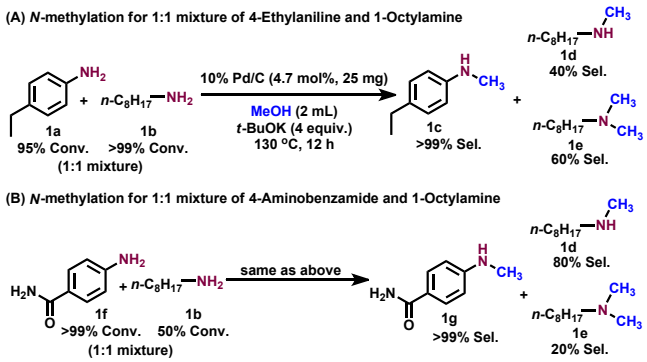
Scheme 4. Pd/C-catalyzed *N*,*N*-dimethylation of nitroaromatics with MeOH.[a] [a]Reaction conditions: 0.5 mmol of nitroarene, 10% Pd/C (4.7 mol% Pd, 25 mg), 2 ml of MeOH as a reagent and solvent, *t*-BuOK (2 mmol, 4 equiv.), 36 h, 150 °C, isolated yields. [b] 48 h. [c] 30 h. [d] 60 h. [e] Pd/C (60 mg), *t*-BuOK (2 mmol, 224 mg), 150 °C, 72 h.

Upon, the successful development of (*N*), *N*-methylation from nitroarenes, we further examined the generality of this *N*-methylation protocol with diverse amines using MeOH as C1 reactant and hydrogen source. As shown in scheme 5, the reaction of cyclohexylamine gave exclusively *N*-methylcyclohexylamine in 95% yield (21, 91%), which is used as a key pharmaceutical ingredient for the synthesis of commercial bromhexine.[33] Other secondary aromatic and aliphatic amine substrates were preceded cleanly and furnished desired products in excellent yields (22-23, 89-95%). Substituted piperdines are versatile pieces in numerous pharmacologically active compounds and pharmaceutical agents.[34] In this respect, our Pd/C catalytic protocol is also tolerant towards *N*-heterocycles such as 2-(4-methylpiperazin-1-yl)pyrimidine, piperdine, morpholine, and tetrahydropyrrole to afford corresponding *N*-methyl tertiary amines with high yields (24-27, 87-90%). Furthermore, didecylamine was easily converted to *N*-methyldidecylamine in excellent yield (28, 92%). Such long chain aliphatic *N*-methylamines are used as fuel additives in spark ignition engines.[35] Finally, our developed reaction conditions were applied to tyramine through the late-stage *N*-methylation process to give hordenine, in moderate yield (29, 54%). Next, we subjected primary anilines for selective mono-*N*-methylation under optimal reaction conditions and achieved corresponding *N*-methylated products in excellent yields (30-32, 96-98%).



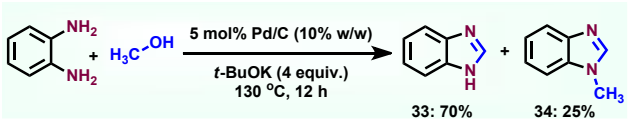
Scheme 5. Pd/C-catalyzed *N*-methylation of amines with MeOH.[a] [a]Reaction conditions: 0.5 mmol of amine, 10% Pd/C (4.7 mol% Pd, 25 mg), 2 ml of MeOH as a reagent and solvent, *t*-BuOK (1 mmol, 2 equiv.), 12 h, 130 °C, isolated yields. [b] 14 h. [c] 16 h. [d] 30 h. [e] GC yields.

In order to assess the reactivity and selectivity between aromatic and an aliphatic amine, two competitive experiments using 1:1 mixture of (A) 4-ethylaniline and 1-octylamine (1a and 1b) and (B) 4-aminobenzamide and 1-octylamine (1f and 1b) were subjected to *N*-methylation with methanol under standard conditions (scheme 6). In both the cases, aromatic amines were exclusively converted to the corresponding mono-*N*-methylated amines in >99% selectivity without formation of *N*,*N*-dimethylated amines. However, with respect to aliphatic primary amine (1b), we observed the mixture of *N*-methylocta-1-amine (1d) *N*,*N*-dimethyloctylamine (1e) in both the cases. These results clearly indicate that aromatic primary amines were highly selective towards mono-*N*-methylation compared to aliphatic amine. Regarding the reactivity, 1-octylamine (1b) is more reactive in presence of electron-donating group amine (1a). Here we observed >95% conversion of 1a and full conversion of 1b (see figure S6a). In contrast, 1b is less reactive in presence of electron-withdrawing group amine (1f). Here, we observed full conversion of 1f and 50% conversion of 1b (see figure S6b).



