Highly Selective N-Monomethylanilines Synthesis From Nitroarene and Formaldehyde via Kinetically Excluding of the Thermodynamically Favorable N,N-Dimethylation Reaction

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Highly Selective N-Monomethylanilines Synthesis From Nitroarene and Formaldehyde via Kinetically Excluding of the Thermodynamically Favorable N,N-Dimethylation Reaction

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ABSTRACT: It maintains as a challenging topic for N-monomethylamine synthesis as the N,N-dimethylation reaction is thermodynamically favorable. The kinetically controlled N-monomethylamine synthesis from nitroarene and paraformaldehyde/H_2 is reported with super-high N-monomethylamine selectivity in the presence of a Pd/TiO_2 catalyst. The superior selectivity should be attributed to the preferential adsorption of the primary amine over N-monomethylamine on the Pd/TiO_2 surface, as elucidated by NH_3/Me_2NH-TPD, while the nice catalytic activity could be associated to the good H_2 activation ability and high amine adsorbing

capacity of the catalyst, as elucidated by NH_3-TPD and H_2-TPR tests. Good results were obtained with a variety of nitroarenes containing methyl, methoxyl, hydroxyl, fluoride, trifluoromethyl, ester, and amide substituents as starting materials, and the potential synthetic utility of this protocol in pharmaceutical is illustrated by N-monomethylation of drug molecules, such as clinidipine, nimesulide, procaine and methyl aminosalicylate.

KEYWORDS: nitroarenes, N-monomethylation, selective adsorption, paraformaldehyde, carbonyl group transformation

INTRODUCTION

The majority of the known agrochemicals and pharmaceuticals contain amino groups, which represent key scaffolds in the vast majority of bio-active compounds. In fact, of the top 200 drugs of 2015, about 85% involves nitrogen (N) and/or amino groups.[1] Among the known reactions of amines, the N-methylation of amines is of significant importance to regulate the physicochemical properties of organic molecules including their biological and pharmaceutical activities.[2] Besides these biological functions, N-methylamines are important building blocks in synthesis of bulk and fine chemicals as well as materials.[3] Nevertheless, the highly selective synthesis of N-monomethyl amines remains a tremendous challenge in synthetic organic and catalysis because N-monomethyl amines possess higher reactivity than primary amines and are prone to further transform into N,N-dimethyl amines. Traditionally, primary amines are usually employed as starting materials for the selective synthesis of N-monomethylamines with a variety of methylating agents, such as MeX, CO_2, methanol, dimethyl carbonate (DMC), HCOOH, and HCHO.[4] Although a number of nice methods have been developed, the known methodologies still suffer from rigorous reaction conditions, low selectivity or low atom economy.

As it is well-known, nitro compounds are cheap and readily available, and the reduction of nitroarenes is one of the most commonly used approaches to synthesize primary amines.[5] Thus, it is an attractive to perform the one-pot N-monomethylation reactions using nitro compounds as the flexible feedstock. To date, however, only a few catalytic systems dealing with N-monomethylation of nitro compounds have been reported. By using CO_2 and H_2 as methylating agent, the N-monomethylation of nitroarenes can be realized with Pd/CuZrOx as catalyst. Nevertheless, it suffers from high pressure (3.5 MPa) and high temperature (150 ^oC).[6] Besides CO_2, methanol could also be used as a methylating reagent. One example of N-monomethylation of 4-nitrotoluene with methanol using $[Ru(p\text{-cymene})Cl_2]_2$, DPPB, and K_2CO_3 catalyst system was revealed.[7] Recently, the tandem reductive N-monomethylation of nitroarenes with methanol was reported in the presence of Ru(II) complexes, bearing phenpy-OMe ligand and NaOMe.[8] However, the rigorous reaction conditions and the necessity using of complex organic ligands/base reduced the appeal of these protocols. Compared with above methods, one-pot reductive N-monomethylation of nitroarene with formaldehyde represents one of the economic and clean pathways. However, normally, only N-monoalkylation of nitro compounds with higher aldehydes[9] were reported, and poor results were obtained if HCHO was used as the methyl source.[10] *Till now, no general methodology of highly selective N-monomethylation of nitroarene with HCHO has been developed, which is mainly limited by the further N-methylation of the desired molecule to N,N-dimethylamine.* The key point to realize the selective N-monomethylamine synthesis is to find the way to overcome the thermodynamically favorable N,N-dimethylation. Undoubtedly, kinetic regulation seems to be the sole method.

In order to kinetically regulate the reaction, the reaction steps should be first clarified. In general, the reductive N-methylation of nitroarenes with paraformaldehyde/H_2 proceeds through

three main consecutive reactions, i.e., hydrogenation of nitroarene to generate primary amine, N-monomethylation of primary amine and further N-methylation of the N-monomethylamine to N,N-dimethylamine (Figure 1a). Out of doubt, the adsorption of reactant molecule onto the surface of catalyst is the initial step of the reaction with heterogeneous catalyst, and the hydrogen bond plays an important role in this process. Noteworthy, primary amine possesses more hydrogen atoms than N-monomethylamine, which may result in preferential adsorption and difficult desorption of primary amine while nondominant adsorption and easy desorption of N-monomethylamine on the catalyst surface.[11] This inspired us that an active and selective catalyst might be designed and prepared for the highly selective N-monomethylamine synthesis via kenetic inhibition of N,N-dimethylation via nondominant adsorption and easy desorption of N-monomethylamine on the catalyst surface (Figure 1a). Typically, metal oxides and carbon possess abundance of oxygen species on their surfaces, which are benefiting to form hydrogen bond, and supported nano-Pd is potentially an active catalyst for nitroarene reduction and the following N-methylation reaction. So we envisioned that nano-Pd loaded on appropriate support might provide a suitable catalyst for reductive N-monomethylation of nitroarene with HCHO/H_2.

