Topics in Current Chemistry (2022) 380:27
https://doi.org/10.1007/s41061-022-00382-w

REVIEW

Methods for Direct Reductive *N*-Methylation of Nitro Compounds

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Received: 3 December 2020 / Accepted: 18 April 2022 / Published online: 24 May 2022

Abstract

Direct reductive *N*-methylation of inexpensive and readily available nitro compounds as raw material feedstocks is more attractive and straightforward compared with conventional *N*-methylation of amines to prepare biologically and pharmaceutically important *N*-methylated amine derivatives. This strategy for synthesis of *N*-methylamines avoids prepreparation of NH-free amines and therefore significantly shortens the separation and purification steps. In recent years, numerous methylating agents and catalytic systems have been reported for this appealing transformation. Thus, it is an appropriate time to summarize such advances. This review elaborates on the most important discoveries and advances in this research arena, with special emphasis on the mechanistic aspect of reactions that may provide new insights into catalyst improvement.

Keywords Nitro compounds · *N*-Methylamines · *N*-Methylation · Reduction · Methanol · Formaldehyde

Dedicated to Dr. Morteza Abdoli for his distinguished scientific efforts for our research group.

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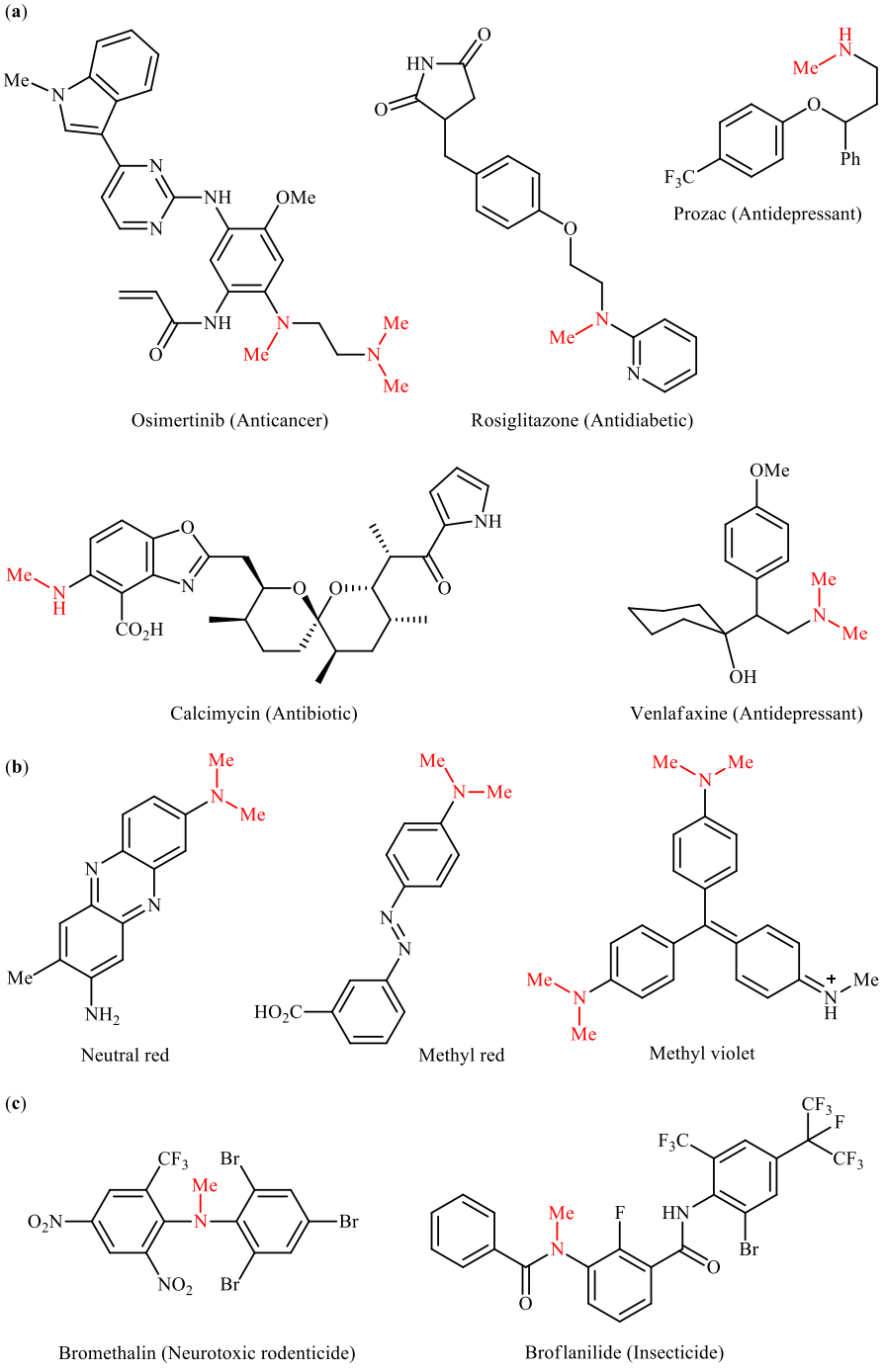
1 Introduction

N-Methylated amines represent important fine and bulk chemicals as they occur in many medicines [14], dyes [5], and pesticides [6, 7] (Scheme 1). These structural motifs also serve as valuable intermediates in organic synthesis [8–11]. Moreover, they are common motifs in surfactants [12]. The development of convenient and cost-effective methods for their preparation is thus of scientific interest. This special class of amines has traditionally been synthesized by *N*-methylation of NH-free amines using methylating reagents such as methyl halides methanol, dimethyl carbonate, dimethyl sulfate, dimethyl sulfoxide (DMSO), formaldehyde, etc. [13, 14]. As is well known, one of the main methods to generate primary amines is reduction of nitro compounds [15–18]. Therefore, without question, the development of new and efficient approaches to construct *N*-methylated amines directly from corresponding nitro compounds is highly desirable in economic terms.

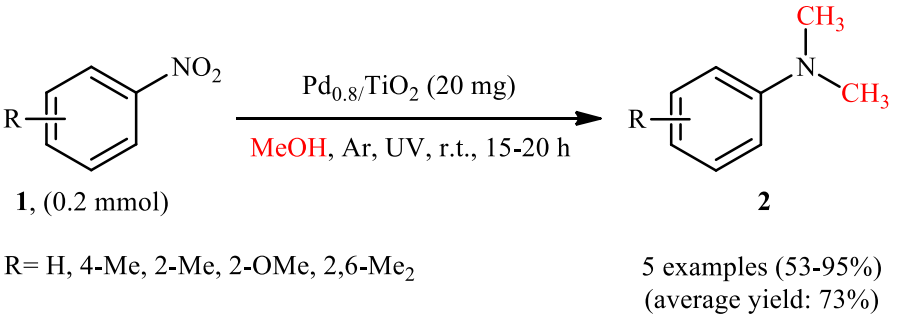
Fortunately, in recent years, a number of unique methodologies have been developed for one-pot synthesis of *N*-methylated amines from nontoxic, low-cost, and readily available nitro compounds through a sequential hydrogenation and methylation process. Despite the remarkable progress that has been achieved in this appealing research arena, a comprehensive overview of this domain has not appeared in literature to date. Our aim in this review is to try to provide an up-to-date overview of the most important advances and developments regarding direct reductive *N*-methylation of nitro compounds, with particular emphasis on the mechanistic aspects of such reactions. For clarity, the review is structured based on the type of methylating agent applied (i.e., MeOH, DMSO, HCHO, HCOOH, and CO_2/H_2).