Scheme 6. Competitive experiment under optimized conditions.

This simple and facile methodology was also applicable for the synthesis of benzimidazole using MeOH as a C1 reactant under our Pd/C-catalyzed established conditions. In this respect, we attempted a reaction between *ortho*-phenylenediamine (OPDA) and MeOH in presence of Pd/C, *t*-BuOK at 130 °C for 12 h, afforded full conversion. Benzimidazole and *N*-methylbenzimidazole were obtained as major and minor products, respectively (scheme 7). With respect to the reaction mechanism, we believe that the reaction is following the similar footsteps as proposed in the reported literature.[36]



Scheme 7. Synthesis of benzimidazole and *N*-methyl benzimidazole from *ortho*-phenylenediamine. Reaction conditions: *ortho*-phenylenediamine (0.5 mmol), 10% Pd/C (4.7 mol% Pd, 25 mg), 2 ml of MeOH as a reagent and solvent, *t*-BuOK (2 mmol, 4 equiv.), 130 °C, 12 h.

To understand the reaction mechanism of this tandem reaction, methanol degradation experiments were conducted. MeOH was reacted in the presence of Pd/C and *t*-BuOK at 130 °C. GC analysis revealed the formation of H_2, CO_2 and CO. To quantify the hydrogen evaluation during the reaction, an *in-situ* experiment has been conducted by coupling a Parr reactor with a modified RGA analyser. In first hour 89%, hydrogen

was evolved and increased up to 92.6% after three hours (see SI, Figure S4). The amount of hydrogen evolved in the process clearly evidences the participation of methanol as a hydrogenating agent. Based on the result of methanol degradation and reported literature,[12a, 26b, 27b, 21e] a plausible reaction mechanism was proposed and illustrated in figure 2. Initially, Pd abstracts hydrogen from methanol in the presence of Pd and produces Pd-H species and formaldehyde intermediate. At the same time, Pd also participates in the transfer hydrogenation of nitrobenzene to give aniline. Subsequently, imine is formed *via* the condensation reaction of formaldehyde with the assistance of base.[20] Next, imine is hydrogenated by Pd-H species to form *N*-methylaniline. Then, *N*-methylaniline again undergoes condensation with formaldehyde followed by the hydrogenation to give *N*,*N*-dimethylaniline.

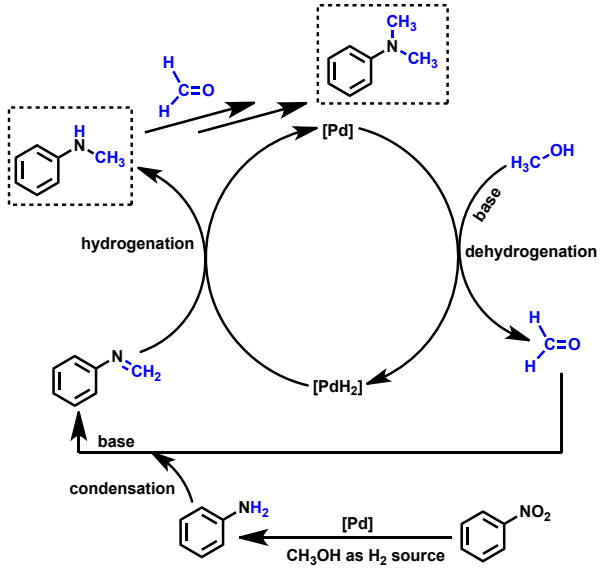


Figure 2. Plausible reaction mechanism for Pd/C-catalyzed N-methylation of nitroarenes

CONCLUSIONS

In summary, we have developed environmentally benign and practical (*N*), *N*-methylation of nitroaromatics and amines using MeOH as both C1 and H_2 source with commercial Pd/C. This methodology proceeds without the use of external hydrogen and also suitable for *N*-methylation of bioactive compounds and benzimidazole synthesis. Moreover, selective mono-*N*-methylation and deuteration of nimesulide has also been realized through the late-stage functionalization.