Based on the above discussions, herein, a series of supported nano-Pd catalysts were prepared, in which Pd/TiO_2 exhibited excellent activity and superior selectivity in N-monomethylation of nitroarenes with paraformaldehyde/H_2 enabled by the selective adsorption of primary amine intermediate onto the catalyst surface, and the easy desorption of N-monomethylamine (Figure 1b).

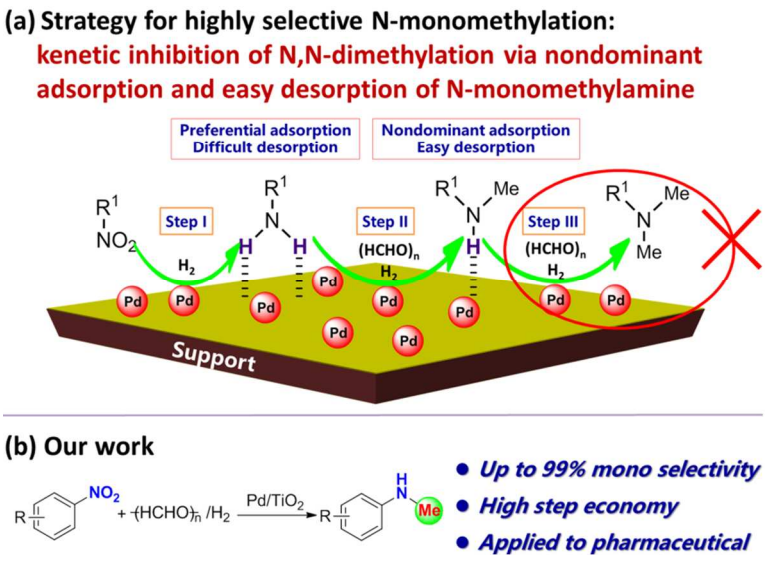


Figure 1. (a) Strategy for highly selective N-monomethylation. (b). Selective N-monomethylation of nitroarenes with HCHO/H_2.

EXPERIMENTAL SECTION

Catalyst preparation

The supported Pd catalysts were prepared with deposition–precipitation method with TiO_2, γ-Al_2O_3, C, SiO_2, Fe_2O_3, and CuO as supports. TiO_2 (0.5 g, P25, J&K Scientific, anatase/rutile = 80/20,) was dispersed in deionized water (25 mL) and K_2PdCl_4 aqueous solution (1.0 mL, [Pd] 5.0 mg/ mL) were added into the solution under vigorous stirring. The pH value was adjusted to about 10 using 0.2 M NaOH and the solution was stirred for another 3 h at room temperature. Then 4.0 mL of hydrazine solution (hydrazine/H_2O = 1/3 V/V) was added to the solution and stirred for 4 h. The solid sample was recovered by centrifugation and washed with water. The obtained solid was dried at 80 ^oC for 12 h. A grey solid sample was obtained and denoted as 1% Pd/TiO_2. The other catalysts were prepared with the same operations.

Characterization.

XRD measurements were conducted by using a STADIP automated transmission diffractometer (STOE) equipped with an incident beam curved germanium monochromator with CuKa1 radiation and current of 40 kV and 150 mA, respectively. The XRD patterns were scanned in the 2 Theta range of 10-90 ^{o}C. XPS were obtained using a VG ES-CALAB 210 instrument equipped with a dual Mg/Al anode X-ray source, a hemispherical capacitor analyzer, and a 5 keV Ar^{+} iron gun. The electron binding energy was referenced to the C1s peak at 284.8 eV. The background pressure in the chamber was less than 10-7 Pa. The peaks were fitted by Gaussian–Lorentzian curves after a Shirley background subtraction. For quantitative analysis, the peak area was divided by the element-specific Scofield factor and the transmission function of the analyzer. The BET surface area measurements were performed on a Quantachrome IQ_2 at the temperature of 77 K. The pore size distribution was calculated from the desorption isotherm by using the Barrett, Joyner, and Halenda (BJH) method. Prior to measurements, the samples were degassed at 300 ^{o}C for 3 h, at a rate of 10 ^{o}C•min^{-1}. TEM was carried out by using a Tecnai G2 F30 S-Twin transmission electron microscope operating at 300 kV. For TEM investigations, the catalysts were dispersed in ethanol by ultrasonication and deposited on carbon-coated copper grids. Temperature programmed reduction (TPR) experiments were performed on a Quantachrome IQ_2. 30 mg of catalyst was placed in a quartz tube, and it was heated up to 350 ^{o}C under 20 mL•min^{-1} O_2 flow (10 ^{o}C•min^{-1}) and maintained 100 min. The sample was cooled to room temperature and purged with highly pure Ar for 1 h. Then it was reduced with 10% H_2 (balanced with N_2) with the increasing of the temperature to 350 ^{o}C (10 ^{o}C •min^{-1}). The amount of hydrogen uptake was monitored on-line by a TCD detector and recorded as a function of temperature. NH_3-TPD and $HNMe_2$-TPD were carried out on a Micromeritics 2750

chemisorption system. The weighed sample (100 mg) was pretreated at 450 ^{o}C for 1 h under He and cooled to 20 ^{o}C. The NH_3 gas was introduced instead of He at this temperature for 1 h to ensure the saturation adsorption of NH_3. The sample was then purged with He for 1 h until the signal returned to the baseline as monitored by a thermal conductivity detector (TCD). The desorption curve of NH_3 was acquired by heating the sample from 20 ^{o}C to 600 ^{o}C at 10 ^{o}C•min^{-1} under He with the flow rate of 30 ml•min^{-1}. NMR spectra were measured by using a Bruker ARX 400 or ARX 100 spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C). Chemical shifts were reported in parts per million (ppm) down field from TMS with the solvent resonance as the internal standard. Coupling constants (J) were reported in Hz and refered to apparent peak multiplications.