2 Methylations with Methanol

Direct *N*-methylation of nitro compounds using methanol as the methyl source is probably the area of this field that has experienced most growth over the past few years. The story of synthesis of *N*-methylamines through reductive methylation of nitro compounds with methanol started with Li and coworkers, who reported that heating (170 °C) of nitrobenzene in methanol in the presence of a pretreated Raney-Ni catalyst under an inert atmosphere afforded *N*,*N*-dimethylaniline in up to 98% yield [19]. In this reaction, methanol plays a dual role, as substrate and solvent. Moreover, it acts not only as a methyl source but also as a hydrogen source. Although only one example was provided, and under harsh conditions, that paper represents the first example of direct *N*-methylation of nitro compounds with methanol. Six years later, Shi and colleagues developed a practical Pd-catalyzed *N*,*N*-dimethylation of a library of electron-rich nitrobenzenes **1** with methanol under mild conditions [20]. The reactions proceeded in the presence of a catalytic amount of TiO_2-supported palladium nanoparticles ($Pd_{0.8}$/

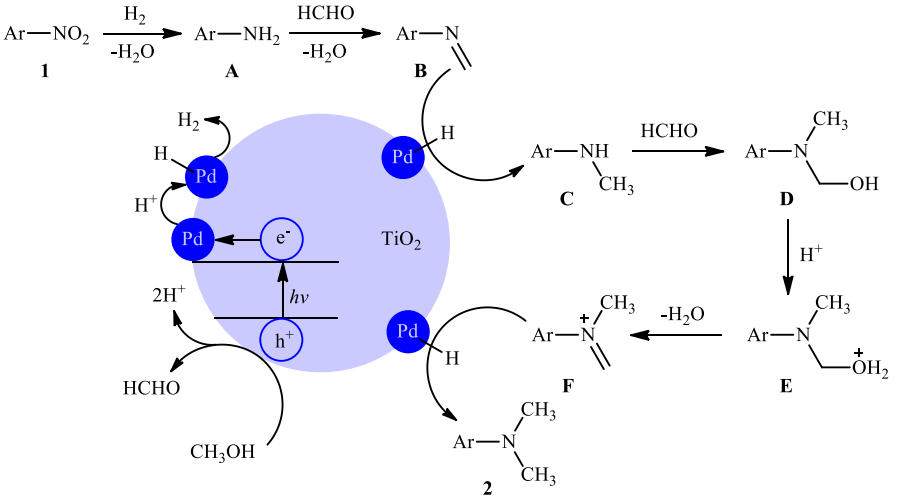


Scheme 1 Examples of *N*-methylamines: **a** medicines, **b** dyes, and **c** pesticides

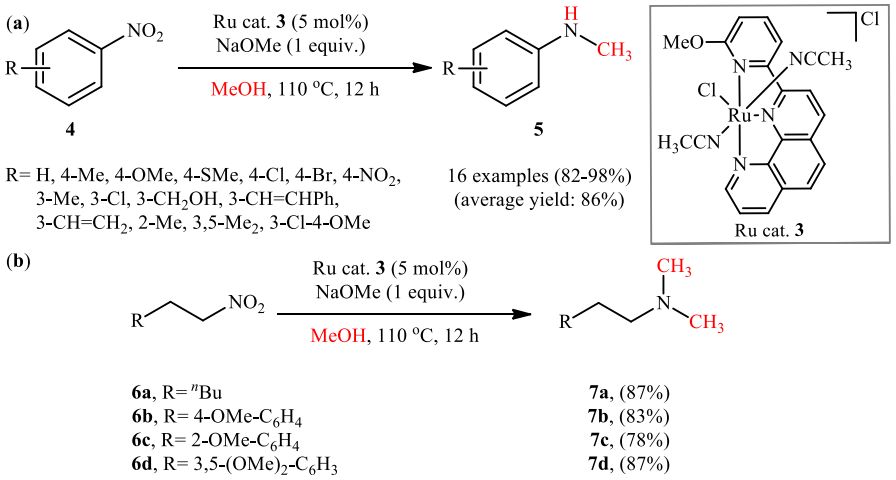


Scheme 2 Shi's synthesis of *N*,*N*-dimethylanilines **2**

TiO_2) under irradiation by ultraviolet (UV) light at room temperature to give the corresponding *N*,*N*-dimethylaniline products **2** in moderate to excellent yields (Scheme 2). The results indicated that increasing or decreasing the Pd loading reduced the product yields. Noteworthily, other TiO_2-supported metal catalysts (e.g., Au/TiO_2, Pt/TiO_2, and Pt/TiO_2) failed to promote this reaction. Based on the quantitation of intermediates by the gas chromatography–mass spectrometry (GC–MS) method for the reaction of aniline with methanol, the authors proposed that this reductive methylation reaction proceeds though the following key steps (Scheme 3): (1) photoexcitation of TiO_2 to form electron (e^-) and positive hole (h^+) pairs; (2) oxidation of methanol with h^+ to furnish formaldehyde and H^+; (3) reduction of H^+ on the surface of Pd particles by the e^- transferred from the TiO_2 conduction band to produces a hydride on the particles (H–Pd species); (4) condensation of formaldehyde and aniline **A** (generated in situ by reduction of nitrobenzene **1**) with the help of Lewis-acid site on the TiO_2 surface to afford



Scheme 3 Proposed mechanism for formation of *N*,*N*-dimethylanilines **2**

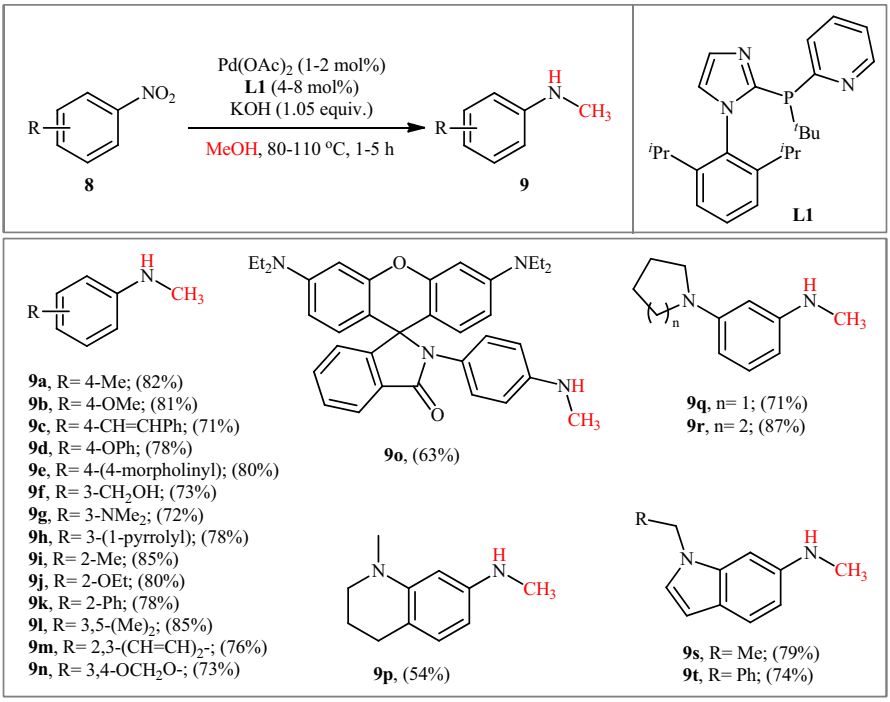


Scheme 4. Ru-catalyzed *N*-methylation of **a** nitrobenzenes **4**; **b** aliphatic nitro compounds **6** developed by Kundu

imine **B**; (5) hydrogenation of imine **B** by H–Pd species on the surface of TiO_2 to yield *N*-methylaniline **C**; (6) coupling of formaldehyde and *N*-methylaniline **C** to provide aminium **F** through intermediates **D** and **E**; and (7) hydrogenation of aminium **F** by H–Pd species to generate the final *N*,*N*-dimethylaniline products **2**.