EXPERIMENTAL SECTION

General information: All chemicals were purchased from Sigma-Aldrich and TCI and were used as received unless stated otherwise. 10 wt% Pd/C was purchased from Sigma-Aldrich with product number 205699-10G). Methanol was received from merck (AR Grade) and used without additional purification. Gas-chromatography (GC-MS) analysis was performed 5977A MSD attached to 7890B, Agilent GC equipped with 30 m × 0.32 mm i.d and 0.25 µm mid-polarity capillary column (DB35MS, 35% phenyl/65% dimethylpolysiloxane). High resolution mass spectra (HRMS) of new compounds was recorded on bruker daltronics microTOF-Q Ⅱ® spectrophotometer using ESI ionization. NMR spectra were obtained at 25 °C on Bruker AVANCE III 500 MHz spectrometer using $CDCl_3$ or DMSO-d^6 as solvent. Transmission electron microscopy measurements were performed on a JEM 2100 (JEOL, Japan) microscope and samples were deposited on Lacey carbon formvar Cu grid upon dispersing in ethanol.

Note: Unless otherwise mentioned, all *N*-methylation reactions using MeOH in this study were performed in sealed ACE® pressure tubes.

***General Procedure for N-Methylation of Nitroarenes*:** An oven dried 15 mL pressure tube, equipped with a stirring bar, was charged with 10% Pd/C (4.7 mol% Pd, 25 mg), *t*-BuOK (2 mmol, 4 equiv) and nitroarene (0.5 mmol), and then methanol (2 mL, 9.37 mmol) was slowly added to the mixture. The pressure tube was flushed with nitrogen and sealed with a suitably strong screw cap and heated to 130 °C (oil bath) for 20-48 h. After the completion of reaction, the pressure tube was cooled to room temperature, and the pressure build-up in the tube has been released slowly by losing the screw cap with caution in a fume hood. The catalyst was separated from the mixture by filtration through a filter paper and the solid catalyst was washed with ethyl acetate. After evaporating the solvent, the obtained crude product was purified by column chromatography (Hexane: EtOAc) to achieve the pure product which was further submitted for analysis.

General Procedure for N, N-Dimethylation of Nitroarenes: An oven dried 15 mL pressure tube, equipped with a stirring bar, was charged with 10% Pd/C (4.7 mol% w/w, 25 mg), *t*-BuOK (2 mmol, 4 equiv) and nitroarene (0.5 mmol), and then methanol (2 mL, 9.37 mmol) was slowly added to the mixture. The pressure tube was flushed with nitrogen and sealed with a suitably strong screw cap and heated to 150 °C (oil bath) for 36 h. After the completion of reaction, the pressure tube was cooled to room temperature, and the pressure build-up in the tube has been released slowly by losing the screw cap with caution in a fume hood. The catalyst was separated from the mixture by filtration through a filter paper and the solid catalyst was washed with ethyl acetate. After evaporating the solvent, the obtained crude product was purified by column chromatography (Hexane: EtOAc) to achieve the pure product which was further submitted for analysis.

General Procedure for N-methylation of Amines: An oven dried 15 mL pressure tube, equipped with a stirring bar, was charged with 10% Pd/C (4.7 mol%, 25 mg), *t*-BuOK (2 mmol, 4 equiv) and amine (0.5 mmol), and then methanol (2 mL) was slowly added to the mixture. The pressure tube was flushed with nitrogen and sealed with a suitably strong screw cap and heated to 130 °C (oil bath) for 12 h. After the completion of reaction, the pressure tube was cooled to room temperature, and the pressure build-up in the tube has been released slowly by losing the screw cap with caution in a fume hood. The catalyst was separated from the mixture by filtration through a filter paper and the solid catalyst was washed with ethyl acetate. After evaporating the solvent, the obtained crude product was purified by column chromatography (Hexane: EtOAc) to achieve the pure product which was further submitted for analysis.

Representative Procedure for N-Methylation of nimesulide with deuterated methanol: An oven dried 15 mL pressure tube, equipped with a stirring bar, was charged with 10% Pd/C (4.7 mol%, 25 mg), *t*-BuOK (2 mmol, 4 equiv) and nimesulide (0.5 mmol), and then CD_3OD (2 mL) was slowly added to the mixture. The pressure tube was flushed with nitrogen and sealed with a suitably strong screw cap and heated to 130 °C (oil bath) for 24 h. After the completion of reaction, the pressure tube was cooled to room temperature, and the pressure build-up in the tube has been released slowly by losing the screw cap with caution in a fume hood. The catalyst was separated from the mixture by filtration through a filter paper and the solid catalyst was washed with ethyl acetate. After evaporating the solvent, the obtained crude product was purified by column chromatography (Hexane: EtOAc) to achieve the pure product which was further submitted for analysis.