Catalytic performance test

A mixture of nitroarenens (1.0 mmol), paraformaldehyde (75 mg, 2.5 mmol), 1% Pd/TiO_2 (40 mg) and 1,4-dioxane (4 mL) were added a glass tube which was placed in an 100 mL autoclave. Then the autoclave was purged and charged with H_2 (1.0 MPa) three times. The reaction mixture was stirred at 40 ^{o}C for 6 h. Then, the autoclave was cooled to room temperature and the pressure was carefully released. Subsequently, the reaction mixture was diluted with 10 mL ethyl acetate for quantitative analysis by GC-MS (Agilent 7890B-5977A).

The procedure for recovery of catalyst

The Pd/TiO_2 catalyst was separated from the reaction mixtures by centrifuging, washed by using 1,4-dioxane (10 mL x 3) and H_2O (10 mL x 2), dried at 80 ^{o}C for 5 h and then reused for the next run. The catalyst can be recovered and reused for at least 3 times without obvious loss in catalytic performance, providing the desired product in 90% yield at the 3rd run.

RESULTS AND DISCUSSION

The supported Pd catalysts were characterized by XRD, TEM, XPS and N_2 adsorption-desorption instruments to reveal their structures. XRD measurements showed neither palladium oxide nor metallic palladium diffraction pattern was detectable in all the catalysts (Figure S1), which might be attributed to the low Pd loadings or that the Pd species were amorphous and highly dispersed. The morphologies of the catalysts were further characterized by TEM (Figure 2 and Figure S2). The TEM results revealed that the Pd nanoparticles homogeneously dispersed on TiO_2 and have an average diameter of 2-4 nm in both fresh Pd/TiO_2 and Pd/TiO_2 used three times, respectively. Next, the HR-TEM characterizations (Figure S3) revealed that these Pd particles are amorphous, which is confirmed by the XRD in Figure S1. It might be attributed to the low catalyst preparation temperature, i.e., 80 ^{o}C. So the crystallizing degree of palladium particle should be low. We then performed the elemental distribution using high-angle annular dark-field transmission electron microscopy (HAADFSTEM) and the results are shown in Figure 3. The mappings clearly describe that Ti, O and Pd are uniformly distributed in the Pd/TiO_2 catalyst. Moreover, XPS studies of the catalysts were performed to determine the chemical state of Pd nano-particles. As shown in Figure 4 and Figure S4, weak peaks of Pd 3d5/2 were found in Pd/TiO_2, Pd/Al_2O_3, Pd/Fe_2O_3 and Pd/TiO_2 used three times but not observable in Pd/C and Pd/SiO_2, which might be attributed to the lower palladium loadings. The Pd 3d5/2 signals of fresh Pd/TiO_2 and used Pd/TiO_2 catalysts appeared at 334.8 and 334.6 eV, respectively, which suggested that metallic Pd was mainly formed on the surface of catalysts. The XPS spectra of catalysts Pd/Al_2O_3, Pd/Fe_2O_3 and Pd/CuO support the formation of metallic Pd, too. The N_2 adsorption-desorption tests (Figure S5) showed that the BET surface areas of the catalysts (Table

S1) were in the range of 8-280 m^2/g, in which the BET surface area of Pd/TiO_2 is 60.72 m^2/g. So the high activity of Pd/TiO_2 should not be attributed to its high surface area.

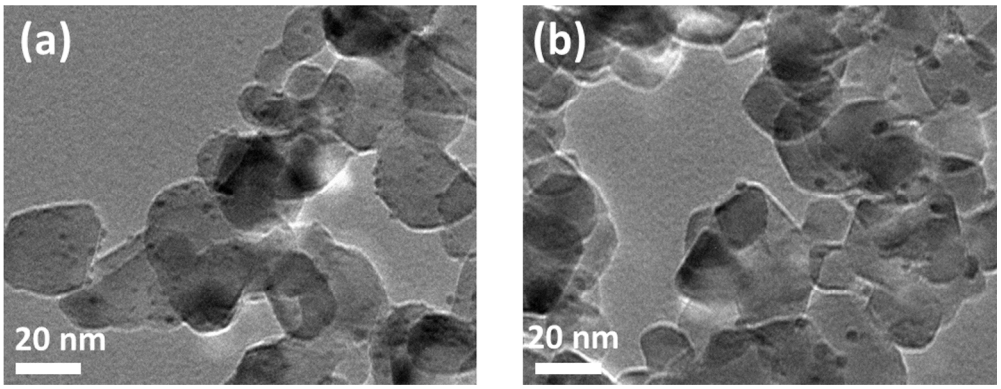


Figure 2. TEM images of the catalysts. (a) fresh 1% Pd/TiO_2. (b) used three times 1% Pd/TiO_2.

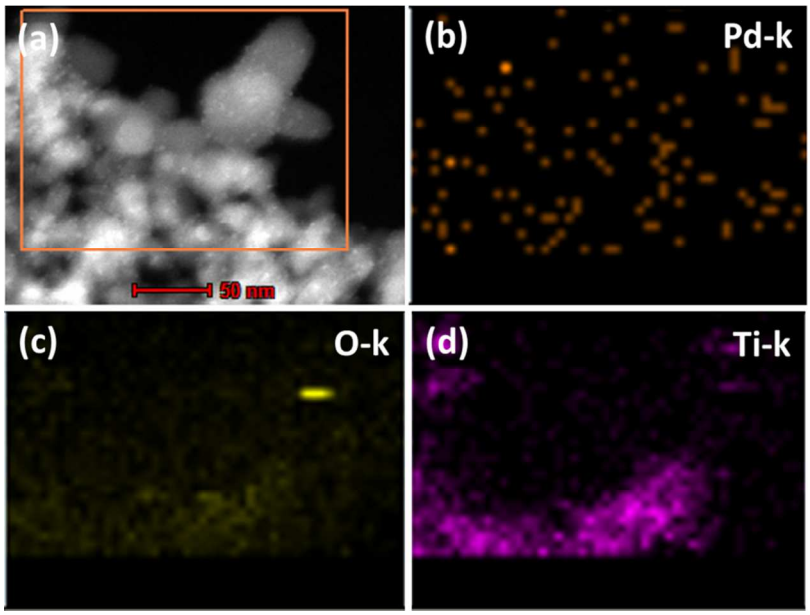


Figure 3. (a) HAADF-STEM images of 1% Pd/TiO_2 and (b), (c), (d) the corresponding EDX mapping of orange rectangular area from (a).