In this context, Kundu's group developed an efficient conversion of nitrobenzene derivatives **4** to the corresponding *N*-methylanilines **5**, using a homogeneous ruthenium [NNN]-type pincer complex **3** as catalyst and NaOMe as base under open air (Scheme 4a) [21]. This selective *N*-monomethylation reaction was experimentally simple, performed by heating the substrates at 110 °C in MeOH, and was applicable to both electron-rich and electron-poor nitroarenes. Moreover, the optimized condition was also successfully applied for *N*-monomethylation of a nitroheteroaromatic compound and a series of α,β-unsaturated nitro compounds. Interestingly, when aliphatic nitro compounds **6** were used as substrates under the identical conditions, the corresponding *N*,*N*-dimethylamines **7** were obtained as the sole products (Scheme 4b). The authors ascribed the diselectivity of aliphatic nitro compounds to more nucleophilic intermediates.

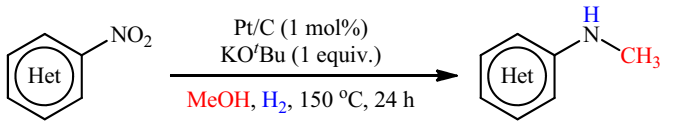
In 2019, Xu's research team reported another example of selective *N*-monomethylation of nitroarenes with methanol using an encapsulated iridium nanocatalyst in combination with ^{t}BuOK base at 170 °C [22]. The reaction showed good tolerance for nitroarenes with electron-donating functional groups. However, this catalytic system was unfruitful with nitro compounds bearing a strongly electron-withdrawing groups (e.g., CN), and lower yields were obtained with nitro compounds bearing halogen groups due to side-reactions. Concurrently, Beller and coworkers implemented selective *N*-monomethylation of a number of electron-rich and electron-poor nitroarenes **8** with methanol catalyzed by easily available $Pd(OAc)_2$ in the presence of a specific phosphine ligand containing nitrogen atoms **L1** (Scheme 5) [23]. A relatively wide range of sensitive functional groups such as hydroxyl, amino, and



Scheme 5 Selective *N*-monomethylation of nitroarenes **8** with methanol catalyzed by $Pd(OAc)_2$

ether functionalities in different positions on phenyl rings of nitroarenes were well tolerated by this synthetic methodology, but some drawbacks still existed, such as high reaction temperature (80–110 °C) and narrow application (only aromatic nitro compounds). A similar *N*-monomethylation of nitroarenes with methanol was also reported by Zhang, Ibrahimu, and Yang, employing $[RuCl_2(p\text{-cymene})_2]_2$ as catalyst and an NNN pincer (amine–pyridine–imine, API) as ligand [24]. Notably, a diverse set of important functional groups (e.g., OMe, Cl, Br, CO_2Me, OH, CN, and $NHSO_2Me$) were compatible with the reaction conditions employed, and other aliphatic and benzylic alcohols such as ethanol, propan-2-ol, butan-1-ol, cyclohexanol, and (4-methoxyphenyl)methanol were also successfully subjected to this reaction.

In the same year, Siddiki and Shimizu and their coworkers rertpoed a general protocol for selective *N*-monomethylation of nitroarenes with methanol in presence of molecular hydrogen under basic conditions using carbon-supported Pt nanoparticles (Pt/C) as heterogeneous catalyst [25]. Choice of an appropriate base had a substantial effect on the facility of the reaction. Screening of a number of common bases such as Et_3N, DBU, K_2CO_3, Na_2CO_3, Cs_2CO_3, NaOEt, NaOMe, NaO^{t}Bu, KO^{t}Bu, NaOH, and KOH revealed KO^{t}Bu as the most suitable for this conversion. Both aromatic and heteroaromatic nitro compounds **10** took part in the reaction easily and provided the expected *N*-methylamines **11** in high to excellent yields ranging from 76% to 92% (Scheme 6). However, the requirement for high temperature and hydrogen atmosphere may limit the range of application of this protocol in



10 **11**

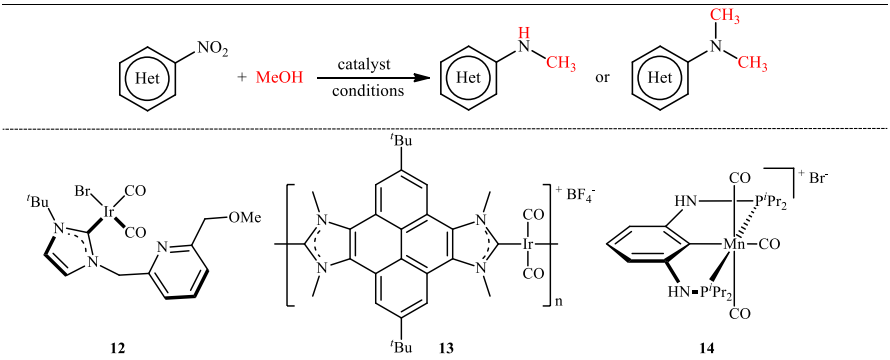
10 examples (76-93%)
(average yield: 87%)

(Het)Ar= Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-Cl-C_6H_4, 3-Me-C_6H_4, 2,3-Me_2-C_6H_3, 3,5-Me_2-C_6H_4, 2,3-$(CH{=}CH)_2$-C_6H_3, 3,4-OCH_2CH_2O-C_6H_3, 3-pyridyl

Scheme 6. Pt/C-catalyzed *N*-monomethylation of nitroarenes **10** with methanol in presence of molecular hydrogen

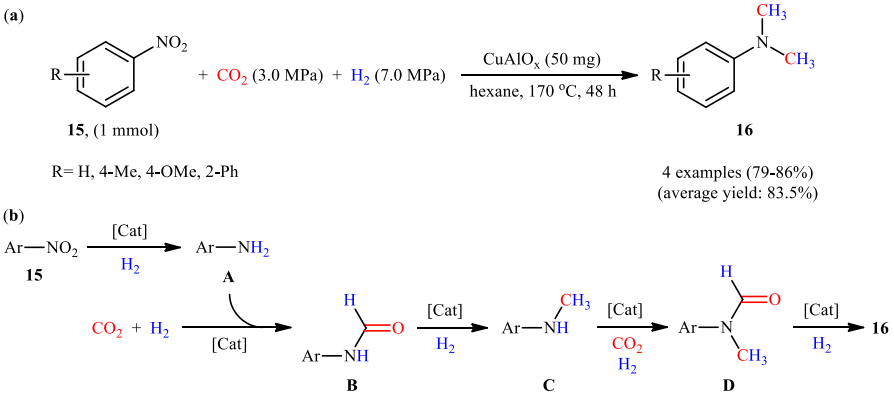
organic synthesis. Concurrently, in a closely related study, Natte's research group synthesized 12 *N*-methylaniline derivatives in good to excellent yields (up to 95%) via reductive methylation of the corresponding nitroarenes with methanol as both carbon and hydrogen source using commercially available Pd/C in combination with KO^{t}Bu as a catalytic system under open air [26]. Interestingly, the use of the reaction conditions developed for *N*-monomethylation for an extended time (36 h) at slightly higher temperature (150 °C) led to *N*,*N*-dimethylated products in fair to excellent yields.