Representative Procedure for synthesis of *4-(2-fluoro-4-nitrophenyl)morpholine*

4-(2-fluoro-4-nitrophenyl)morpholine was prepared by using already reported literature.[38] An oven dried 100 mL pressure tube, equipped with a stirring bar, was charged with morpholine (20.6 mmol), triethyl amine (20.72 mmol) and ethyl acetate (10 mL) stirred for 10 min at 40 °C (oil bath). Then 3,4-difluoronitribenzene (6.28 mmol) was added gradually to the reaction mixture and allowed to stir for 10 h at 45-50 °C. Afterward, the reaction was allowed to cool at room temperature. The solid product was extracted by brine solution and Na_2SO_4 and the solvent was evaporated under reduced pressure to obtain the yellow solid product.

Gram scale reaction for N-methylation of 4-(2-fluoro-4-nitrophenyl) morpholine: An oven dried 100 mL pressure tube, equipped with a stirring bar, was charged with 10% Pd/C (65.8 mol%, 350 mg), *t*-BuOK (22.32 mmol, 2.5g), and 4-(2-fluoro-4-nitrophenyl) morpholine (4.42 mmol, 1.01g) then methanol (10 mL, 46.85 mmol) was slowly added to the mixture. The pressure tube was flushed with nitrogen and sealed with a suitably strong screw cap and heated to 130 °C (oil bath) for 28 h. After the completion of reaction, the pressure tube was cooled to room temperature, and the pressure build-up in the tube has been released slowly by losing the screw cap with caution in a fume hood. The catalyst was separated from the mixture by filtration through a filter paper and the solid catalyst was washed with ethyl acetate. After evaporating the solvent, the obtained crude product was purified by column chromatography (Hexane: EtOAc) to achieve the pure product which was further submitted for analysis.

Reaction Procedure for N-Methylation of 1:1 mixture of aromatic and aliphatic amines**:** An oven dried 15 mL pressure tube, equipped with a stirring bar, was charged with 10 % Pd/C (4.7 mol%, 25 mg), *t*-BuOK (4 mmol, 224 mg, 4 equiv), 4-ethyl benzene (0.5 mmol) and 1-octylamine (0.5 mmol), and then methanol (2 mL, 9.37 mmol) was slowly added to the reaction mixture. The pressure tube was flushed with nitrogen and sealed with a suitably strong screw cap and heated to 130 °C (oil bath) for 12 h. After the completion of reaction, the pressure tube was cooled to room temperature, and the pressure build-up in the tube has been released slowly by losing the screw cap with caution in a fume hood. Afterward, the mixture was cooled to room temperature. The catalyst was separated from the mixture by filtration through a filter paper and the solid catalyst was washed with ethyl acetate. After evaporating the solvent, the obtained crude product was submitted to GC-MS for further analysis. In another set of example, 4-aminobenzamide (0.5 mmol) and 1-octylamine (0.5 mmol) were used as substrates and conducted the reaction under same reaction conditions.

Reaction procedure for the synthesis of Benzimidazole: An oven dried 15 mL pressure tube, equipped with a stirring bar, was charged with 10% Pd/C (4.9, 25 mg), *t*-BuOK (2 mmol, 4 equiv) and o-phenylenediamine (0.5 mmol), and then methanol (2 mL, 9.37 mmol) was slowly added to the reaction mixture in the presence of an ice bath. The pressure tube was flushed with nitrogen and sealed with a suitably strong screw cap and heated to 130 °C for 12 h. After the completion of reaction, the pressure tube was cooled to room temperature, and the pressure build-up in the tube has been released slowly by losing the screw cap with caution in a fume hood. The catalyst was separated from the mixture by filtration through a filter paper and the solid catalyst was washed with ethyl acetate. After evaporating the solvent, the obtained crude product was purified by column chromatography (Hexane: EtOAc) to achieve the pure product which was further submitted for analysis.