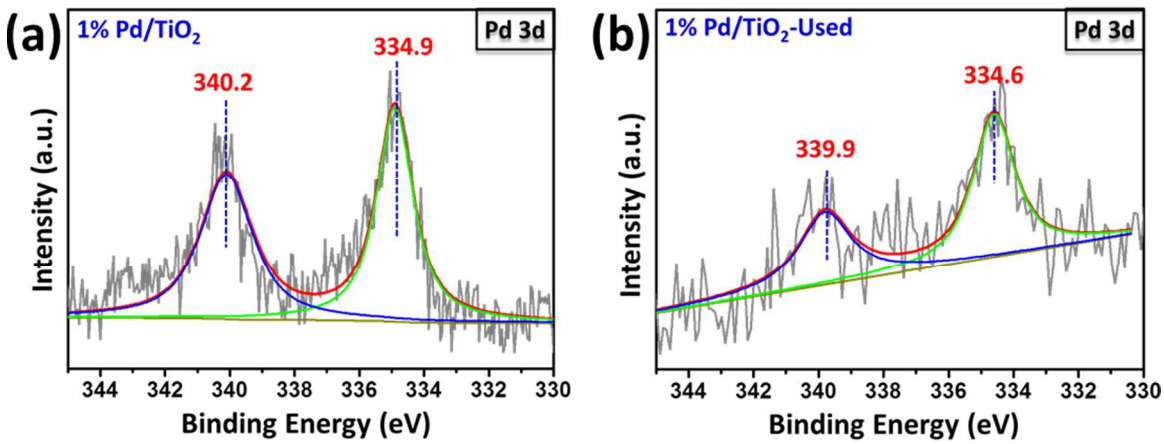
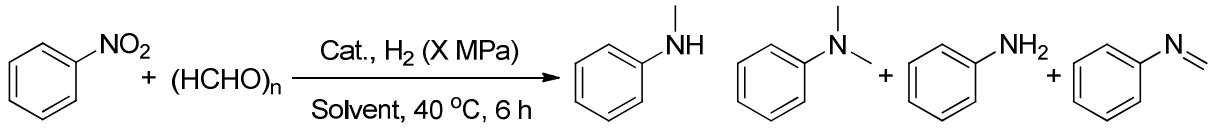


Figure 4. XPS spectra of the catalysts. (a) fresh 1% Pd/TiO_2. (b) used three times 1% Pd/TiO_2.

To search for the best catalyst in terms of selectivity toward N-monomethylation, we began our exploration with reductive N-monomethylation of nitrobenzene with paraformaldehyde and H_2 as the model reaction (Table 1). The influence of the solvent on the reactivity and selectivity of this reaction was first investigated (Table 1, entries 1-5). Although 100% conversions of nitrobenzene were observed in all the reactions, it can be seen that 65.1% N-monomethylaniline selectivity and excellent ratio (65.1 : 0.9) between N-monomethylaniline and N,N-dimethylaniline were achieved when 1,4-dioxane was used (entry 5). Following, the catalytic performance of nano-Pd catalysts with different supports was tested (entries 6-10). Clearly, Pd/TiO_2 exhibits the best catalytic performance. If other catalysts including $Pd/\gamma\text{-}Al_2O_3$, Pd/C, Pd/SiO_2, and Pd/Fe_2O_3 were employed, lower yields of N-monomethylaniline were obtained. It should be noted that the ratio between N-monomethylaniline and N-dimethylaniline was decreased when the yield of N-methylaniline was reduced. It means that the selectivity of N-methylaniline is positively associated with the catalytic transformation of aniline to N-methylaniline. TOF values of different catalysts have been calculated for comparison in Table S2. It can be seen that TOF value ranges from 27 to 81. Although TOF up to 81 per hour was

obtained in the presence of Pd/Fe_2O_3 catalyst, the ratios between N-monomethylaniline and N,N-dimethylaniline is only 17:1. Considering the TOF numbers and the ratios between N-monomethylaniline and N,N-dimethylaniline, Pd/TiO_2 gives the best results. In addition, the reducing of the H_2 pressure results in lower yield of N-monomethylaniline (entries 11-12). Surprisingly, the selectivity to N-monomethylamine sharply decreased to 54% if the reaction time was prolonged to 12 h (entry 13). Importantly, there is no aniline observable at this time, which might be the reason for the fast decreasing of the selectivity to the desired product. These results support our hypothesis that the presence of primary amine (aniline) may be helpful to the high selectivity of N-monomethyl amine and the selectivity would sharply decrease if the primary amine was consumed, which was possibly regulated by the preferential adsorption of primary amine onto the catalyst surface.

Table 1. Optimization of the reaction conditions[a]



1a **2a** **3a** **4a** **5a** **6a**

Entry	Cat.	Solvent	Conv. [%][b]	Sel.[%][b]			
				3a	**4a**	**5a**	**6a**
1	Pd/TiO_2	EtOH	100	13.0	71.0	-	-
2	Pd/TiO_2	EA	100	25.0	75.0	--	--
3	Pd/TiO_2	cyclohexane	100	15.0	77.0	--	8.0
4	Pd/TiO_2	toluene	100	3.0	79.0	--	18.0
5	Pd/TiO_2	1,4-dioxane	100	65.1	0.9	33.0	--
6	Pd/Al_2O_3	1,4-dioxane	100	63.4	1.4	32.9	2.3

7	Pd/C	1,4-dioxane	100	42.6	1.4	55.0	1.0
8	Pd/SiO_2	1,4-dioxane	100	38.4	1.6	57.0	3.0
9	Pd/Fe_2O_3	1,4-dioxane	100	29.3	1.7	55.0	14.0
10	Pd/CuO	1,4-dioxane	n.r	--	--	--	--
11[c]	Pd/TiO_2	1,4-dioxane	100	57.1	0.9	42.0	--
12[d]	Pd/TiO_2	1,4-dioxane	100	54.5	0.5	37.0	8.0
13[e]	Pd/TiO_2	1,4-dioxane	100	54.0	46.0	--	--

[a]Reaction conditions: nitrobenzene (1.0 mmol), paraformaldehyde (2.5 mmol), catalyst (40 mg), H_2 (1.0 MPa), solvent (4.0 mL), 40 ^oC, 6 h. [b]Determined by GC-MS. [c]0.7 MPa. [d]0.4 MPa. [e]Reacted for 12 h.