Table 1 Novel catalytic systems for *N*-methylation of nitroarenes with methanol



12 **13** **14**

Entry	Catalyst	Conditions	Number of examples	Yield (%)		Ref.
				Range	Average	
1	Cu/Al_2O_3-DH	210 °C, continuous flow	8	63–99	94	[17]
2	**12**	Cs_2CO_3, 130 °C, 5–24 h	12	76–100	93	[18]
3	**13**	KO^{t}Bu, 130 °C, 24–48 h	32	48–99	87	[19]
4	**14**	KOH, 110–130 °C, 24–72 h	11	30–90	65.5	[20]



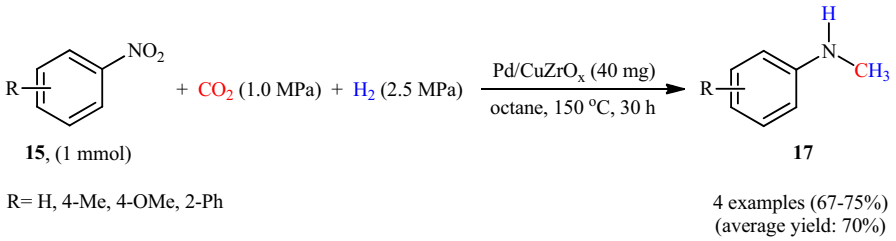
Scheme 7 **a** Cu-catalyzed direct methylation of nitrobenzenes **15** with CO_2 and H_2; **b** proposed mechanistic pathways for formation of *N*,*N*-dimethylaniline derivatives **16**

Several metal-based catalytic systems have also been developed and have showed high catalytic performance for *N*-methylation of nitroarenes with methanol (Tables 1). These include Cu/Al_2O_3-DH [27], $[IrBr(CO)_2(\kappa C\text{-}^t BuImCH_2PyCH_2OMe)]$ (**12**) [28], N-heterocyclic carbene-iridium complex **13** [29], and bench-stable Mn PN^3P pincer precatalyst **14** [30]. Notably, Cu/Al_2O_3-DH also displayed good catalytic activity in selective *N*,*N*-dimethylation of aliphatic nitro compounds. However, only one nitroalkane was subjected to the reaction using this catalyst. *N*-Methylation of aliphatic nitro compounds with methanol was also investigated by using Mn-catalyst **14**. Unfortunately, in this case, starting materials were completely decomposed.

Despite the remarkable accomplishments over the last few years in this appealing research arena, there is still further need for new catalytic systems that are responsive to milder reaction conditions and shorter reaction times.

3 Methylations with Carbon Dioxide

The use of carbon dioxide (CO_2) as an abundant, renewable, nonflammable, and environmentally friendly one-carbon (C1) feedstock has attracted increasing attention [31–36]. Methylation of N–H bond with CO_2 in the presence of a reductant (e.g., H_2, hydrosilanes, hydroboranes) is one of the well-established CO_2-fixation reactions [37]. Although amines have been diversely utilized as *N*-nucleophiles in the title reaction, direct methylation of nitro compounds with CO_2 in a single click remains largely underdeveloped. The first report of direct methylation of nitrobenzenes with CO_2 can be found in a 2014 paper by Shi et al. [38], who showed that treatment of a small series of electron-rich nitrobenzenes **15** with catalytic amounts of $CuAlO_x$ (nano-CuO_x particles deposited on the plane of AlO_x) under CO_2–H_2 atmosphere at 170 °C afforded the corresponding *N*,*N*-dimethylaniline derivatives **16** in good yields via a domino reduction/methylation process (Scheme 7a). Although

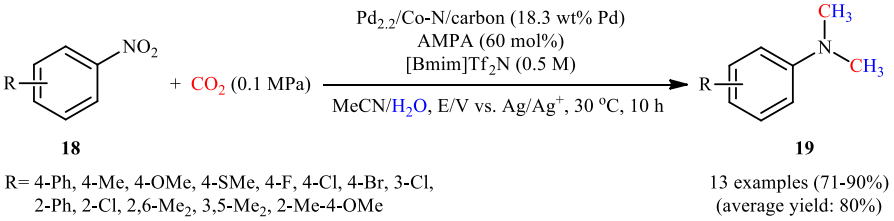


Scheme 8 Selective *N*-monomethylation of nitrobenzenes **15** with CO_2 and H_2 catalyzed by Pd/$ZrCuO_x$

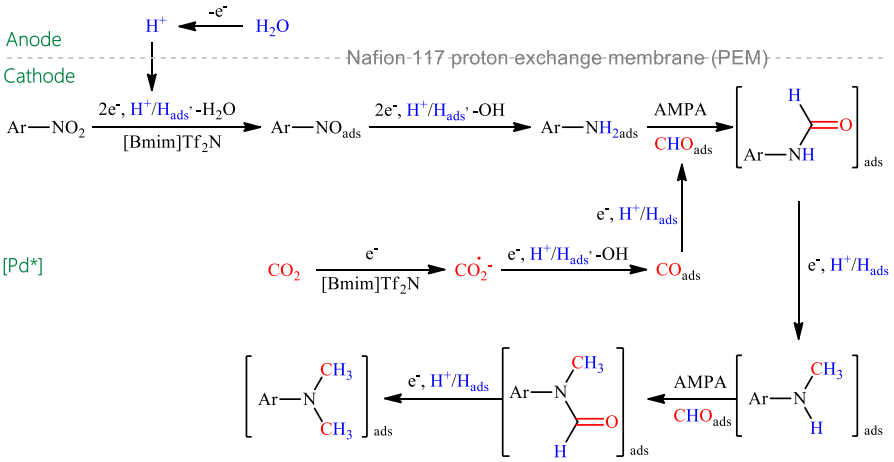
high conversion was obtained for all four nitrobenzenes tested, the requirement for elevated temperature may prevent the application of this protocol to some degree. A mechanism that explains this transformation starts with the hydrogenation of nitrobenzene **15** with H_2 in the presence of catalyst to form aniline **A**, which after carbonylation with CO_2/H_2 generates *N*-phenylformamide **B**. Next, the quick hydrogenation of this intermediate with H_2 leads to the *N*-methylaniline **C**. Finally, *N*-methylaniline **C** again reacts with CO_2/H_2 to afford *N*-methyl-*N*-phenylformamide **D**, which after hydrogenation results in the formation of the observed *N*,*N*-dimethylaniline products **16** (Scheme 7b). On the basis of these results, the same group reported the first example of one-pot methylation of aromatic nitriles with CO_2 into *N*,*N*-dimethylbenzylamines utilizing their heterogeneous catalyst.