Reaction time profile experiments for N-methylation of nitrobenzene: An oven dried 15 mL pressure tube, equipped with a stirring bar, was charged with 5 mol% Pd/C (10% w/w, 25 mg), *t*-BuOK (4 equiv) and nitroarene (0.5mmol), and then methanol (2 mL) was slowly added to the mixture. The pressure tube was flushed with nitrogen and closed with a suitably strong screw cap and sealed with a suitably strong screw cap and heated to 130 °C (oil bath) for 4-20 h. After the completion of reaction, the pressure tube was cooled to room temperature, and the pressure build-up in the tube has been released slowly by losing the screw cap with caution in a fume hood. The crude sample was subjected to GC-MS analysis.

Catalyst recycling: The solid Pd/C catalyst obtained after the reaction similar to the general procedure for *N*-methylation of nitroarenes was washed with water, ethanol and dichloromethane sequentially in each run and the washed catalyst was dried in vacuum oven at 80 °C for overnight and reused for next cycle.

Procedure for detection of gases from methanol: Under the protection of nitrogen, in a 100 mL autoclave, a mixture of 10% Pd/C (4.7 mol%, 25 mg), *t*-BuOK (2 mmol, 4 equiv) and MeOH (2 mL) was stirred at 130 °C. The autoclave was linked with Agilent 7890B GC (2FID & 1TCD) to get the full analyses of products. H_2, CO_2 and CO was detected with Molsieve 5A column connected with thermal conductivity detector (TCD) and methanol was analyzed by DB-WAX column with FID (front ionization detector).

Analytical data for methylated compounds

***N*-Methylaniline *(scheme 2 entry 1).*[30]** It is obtained as pale yellow liquid (48.76 mg, 92%) after purification by column chromatography (n-hexane/EtOAc : 95:5). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, J = 7.9 Hz, 2H), 6.70 (t, J = 7.3 Hz, 1H), 6.52 (d, 1H), 3.63 (s, 1H), 2.79 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.33, 129.18, 117.20, 112.39, 30.68.

3-Ethyl-*N*-Methylaniline ***(scheme 2 entry 2).***[new] It is obtained as colorless liquid (54.67mg, 81%) after purification by column chromatography (n-hexane/EtOAc : 95:5). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.07 (m, 1H), 6.68 (m, 1H), 6.45 (d, J = 9.0 Hz, 2H), 3.46 (s, 1H), 2.83 (s, 3H), 2.73 (q, 2H), 1.25 – 1.19 (t, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.45, 145.44, 129.17, 117.04, 112.12, 109.84, 30.70, 29.08, 15.63; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_9H_{14}N$, 136.1126; found: 136.1130.

N*^{1},*N*^{1},*N*^{3}-Trimethylbenzene-1,3-diamine** ***(scheme 2 entry 3).[30] It is obtained as colorless semi solid (65.25 mg, 87%) after purification by column chromatography (n-hexane/EtOAc : 90:10). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (t, 1H), 6.02 (m, 1H), 5.89 (m, 1H), 5.84 (t, 1H), 3.48 (s, 1H), 2.79 (s, 6H), 2.74 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.68, 149.98, 129.58, 102.77, 101.85, 96.98, 39.95.

N*-Methylbenzo[*d*][1,3]dioxol-5-amine** ***(scheme 2 entry 4).[30] It is obtained as dark brown solid (71.78 mg, 95%) after purification by column chromatography (n-hexane/EtOAc: 98:2). ^{1}H NMR (400 MHz) δ 6.72 – 6.60 (m, 1H), 6.24 (d, *J* = 2.6 Hz, 1H), 5.99 (s, 1H), 5.87 – 5.82 (s, 2H), 3.41 (s, 1H, NH 2.78 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 149.22, 146.7, 141.5, 109.26, 104.75, 101.28, 96.64, 32.45, 31.65.

N*-Methyl-2,3-dihydrobenzo[b][1,4]dioxin-6-amine** ***(scheme 2 entry 5).[20] It is obtained as brown solid (64.42mg, 78%) after purification by column chromatography (n-hexane/EtOAc : 98:2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (d, *J* = 8.4 Hz, 1H), 6.09 (dd, *J* = 11.7, 2.8 Hz, 2H), 4.16 (dd, *J* = 5.2, 2.6 Hz, 2H), 4.11 (dd, *J* = 5.3, 2.5 Hz, 2H), 2.70 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.54, 143.00, 134.52, 116.56, 105.43, 100.03, 63.86, 63.16, 30.44.