To reveal whether the reaction takes place in accordance with the above assumptions, the reaction of nitrobenzene with paraformaldehyde and H_2 was traced by GC-MS to check the possible reaction intermediates with varied reaction times. As shown in Figure 5a, the hydrogenation of nitrobenzene was a fast reaction and it was completely converted to aniline in 0.5 h. Then, the aniline gradually decreased to 3.0% after 9.5 h. Meanwhile, the yield of N-monomethylaniline gradually increased to 91.6% after 9.5 h. Moreover, the concentration of N-methyleneaniline maintains low, suggesting that the reaction of aniline with aldehyde to give imine rather than hydrogenation of imine to N-methylaniline was the rate-limiting step. It should be noted that the yield of N,N-dimethyl aniline is negligible if the aniline exists in the reaction system. When the aniline was exhausted, the amount of N,N-dimethyl aniline sharply increased and the amount of N-methylaniline dramatically decreased. These results confirm the above observations, and support our hypothesis that the preferential adsorption of aniline onto Pd/TiO_2 surface over N-monomethylaniline might be the main reason to gain high N-monomethylamine selectivity.

To verify these, NH_3-TPD and $(Me)_2NH$-TPD experiments were performed to check if the proton quantities in the molecules influence their adsorption onto the catalyst surface. The results of the adsorption of ammonia and dimethylamine on Pd/TiO_2 are shown in Figure 5b and Figure S6. It can be observed that the adsorbing quantity of ammonia is 0.513 mmol/g Pd/TiO_2 while the adsorbing quantity of dimethylamine is only 0.156 mmol/g Pd/TiO_2. Thus primary amine with more protons is preferentially adsorbed onto Pd/TiO_2 surface, and therefore high selectivity to N-monomethylation can be maintained before the complete consumption of primary amine.

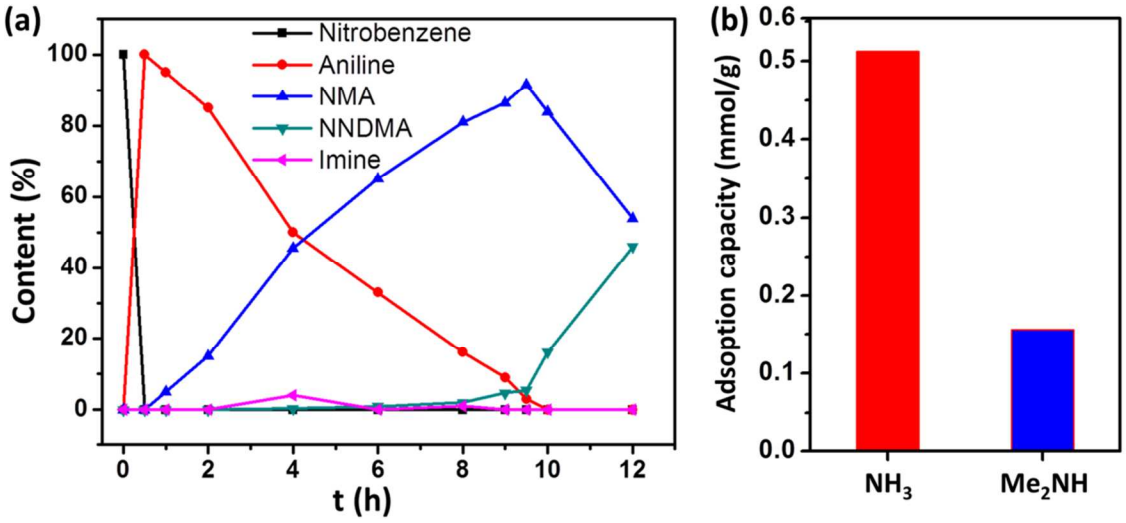
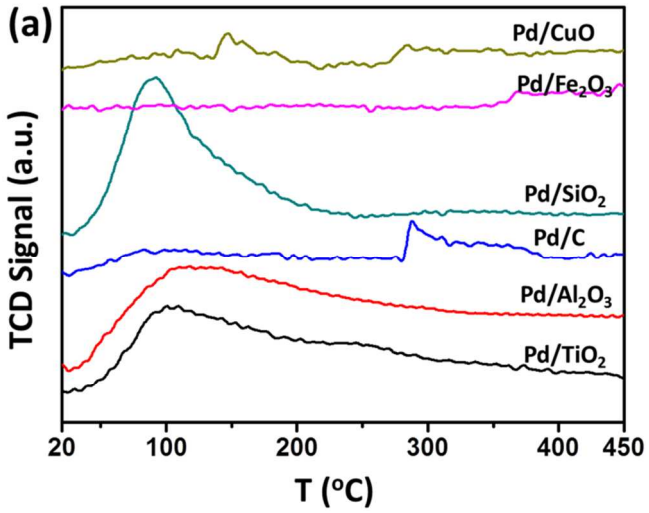


Figure 5. (a) Products distribution during the one-pot reductive methylation of nitrobenzene with HCHO and H_2. Reaction conditions: nitrobenzene (1.0 mmol), paraformaldehyde (2.5 mmol), 1% Pd/TiO_2 (40 mg), H_2 (1.0 MPa), 1,4-dioxane (4.0 mL), 40 ℃. (b) Adsorption capacity of NH_3 and $(Me)_2NH$-TPD on the Pd/TiO_2.