Shortly thereafter, the same authors reported selective *N*-monomethylation of the same set of nitrobenzene **15** employing Pd/$ZrCuO_x$ as catalyst, in which Pd was coloaded on the $ZrCuO_x$ support and the ratio of Pd to Cu and Zr was 1:1.7:2.1 [39]. The reactions were run under 1.0 and 2.5 MPa pressures of CO_2 and H_2, respectively, in octane and generally provided the respective *N*-methylanilines **17** in good yields within 30 h (Scheme 8). However, the reaction conditions were still very harsh (150 °C), and there is further need to development novel catalytic systems that allow *N*-methylation reactions of nitroarenes using CO_2/H_2 as methyl source under milder conditions.

Drawing inspiration from those works, Han et al. developed an elegant electrochemical approach for *N*,*N*-dimethylation of nitroarenes **18** using CO_2/H_2O as methyl source under ambient conditions [40]. They identified $Pd_{2.2}$/Co–N/carbon and 1-amino-methylphosphonic acid (AMPA) as the optimal catalyst and cocatalyst, respectively, and 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([Bmim]Tf_2N) as the ideal supporting electrolyte. The established electrochemical reaction was conducted in a typical H-type cell consisting of a cathode (working electrode), an anode (platinum gauze auxiliary electrode), and an Ag/Ag^+ reference electrode, tolerating several important functional groups (e.g., F, Cl, Br, OMe, and SMe), and providing the expected *N*,*N*-dimethylanilines **19** in good to excellent yields, ranging from 71% to 90% (Scheme 9). It should be mentioned that the presence of the cocatalyst was crucial for the success of this conversation, since in the absence of AMPA only NH-free anilines were formed and could not be further converted to the methylated products even when extending the reaction time. Experiments indicated that AMPA acts as a Brønsted base and could activate the proton on



Scheme 9 Electrochemical synthesis of *N*,*N*-dimethylanilines **19** from nitroarenes **18** using CO_2/H_2O as methyl source

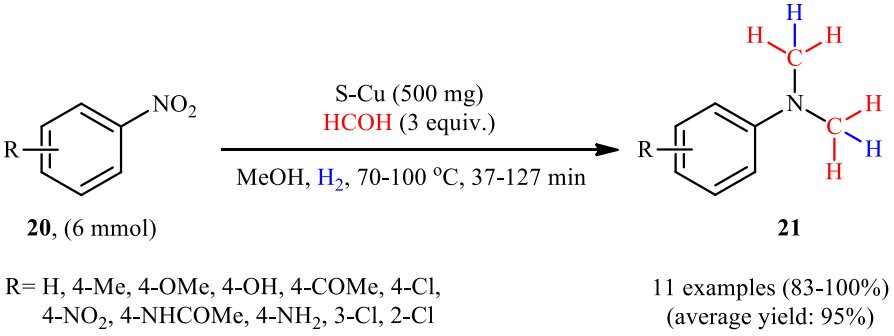


Scheme 10 Plausible mechanistic pathway for the reaction in Scheme 9

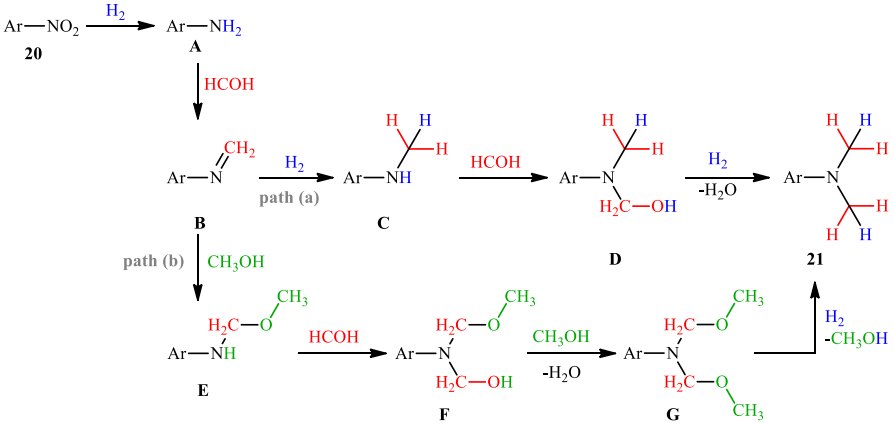
the anilines to promote the formation of *N*,*N*-dimethylanilines. Detailed mechanistic studies showed that nitrosobenzenes, *N*-arylhydroxylamine, formamides, and formyl radical are the key intermediates of this CO_2-fixation reaction (Scheme 10).

4 Methylations with (Para)Formaldehyde

After pioneering work by the groups of Rhee [41] and Isobe [42] on the synthesis of *N*-methylaniline and ethyl 2-(4-methoxy-3-(methylamino)phenyl)acetate, respectively, through selective *N*-monomethylation of the corresponding nitroaryls with formaldehyde (HCOH), the first general report of direct *N*-methylation of nitro compounds utilizing this cheap and readily available methylating reagent was published in 2013 by Rong et al. [43]. In that study, 11 *N*,*N*-dimethylaniline derivatives **21** were efficiently prepared by treatment of the respective nitrobenzenes **20** with 3 equiv. HCOH in the presence of a catalytic amount of skeletal copper in refluxing methanol under molecular hydrogen atmosphere (Scheme 11). The optimized protocol tolerated both electron-rich and electron-poor substrates

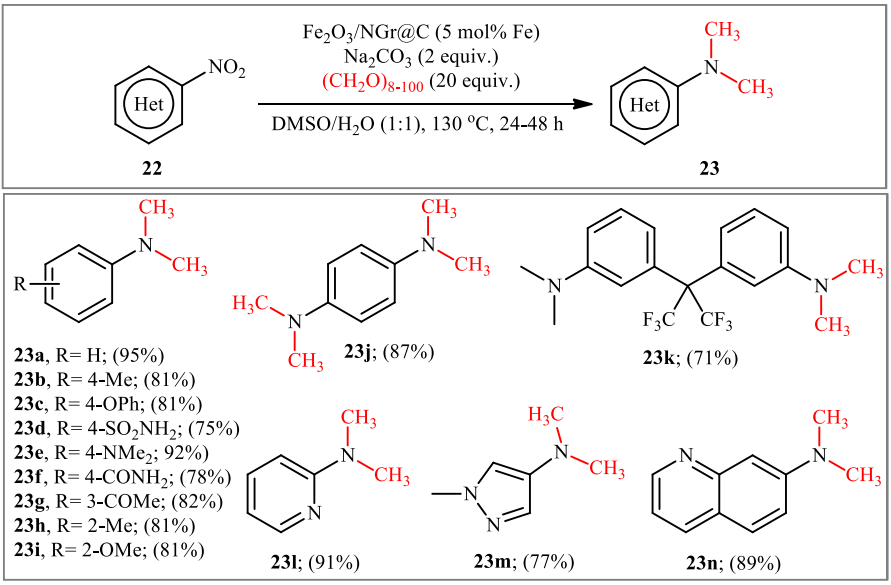


Scheme 11 Rong's synthesis of *N*,*N*-dimethylanilines **21**



Scheme 12 Mechanistic proposal for the generation of *N*,*N*-dimethylanilines **21**