4-(*Methylamino)phenol** ***(scheme 2 entry 6)[12e] It is obtained as colorless liquid (36.91, 60%) after purification by column chromatography (n-hexane/EtOAc : 98:2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 6.98 (m, 4H), 5.67 (s, 1H), 3.01 (s, 1H), 2.93 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 147.99, 142.98, 117.06, 117.03, 30.44.

4*-Methoxy-*N*-Methylaniline** ***(scheme 2 entry 7).[30] It is obtained as a colorless liquid (65.16 mg, 95%) after purification by column chromatography (n-hexane/EtOAc : 9:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 – 6.75 (d, 2H), 6.62 (d, *J* = 6.1 Hz, 2H), 3.76 (s, 3H), 3.41 – 3.11 (s, 1H), 2.81 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.30, 143.09, 114.90, 113.97, 55.53, 31.85.

N*-Methyl-4-morpholinoaniline** ***(scheme 2 entry 8).[30] It is obtained as a white solid (81.71 mg, 85%) after purification by column chromatography (n-hexane/EtOAc : 99:1) ^{1}H NMR (500 MHz, $CDCl_3$): 6.82 (m, 2H), 6.76 (m, 2H), 3.8 (m, 4H), 2.99 (m, 4H), 2, 78 (s, CH3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.81, 143.55, 118.70, 113.72, 67.09, 51.35, 31.59.

3-Fluoro-*N*-methyl-4-morpholinoaniline ***(scheme 2 entry 9).***[new] It is obtained as a light bluish solid (107.44 mg, 95%) after purification by column chromatography (n-hexane/EtOAc : 8:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (t, J = 9.0 Hz, 1H), 6.47 – 6.26 (m, 2H), 3.95 – 3.78 (t, 4H), 3.05, (s, 1H), 3.04 – 2.90 (t, 4H), 2.79 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.4 ($^1J_{CF}$ = 243 Hz), 146 ($^2J_{CF}$ = 10.5), 130 ($^3J_{CF}$ = 9.9 Hz), 101 ($^2J_{CF}$ = 24 Hz), 120 ($^3J_{CF}$ = 5.5), 108 ($^4J_{C\text{-}F}$ = 3.4 Hz), 67.69, 51.95, 31.32; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{11}H_{15}FN_2O$, 211.1241; found: 211.1252.

N*-Methylpyridin-3-amine** ***(scheme 2 entry 10).[30] It is obtained as a colorless liquid (48.60mg, 90%) after purification by column chromatography (n-hexane/EtOAc : 8:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 47.0 Hz, 2H), 7.04 (dt, J = 31.1, 15.6 Hz, 1H), 6.82 (dd, J = 8.2, 1.4 Hz, 1H), 3.72 (s, 1H, NH), 2.79 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.23, 137.11, 134.39, 122.81, 117.33, 29.39.

N*-Methylquinolin-8-amine** ***(scheme 2 entry 11).[30] It is obtained as a black solid (71.10mg, 90%) after purification by column chromatography (n-hexane/EtOAc : 98:2): ^{1}H NMR (500 MHz) δ 8.71 (d, 1H), 8.12 (d, 1H), 7.38 (m, 2H), 7.10 (d, 1H), 6.63 (d, 1H), 6.12 (s, 1H, NH), 3.03 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz) δ 146.89, 146.06, 138.31, 136.20, 129.09, 121.82, 113.65, 104.27, 30.06.

N*-(4-(Methylamino)-2-phenoxyphenyl)methanesulfonamide** ***(scheme 2 entry 12).[12e] It is obtained as a colorless (134.32 mg, 92%) after purification by column chromatography (n-hexane/EtOAc : 85:15): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41(m, 3H), 7.15 (t, *J* = 7.4 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 6.36 (d, *J* = 10.5, 5.2 Hz, 1H), 6.26 (s, 1H), 6.10 (d, 1H), 3.84 (s, 1H, NH), 2.91 (s, 3H), 2.74 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.31, 150.74, 149.50, 130.33, 127.91, 124.04, 118.85, 116.60, 108.03, 102.02, 38.64, 30.57.