In addition, it should be noted that both the amine adsorbing capacity and H_2 activation ability of the catalyst are crucial to gain nice catalytic performance in the reductive N-methylation reaction. Thus, the NH_3-TPD and H_2-TPR characterizations were investigated to understand the catalytic performance of different catalysts (Figure 5). Normally, desorption below 100 ^oC

should be attributed to physical adsorption. Therefore, we mainly compare the desorption data of different catalyst above 100 °C. The NH_3-TPD results suggested that the order of NH_3 adsorption quantity on different catalysts is $Pd/Al_2O_3 \approx Pd/TiO_2 > Pd/SiO_2 >> Pd/C > Pd/CuO > Pd/Fe_2O_3$ (Figure 6a), while the H_2-TPR results suggested that the order of active palladium quantity for H_2 activation is $Pd/TiO_2 > Pd/Al_2O_3 > Pd/SiO_2 > Pd/C > Pd/Fe_2O_3 > Pd/CuO$ (Figure 6b). However, as the reaction temperature in this work is around 60 °C, so only those palladium species active around 60 °C can be involved in the reductive N-methylation of nitrobenzene. Clearly, Pd/TiO_2 and Pd/Fe_2O_3 have more active Pd species than other catalysts in this range. So, we could draw conclusion that the high activity of Pd/TiO_2 should be contributed to its good amine adsorbing capacity, and excellent hydrogen activation performance under our reaction conditions. As to Pd/Fe_2O_3, the poor amine adsorption ability should be responsible for its low activity in the reductive N-monomethylation reaction.



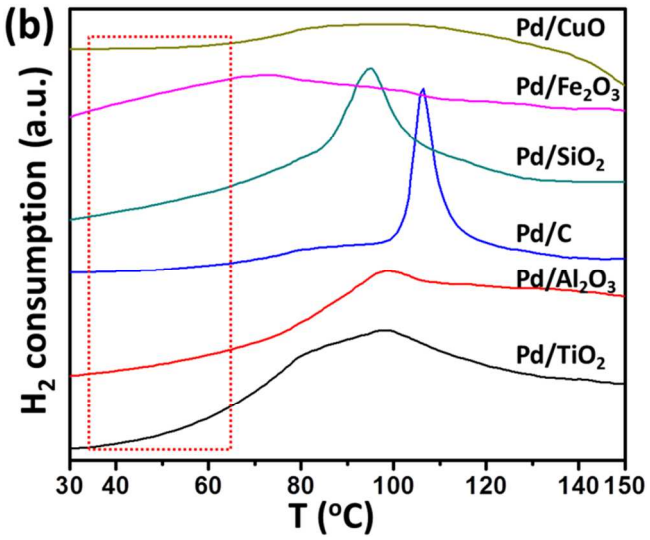


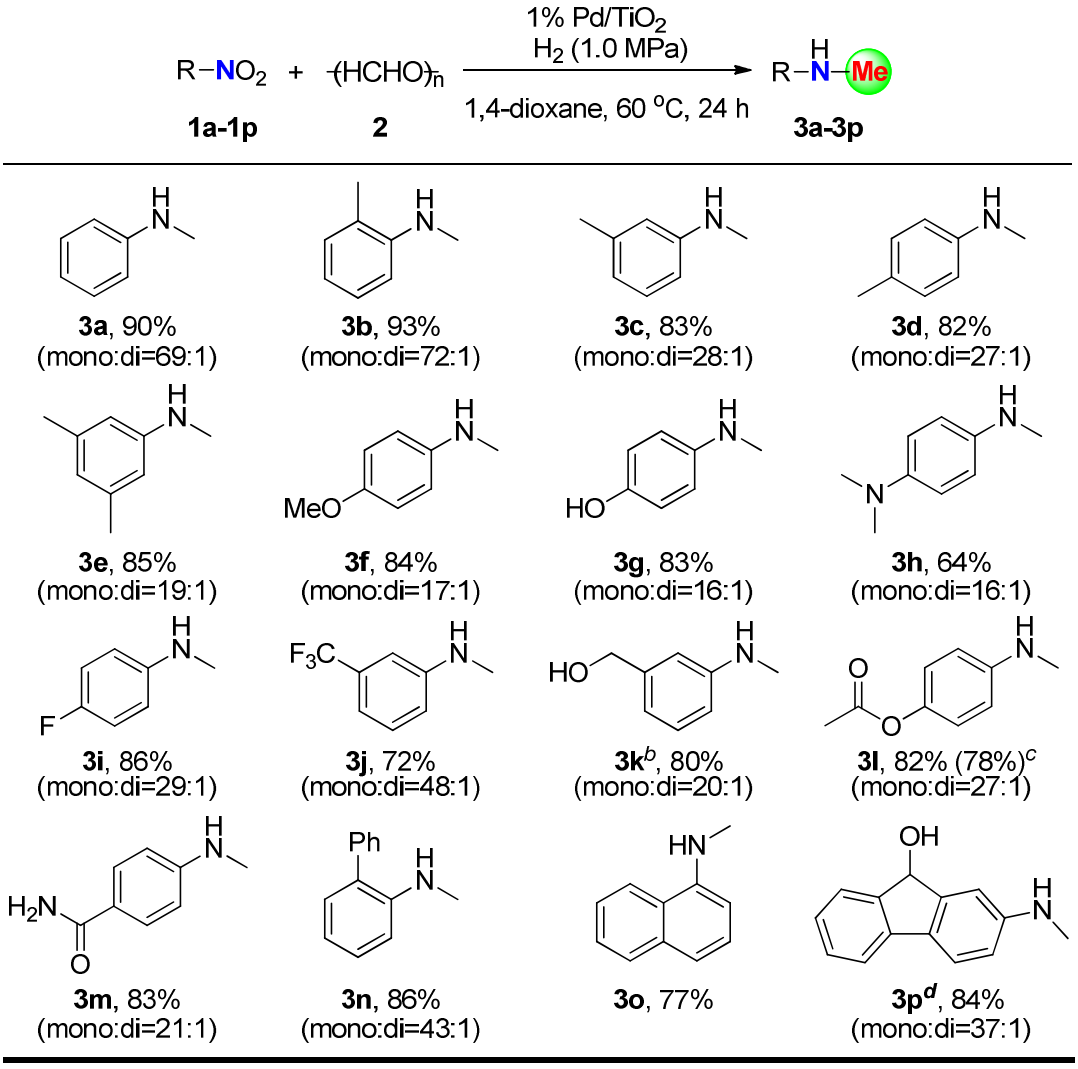
Figure 6. (a) NH_3-TPD profiles of the catalyst. (b) H_2-TPR profiles of various supported palladium catalysts.