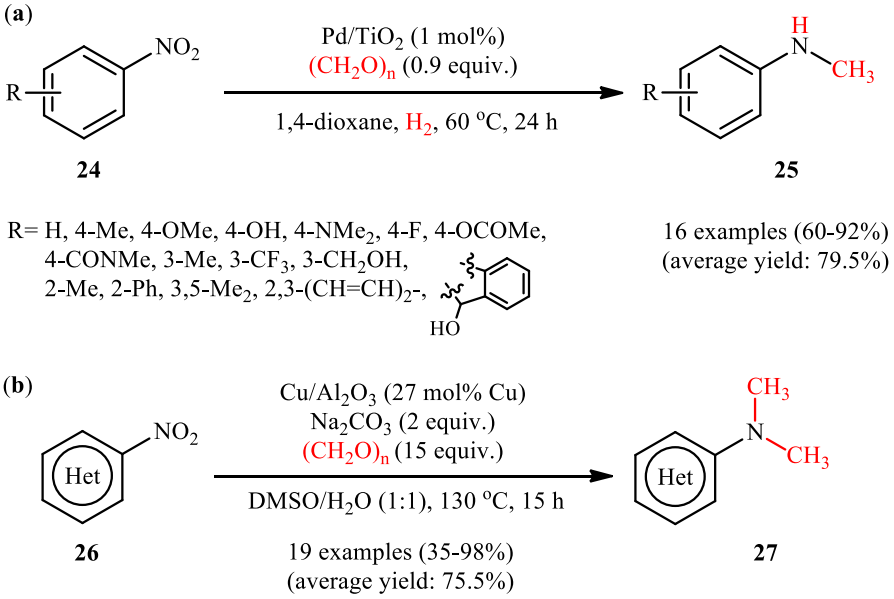
bearing various sensitive functional groups such as chloro, methoxy, hydroxyl, ketone, and amide functionalities, and generally provided the target *N*,*N*-dimethylated products **21** in high to quantitative yields. Needless to say that the amino group (NH_2) was also converted to NMe_2 during the reaction. Scheme 12 outlines a plausible mechanism for this conversion. Firstly, nitrobenzene **20** undergoes reduction by H_2 over S-Cu to produce the aniline **A**, which after condensation reaction with formaldehyde leads to the formation of imine intermediate **B**. Subsequently, hydrogenation of this intermediate with H_2 forms the *N*-methylaniline **C**, which after reaction with another molecule of formaldehyde produces (*N*-methylanilino)methanol intermediate **D**. Finally, dehydration of alcohol moiety of this intermediate and subsequent hydrogenation of the generated carbon–carbon double bond by H_2 afford the observed *N*,*N*-dimethylaniline **21** (Scheme 12, path a). In another possibility, addition of methanol to imine intermediate **B** gives *N*-(methoxymethyl)aniline **E**, which undergoes nucleophilic addition with formaldehyde to yield *N*-ethyl-*N*-(methoxymethyl)aniline **F**. Next,



Scheme 13. Selected examples of Fe-catalyzed *N*,*N*-dimethylation of nitroarenes **22** with paraformaldehyde

some addition and elimination reactions occur to form the desired *N*,*N*-dimethylated product **21** (Scheme 12, path b).

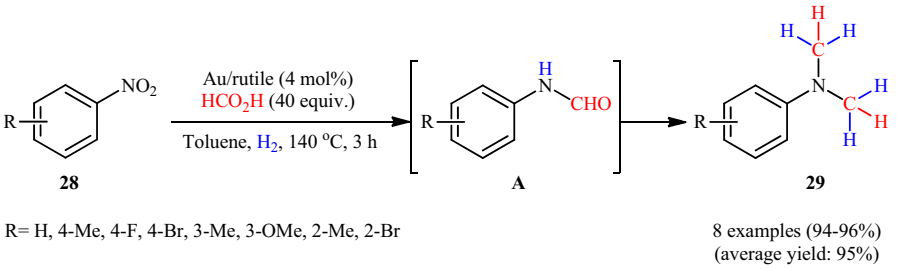
Four years later, an iron-catalyzed version of the title reductive amination was investigated by Beller et al. [44]. They designed and prepared the nonnoble iron oxide-based nanocatalyst (Fe_2O_3/NGr@C = pyrolyzed Fe-phenanthroline complex on carbon), which enables efficient *N*,*N*-dimethylation of a diverse range of nitroarenes **22** using paraformaldehyde as both methylating and reducing agent. The reactions were performed in the absence of external hydrogen in a binary solvent DMSO/H_2O with ratio 1:1, tolerated both aromatic and heteroaromatic nitro compounds, and provided the respective *N*,*N*-dimethylated (hetero)aromatic amines **23** in good to excellent yields within 1–2 days (Scheme 13). However, an elevated temperature (130 °C) was necessary for successful transformation. It is noteworthy that this process can be easily scaled up to provide multigram quantities of the target *N*,*N*-dimethylated amines without sacrificing the yield or outcome of the methodology. Remarkably, the authors successfully applied their protocol to post-modification of several pharmaceuticals (e.g., nimodipine, cilnidipine, nicardipine, and nimesulide) and fluorescent molecules (e.g., fluorenone, rhoamine derivatives). They also nicely expanded their methodology to selective monomethylation of nitro compounds by controlling the concentration of paraformaldehyde and the reaction time. Of note, recycling experiments indicated that their catalyst could be recovered and reused up to five times without significant loss in activity. Concurrently, Jagadeesh's research group identified a related cobalt material (Co_3O_4/NGr@C) as catalyst for selective *N*,*N*-dimethylation of a diverse range of functionalized nitroarenes with aqueous formaldehyde



Scheme 14 **a** Pd/TiO_2-catalyzed synthesis of *N*-monomethylamines **25** from nitrobenzenes **24** and paraformaldehyde in presence of molecular hydrogen; **b** *N*,*N*-Dimethylation of nitrobenzenes **26** with paraformaldehyde catalyzed by Cu/Al_2O_3

in presence of formic acid in *t*-butanol [45]. Importantly, this catalytic system was also active for aliphatic nitro compounds.

Subsequently, Shi and colleagues reported a TiO_2-supported nano-Pd catalyst (Pd/TiO_2) could enable kinetically controlled synthesis of *N*-monomethylamines **25** from nitrobenzenes **24** with paraformaldehyde in presence of molecular hydrogen under mild conditions (Scheme 14a) [46]. Replacing TiO_2 with some other supports (e.g., Al_2O_3, SiO_2, Fe_2O_3, CuO, and C) led to much lower yield and monoselectivity, or even no desired product at all. The superior catalytic activity of Pd/TiO_2 over the other tested catalysts could be associated with the good H_2 activation ability and high amine adsorbing capacity of this catalyst, as elucidated by NH_3-temperature-programmed desorption (TPD) and H_2-temperature-programmed reduction (TPR) analysis, while the high monoselectivity of this catalyst should be attributed to preferential adsorption of the primary amine over *N*-monomethylamine on the Pd/TiO_2 surface, as elucidated by NH_3/Me_2NH-TPD. Very recently, Yang's research team reported efficient reductive *N*,*N*-dimethylation of a library of functionalized and structurally diverse nitrobenzenes **26** to afford the desired *N*,*N*-dimethylanilines **27** in fair to almost