Nimesulide ND_3 ***(scheme 2 entry 13):***[new] It is obtained as bluish semi solid (133.50 mg, 89%) after purification by column chromatography (n-hexane/EtOAc : 85:15): ^{1}H NMR (400 MHz) δ 7.45 (d, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.00 d, *J* = 7.8 Hz, 2H), 6.38 (d, 1H), 6.26 (s, 1H), 6.11 (d, 1H). ^{13}C{^{1}H} NMR (101 MHz) δ 156.00, 150.56, 149.22, 130.01, 127.55, 124.04, 116.61, 108.14, 102.07. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{14}H_8D_8N_2O_3S$, 300.1384; found: 300.1390.

***N,N*-Dimethylaniline** ***(scheme 4 entry 14)*:** It is obtained as colorless liquid (55.05mg, 91%) after purification by column chromatography (n-hexane/EtOAc : 85:15): ^{1}H NMR (400 MHz) δ 7.48 (d, 2H), 7.01 (d, 2H), 3.06 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz) δ 150.58, 129.59, 116.81, 112.69, 104.07, 40.89.

N,N,4*-Trimethylaniline** ***(scheme 4 entry 15):[12a] It is obtained as a brown liquid (57.37 mg, 85%) after purification by column chromatography (n-hexane/EtOAc : 98:2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, 2H), 6.78 (d, 2H), 2.87 (s, 6H), 2.25 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 148.81, 129.56, 126.17, 113.19, 41.03, 20.40.

4*-Methoxy-N,N-dimethylaniline** ***(scheme 4 entry 16).[12a] It is obtained as a colorless liquid (41.52mg, 55%) after purification by column chromatography (n-hexane/EtOAc : 98:2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 – 6.88 (m, 1H), 6.26 – 6.08 (m, 3H), 3.66 (s, 3H), 2.79 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.81, 152.11, 129.86, 105.84, 101.51, 99.20, 55.14, 40.65.

1-(3-(Dimethylamino)phenyl)ethanone (scheme 4 entry 17).[12a] It is obtained as a semi solid (39.12 mg, 48%) after purification by column chromatography (n-hexane/EtOAc : 20:80). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, 3H), 6.69 (s, 1H), 3.03 (s, 6H), 2.62 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz,

$CDCl_3$) δ 198.72, 153.17, 136.20, 131.20, 117.69, 110.88, 40.68, 27.01.

***N,N*-Dimethylpyridin-4-amine *(scheme 4 entry 18)*.**[12a] It is obtained as a white solid (55.5 mg, 91%) after purification by column chromatography (n-hexane/EtOAc : 9:1) . ^{1}H NMR (500 MHz, CDCl3) δ 8.22 (dd, J = 5.0, 1.5 Hz, 1H), 6.48 (dd, J = 5.0, 1.5 Hz, 1H), 2.99 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.36, 150.43, 106.56, 39.16.

***N, N*-Dimethyl-4-morpholinoaniline (scheme 4 entry 19).**[12a] It is obtained as a colorless solid (79 mg, 77%) after purification by column chromatography (n-hexane/EtOAc : 99:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (m, 2H), 6.77 (m, 2H), 3.38 (m, 4H), 2.97 (m, 4H), 2.59 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.88, 143.21, 118.24, 114.49, 67.13, 51.08, 41.51.

***N*-(4-(Dimethylamino)-2-phenoxyphenyl)methanesulfonamide *(scheme 4 entry 20)*.**[12a] It is obtained as a colorless solid (90.25 mg, 59%) after purification by column chromatography (n-hexane/EtOAc : 85:15): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, 1H), 7.28 (m, 2H), 7.16 (m, 1H), 6.89 (m, 2H), 6.41 (d, 1H), 6.14 (d, 2H), 2.89 (s, 3H), 2.87 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 155.96, 149.88, 148.95, 130.02, 126.87, 122.88, 117.27, 115.34, 107.62, 102.93, 102.24, 40.41, 37.98.

***N*-Methylcyclohexanamine *(scheme 5 entry 21)*.**[12d] It is obtained as a colorless liquid (51.50mg, 91%) after purification by column chromatography (n-hexane/EtOAc : 99:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.34 – 2.26 (m, 1H), 1.98 – 1.84 (m, 2H), 1.76 – 1.71 (m, 2H), 1.65 – 1.58 (m, 1H), 1.40 (s, 1H), 1.32 – 1.12 (m, 3H), 1.03 (qd, J = 12.6, 3.2 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 58.69, 33.59, 33.16, 26.15, 24.96.