Continued from the above discussions, now we could draw a definitive conclusion that high selectivity of N-monomethylamine would be achieved if aniline maintains in the reaction system. Therefore, to make the operation simple, the reductive N-monomethylation reaction was performed with 1.1 equiv., of nitrobenzene and 1.0 equiv., of paraformaldehyde in the presence of 40 mg 1% Pd/TiO_2 under 1.0 MPa H_2 in 1,4-dioxane at 60 °C for 24 h. To our delight, 90% yield of N-monomethylaniline was obtained. Importantly, the catalyst can be recovered and reused for at least 3 times without obvious loss in catalytic performance, providing the desired product in 90% yield at the 3rd run.

With the optimized conditions in hand, the selective N-monomethylation of various nitroarenes with paraformaldehyde and H_2 was investigated. As shown in Table 2, the nitroarenes with both electron-withdrawing and electron-donating groups on the phenyl ring underwent the reductive N-methylation to the corresponding N-monomethylamines with good to excellent yields. Reductive N-monomethylation of electron-rich methyl-, hydroxyl, methoxy and dimethylamino

substituted nitroarenes proceeded smoothly to provide the corresponding products in 82-93% yields with a mono: di ratio of 16:1 to 72:1 (**3b**-**3h**). Clearly, the electron donating groups on nitroarenes led to slight decrease of the selectivity to N-monomethylanilines. For example, the presence of methoxy group in para position led to a mono: di ratio of 17: 1 in N-monomethylation (**3f**). The steric hindrance at the orth position of the nitrobenzene showed a positive effect on the selectivity of this transformation, and 2-methylnitrobenzene as starting material gave an excellent mono: di ratio of 72: 1 (**3b**). Electron-deficient nitroarenes bearing fluoride, trifluoromethyl, ester and amide groups also proceeded well, affording their corresponding products in good yields with excellent selectivities, too (**3i**-**3m**). In the case of 3-nitrobenzaldehyde and 2-nitro-9-fuorenone, the reduction of the formyl (**3k**) and ketone (**3p**) groups was observed. In addition, the fused-ring 2-nitronaphthalene was also successfully converted to the corresponding N-monomethylamine in 77% yield (**3o**).

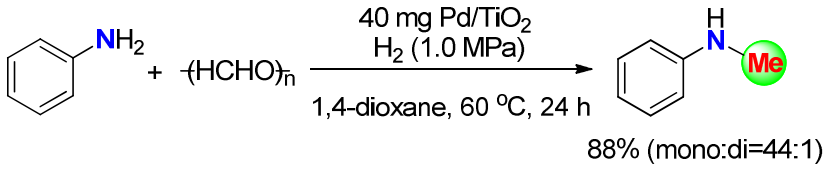
Table 2. Results of the N-monomethylation of nitroarenes with HCHO/H_2[a]



[a]Reaction conditions: nitroarene (1.1 mmol), paraformaldehyde (1.0 mmol), 1% Pd/TiO_2 (40 mg), H_2 (1.0 Mpa), 1,4-dioxane (4.0 mL), 60 ℃, 24 h. The mono/di methyl amines ratios within parentheses were determined by ^{1}H NMR analysis. [b]Reduction of formyl. [c]Isolated yield. [d]Reduction of ketone.

Importantly, this protocol is also applicable in the reductive N-monomethylation of aniline and high N-monomethylaniline selec-tivity and yield are obtained (Scheme 1).

Scheme 1. Pd/TiO_2 catalyzed highly selective N-monomethylation of aniline with HCHO/H_2



To demonstrate the potential application of this methodology, we performed the selectively N-monomethylation of nitro and amines groups to N-methylated analogues in biological active molecules (Figure 7), as N-methylation is an important tool to regulate the biological and pharmaceutical activities of life science molecules. Notably, the N-monomethylation of clinidipine, which inhibit the flow of extracellular calcium through ion-specific channels that span the cell wall as reduce the systemic vascular resistance and arterial pressure,[12] has been realized with 80% yield (Figure 7a). In addition, the N-monomethylation of nimesulide, a non-steroidal anti-flammatory drug with analgestic and antipyretic properties,[13] has been obtained in 77% yield (Figure 7a). Further, the N-monomethyl moiety has been successfully introduced into procaine and methyl 4-aminosalicylate with up to 95% yield, which are used as anesthetic[14] and antituberculous drugs,[15] respectively (Figure 7b).