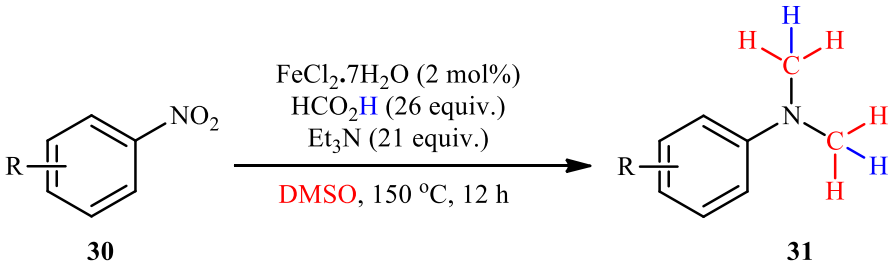


Scheme 15 Synthesis of *N*,*N*-dimethylanilines **29** by reaction of nitroarenes **28** with formic acid

quantitative yields (35–98%), employing paraformaldehyde as CH_3 source and Cu nanoparticles (20 nm) supported on amorphous Al_2O_3 (Cu/Al_2O_3) as heterogeneous catalyst in the absence of external molecular hydrogen (Scheme 14b) [47]. *Cal*-Cu/Al_2O_3 and *ip*-Cu/Al_2O_3 were also found to be relatively effective catalysts, whereas Ni/Al_2O_3, Co/Al_2O_3, CuAl-LDH, NiAl-LDH, and CoAl-LDH proved to be completely ineffective. Regarding the influence of substituents, nitroarenes bearing electron-donating substituents on the phenyl ring delivered the products in better yields compared with those incorporating electron-withdrawing groups.

5 Methylations with Formic Acid

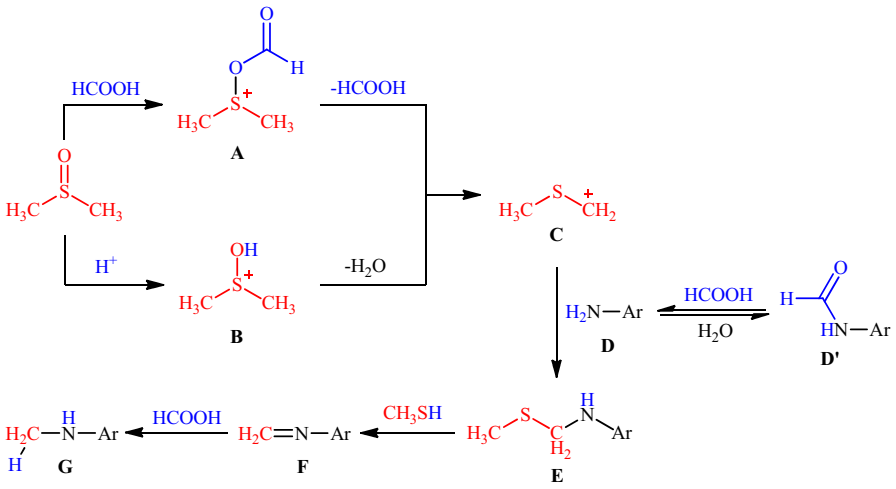
Despite the remarkable advances in hydrogenation and formylation of nitroaromatics using formic acid over the last few years [48, 49], reported examples of direct *N*-methylation of nitrocompounds using formic acid as methylating agent are scarce. To the best of the authors' knowledge, only one example of this kind of reaction has been reported in literature to date. In this preliminary work, eight *N*,*N*-dimethylanilines **29** were synthesized in excellent isolated yields by reaction of nitroarenes **28** with formic acid with 4 mol.% gold-based solid catalyst (Au/rutile) in refluxing toluene under hydrogen atmosphere (Scheme 15) [50]. Interestingly, the efficiency of this synthetic strategy was not dependent on the electronic and steric effects of the group directly bonded onto the phenyl ring. It is noteworthy that, when the reaction was carried out with *o*-dinitrobenzenes under inert atmosphere, the corresponding benzimidazoles were obtained in almost quantitative yields. Although those authors did not propose a reaction mechanism for the formation of *N*,*N*-dimethylanilines, based on literature [51], a *N*-formylamine intermediate **A** might be involved in this transformation. Of note, at the beginning of the 1990s, in a related investigation, Jenner and Taleb reported the synthesis of a small library of *N*,*N*-dimethylanilines by direct methylation of corresponding nitroarenes utilizing methyl formate (HCO_2Me) as methyl group source in the presence of a combination of $Ru_3(CO)_{12}$ and Bu_4PBr as a catalytic system under solvent-free conditions at 220 °C [52].



Scheme 16. Fe-catalyzed methylation of nitroarenes **30** with DMSO

6 Methylations with Dimethyl Sulfoxide

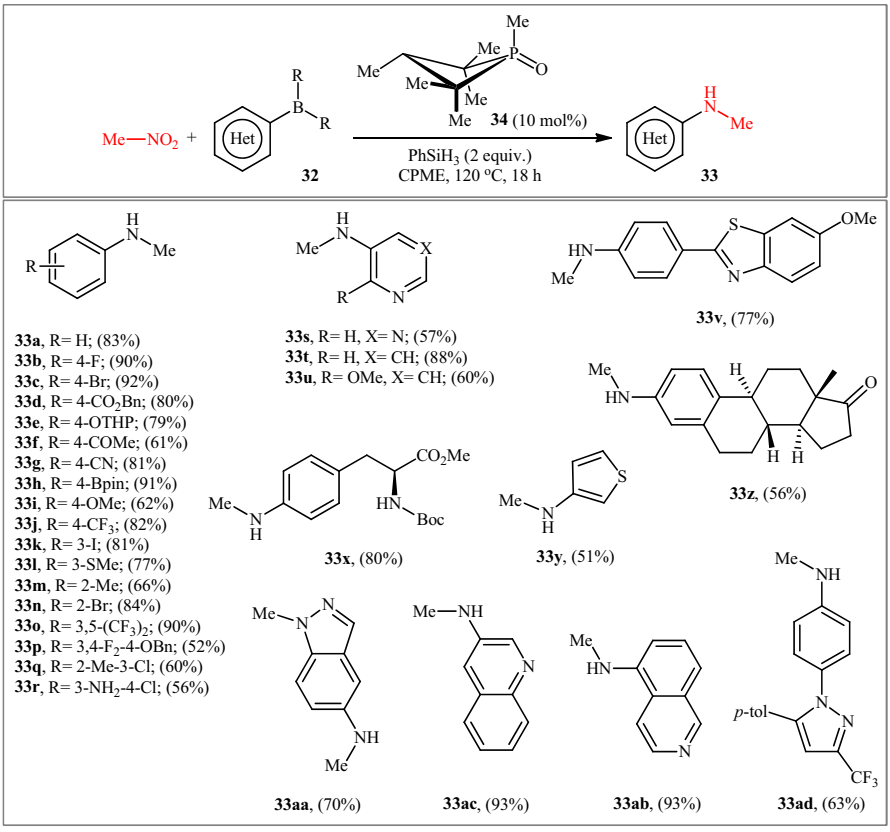
Dimethyl sulfoxide (DMSO) is an inexpensive and low-toxicity organosulfur compound that is widely used as a polar aprotic solvent, radical scavenger, oxidant, and source of –Me, –CHO, –CN, –SMe, $–SO_2Me$, and –O [53]. Despite the variety of protocols for methylation of amines using DMSO as methyl group source, reported examples of direct methylation of nitro compounds using this reagent are very scarce. In 2014, Wang et al. communicated the first and only example of direct *N*-methylation of nitro compounds with DMSO as methyl group source, in presence of formic acid as hydrogen source [54]. They showed that heating of nitroarenes **30** in DMSO in the presence of a catalytic amount of $FeCl_2·7H_2O$ and over-stoichiometric amounts (20-fold excess) of formic acid and trimethylamine afforded the *N*,*N*-dimethylanilines **31** in good to high yields within 12 h (Scheme 16). The reaction proved to be efficient on various nitrobenzenes bearing electron-withdrawing groups (e.g., Cl, Br, and I) and electron-donating groups (e.g., OMe and SMe), affording exclusively dimethylated products. Of note, primary and secondary amines as well as nitrogen-containing heterocycles could also be easily *N*-methylated under the identical conditions. This methodology was also successfully applied in the high-yielding synthesis of galipinine, an alkaloid used against fever, from its corresponding tetrahydroquinoline precursor. The results of deuterium labeling experiments demonstrated that, in each CH_3 group of dimethylated amines, two protons come from DMSO and one from HCO_2H. Regarding the plausible mechanistic course for this transformation (Scheme 17), the authors speculated that the reaction starts with the generation of acylated intermediate **A** through the reaction of DMSO with formic acid anhydrides that, after Pummerer rearrangement, affords key intermediate **C**. In another possibility, protonation of DMSO by HCO_2H leads to the formation of intermediate **B**, which after dehydration under high temperature provides intermediate **C**. Subsequently, intermediate **C** intercepts amine **D** (generated in situ by reduction of nitro compound **30** under the reaction condition) to form intermediate **E**, which after elimination of methanethiol furnishes imine **F**. Finally, reduction of imine **F** by formic acid yields the methylated amine product **G**.