***2*-(4-Methylpiperazin-1-yl)pyrimidine *(scheme 5 entry 24)*.**[37] It is obtained as a light yellowish liquid (77.43 mg, 87%) after purification by column chromatography (n-hexane/EtOAc : 95:5). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 12.5, 4.8 Hz, 2H), 6.48 (t, *J* = 4.7 Hz, 1H), 3.90 – 3.79 (m, 4H), 2.53 – 2.44 (m, 4H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.88, 157.71, 109.89, 54.61, 46.3, 43.53.

***4*-Methylmorpholine *(scheme 5 entry 25)*.**[12d] It is obtained as a brown liquid (45.51 mg, 90%) after purification by column chromatography (n-hexane/EtOAc : 95:5). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (t, 4H), 2.42 (t, 4H), 2.29 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 66.89, 55.39, 46.42.

***N*-Decyl-*N*-methyldecan-1-amine *(scheme 5 entry 28)*.**[39] It is obtained as a brown semi-solid (71.61 mg, 92%) after purification by column chromatography (n-hexane/EtOAc : 85:15). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 – 2.26 (m, 3H), 2.18 (s, 2H), 1.23 (d, *J* = 37.0 Hz, 29H), 0.84 – 0.77 (m, 6H). ^{13}C NMR {1H} (126 MHz, $CDCl_3$) δ 58.69, 33.59, 333.16, 26.15, 24.96.

4-(2-(Dimethylamino)ethyl)phenol *(scheme 5 entry 29)*.[12a] It is obtained as a colorless solid (44.55 mg, 54%) after purification by column chromatography (n-hexane/EtOAc : 85:15). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 7.5 Hz, 2H), 2.73 (t, 3H), 2.65 (t, 3H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.66, 129.68, 1298.89, 113.67, 60.79, 42.98, 31.61.

***N,*^{4}-Dimethylaniline *(scheme 5 entry 30)*.**[37] It is obtained as a yellowish liquid (59 mg, 98%) after purification by column chromatography (*n*-hexane/EtOAc : 85:15).^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.0 Hz, 2H), 6.48 (d, *J* = 8.3 Hz, 2H), 2.74 (s, 3H), 2.17 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.88, 125.31, 111.78, 30.15, 19.12.

… *4*-Methoxy-*N*-Methylaniline *(scheme 5 entry 31)*.[30] It is obtained as a colorless liquid (65.5 mg, 96%) after purification by column chromatography (n-hexane/EtOAc : 9:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 – 6.75 (d, 2H), 6.62 (d, *J* = 6.1 Hz, 2H), 3.76 (s, 3H), 3.41 – 3.11 (s, 1H), 2.81 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.30, 143.09, 114.90, 113.97, 55.53, 31.85.

… *N*-Methylbenzo[*d*][1,3]dioxol-5-amine *(scheme 2 entry 4)*.[30] It is obtained as dark brown solid (73 mg, 98%) after purification by column chromatography (n-hexane/EtOAc: 98:2). ^{1}H NMR (400 MHz) δ 6.72 – 6.60 (m, 1H), 6.24 (d, *J* = 2.6 Hz, 1H), 5.99 (s, 1H), 5.87 – 5.82 (s, 2H), 3.41 (s, 1H, NH 2.78 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 149.22, 146.7, 141.5, 109.26, 104.75, 101.28, 96.64, 32.45, 31.65.

***1H*-Benzo[*d*]imidazole *(scheme 7 entry 33)*.**[36c] It is obtained as a white solid (41.30 mg,70%) after purification by column chromatography (n-hexane/EtOAc : 9:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.61 (dd, 2H), 7.28 (m, 2H), 4.99 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 139.48, 136.58, 122.14, 114.52.

ASSOCIATED CONTENT

Supporting Information

Safety precautions for the reaction carrying out methanol in ACE® pressure tubes at >150 °C; catalyst recycling; reaction time profile experiments for *N*-Methylation of nitrobenzene; procedure for the detection of gases from methanol; limitations of the protocol; GC-MS analysis for competitive experiment and copies of ^{1}H, ^{13}C NMR spectra.

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors thank the Director, CSIR-Indian Institute of Petroleum, Dehradun, for his generous support. V. Goyal and J. Gahtori are thankful to Council of Scientific and Industrial Research (CSIR) New Delhi, for awarding junior research fellowship. The authors thank Dr. Jagadeesh Rajenahally, Leibniz Institute for Catalysis (LIKAT, Germany) for useful discussions.

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