Scheme 17 Plausible mechanism for the reaction in Scheme 16

7 Miscellaneous Reactions

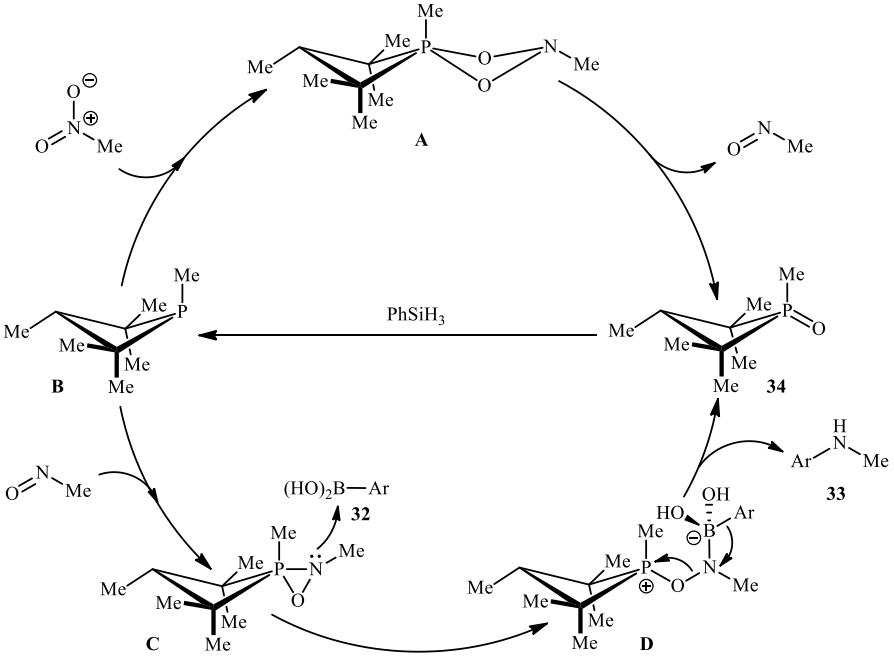
In 2020, the innovative research group of Radosevich established a robust P(III)/P(V)-catalyzed C–NMe bond formation reaction through reductive coupling of inexpensive and easy-to-handle nitromethane ($MeNO_2$) as methylamine surrogate with arylboronic acid derivatives **32**, affording *N*-methylanilines **33** by using a small ring organophosphorus-based catalyst (1,2,2,3,4,4-hexamethylphosphetane *P*-oxide, **34**) and a mild terminal reductant hydrosilane ($PhSiH_3$) in nitrogen atmosphere [55, 56]. The broad synthetic scope of this process was established by using a library of various (hetero)aromatic boronic acids and esters bearing both electron-donating and electron-withdrawing functional groups (Scheme 18). This synthetic strategy was also successfully applied for fabrication of isotopically labeled *N*-methylanilines from various stable isotopologues of nitromethane (i.e., CD_3NO_2, $CH_3{}^{15}NO_2$ and $^{13}CH_3NO_2$), indicating that this compound is a versatile precursor for direct installation of the methylamino group. The authors speculated that this C–N bond-forming reaction proceeds via formation of reactive phosphorane **B** through (3 + 1) cheletropic addition of phosphetane **A** and nitromethane, followed by its simultaneous fragmentation to give nitrosomethane (MeNO) and phosphetane *P*-oxide **34**, which after reduction with hydrosilane regenerate the catalyst. Next, (2 + 1) addition of phosphine catalyst and MeNO forms oxazaphosphirane intermediate **C**, which undergoes reaction with boronic acid **32** to furnish betaine intermediate **D**. Finally, 1,2-metallate rearrangement of **D** delivers the desired *N*-methylaniline **33** and regenerates the catalyst (Scheme 19).



Scheme 18 P(III)/P(V)-catalyzed reductive coupling of NO_2 with (hetero)aromatic boronic acid derivatives **32**

8 Conclusion

N-Methylamines belong to a highly important class of amines that are present in many natural and synthetic drugs (e.g., calcimycin, oxycontin, venlafaxine, and Lexapro), dyes (e.g., toluylene red, methyl red, methyl yellow, and methyl violet), and pesticides (e.g., bromethalin). There is therefore special scientific interest in the development of straightforward and efficient protocols for their preparation. Recently, direct reductive *N*-methylation of nitro compounds with various methylating agents (e.g., MeOH, DMSO, HCHO, HCOOH, and CO_2/H_2) has emerged as a concise and convenient strategy to access *N*-methyl- and *N*,*N*-dimethylamines that, beside high step economy, offers main advantages such as inexpensive and easily available starting materials, simplicity, and the avoidance of prepreparation of NH-free amines. Interestingly, most of the procedures covered in this review exhibit high selectivity for challenging *N*-monomethylation reactions. However, this new page of *N*-methylated amine synthesis generally required high temperature. Thus, the



Scheme 19 Proposed mechanistic pathway for formation of *N*-methylanilines **2**

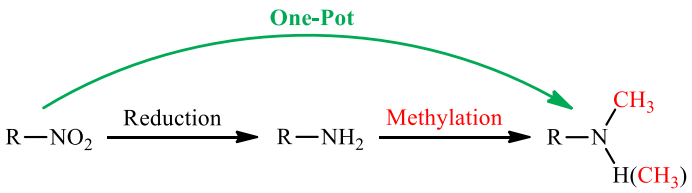


Fig. 1 Synthesis of *N*-methylamines through direct reductive *N*-methylation of nitro compounds

development of new catalytic systems that allow this transformation under milder conditions would be desirable. Moreover, the substrate scope is mainly limited to aromatic nitro compounds. Therefore, without question, there is still further need to study the scope and limitations of this synthetic procedure (Fig. 1).

Acknowledgements This research was funded by the Shaanxi Science and Technology project (Grant No. 2021JQ-861).

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