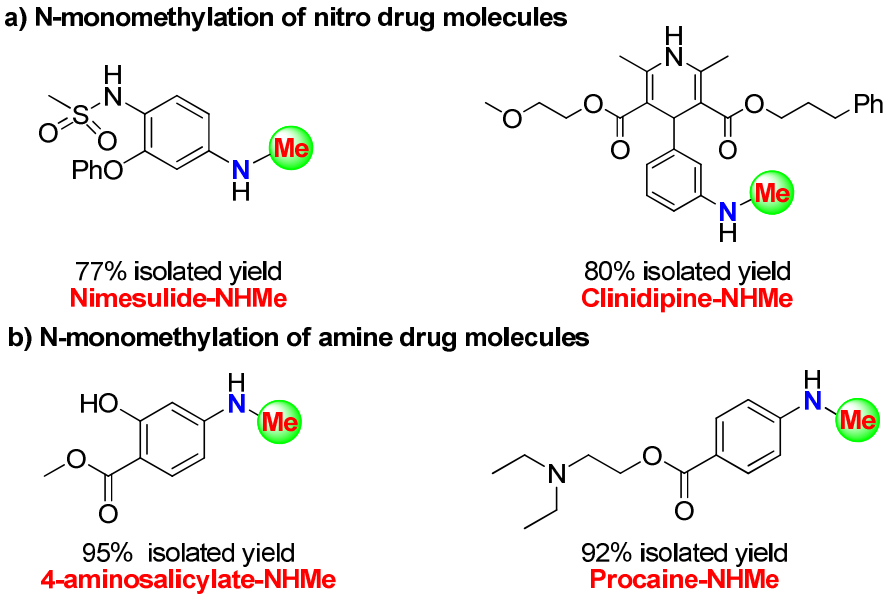


Figure 7. N-Monomethylation of drug molecules. (a) N-momomethylation of Nimesulide and Clinidipine. (b) N-momomethylation of 4-aminosalicylate and Procaine.

CONCLUSIONS

In conclusion, we have developed extraordinarily highly selective N-monomethylation reaction starting from easily available nitroarenes with paraformaldehyde and H_2 using Pd/TiO_2 as catalyst. A series of functional N-monomethylamines were synthesized by applying this simple catalyst system. This work offers a straightforward, step economic and clean methodology for the selective synthesis of N-monomethylamines. The synthetic utility of this reaction is specifically demonstrated using various bio-active molecules including existing pharmaceuticals. The superior selectivity should be attributed to the preferential adsorption of the primary amine over N-monomethylamine on the Pd/TiO_2 surface, as elucidated by NH_3/Me_2NH-TPD, while the nice catalytic activity could be associated to the good H_2 activation ability and high amine adsorbing capacity of the catalyst, as elucidated by NH_3-TPD and H_2-TPR tests.

ASSOCIATED CONTENT

Supporting Information. The following files are available free of charge.

Detailed experimental procedures, characterizations of catalysts and products (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) http://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/Top200PharmaceuticalProductsRetailSales2015LowRes.pdf.

(2) (a) Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. The Methylation Effect in Medicinal Chemistry. *Chem. Rev.* **2011**, *111*, 5215-5246. (b) Chatterjee, J.; Rechenmacher, F.; Kessler, H. N-Methylation of Peptides and Proteins: An Important Element for Modulating Biological Functions. *Angew. Chem., Int. Ed.* **2013**, *52*, 254-269.

(3) (a) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*, Cambridge University Press: Cambridge, 2004. (b) Ricci, A. *Amino Group Chemistry, From Synthesis to the Life Sciences,* Wiley-VCH: Weinheim, 2008. (c) Weissermel, A. K. Arpe, H.-J. *Industrial Organic Chemistry*, Wiley-VCH: Weinheim, 2003. (d) Ali, M. F.; Ali, B. M. E.; Speight, J. G. *Handbook of Industrial Chemistry: Organic Chemicals*, McGraw-Hill Education: New York, 2005.

(4) (a) Tundo, P.; Selva, M. The Chemistry of Dimethyl Carbonate. *Acc. Chem. Res.* **2002**, *35*, 706-716. (b) Selva, M.; Perosa, A. Green Chemistry Metrics: a Comparative Evaluation of Dimethyl Carbonate, Methyl Iodide, Dimethyl Sulfate and Methanol as Methylating Agents. *Green Chem.* **2008**, *10*, 457-467. (c) Li, W.; Wu, X.-F. The Applications of (Para)formaldehyde in Metal-Catalyzed Organic Synthesis. A*dv. Synth. Catal.* **2015**, *357*, 3393-3418. (d) Klankermayer, J.; Wesselbaum, S.; Beydoun, K.; Leitner, W. SelectiveCatalytic Synthesis Using the Combination of Carbon Dioxide and Hydrogen:Catalytic Chess at the Interface of Energy

and Chemistry. *Angew. Chem., Int. Ed.* **2016**, *55*, 7296-7343. (e) Natte, K.; Neumann, H.; Beller, M.; Jagadeesh, R. V. Transition-Metal-Catalyzed Utilization of Methanol as a C1 Source in Organic Synthesis. *Angew. Chem. Int. Ed.* **2017**, *56*, 6384-6394. (f) Li, Y.; Cui, X.; Dong, K.; Junge, K.; Beller, M. Utilization of CO_2 as a C1 Building Block for Catalytic Methylation Reactions. *ACS Catal.* **2017**, *7*, 1077-1086.

(5) (a) Blaser, H.-U.; Siegrist, U.; Steiner, H. *Aromatic Nitro Compounds: Fine Chemicals through Heterogeneou Catalysis*, Sheldon, R. A.; van Bekkum, H. Eds. Wiley-VCH: Weinheim, 2001. (b) Orlandi, M.; Brenna, D.; Harms, R.; Jost, S.; Benaglia, M. Recent Developments in The Reduction of aromatic and aliphatic nitro compounds to amines. *Org. Process Res. Dev.* **2016**. http://dx.doi.org/10.1021/acs.oprd.6b00205.

(6) (a) Cui, X.; Zhang, Y.; Deng, Y.; Shi, F. N-Methylation of Amine and Nitro Compounds with CO_2/H_2 Catalyzed by Pd/CuZrOx under Mild Reaction Conditions. *Chem. Commun.* **2014**, *50*, 13521-13524. (b) Cui, X.; Dai, X.; Zhang, Y.; Deng, Y.; Shi, F. Methylation of Amines, Nitrobenzenes and Aromatic Nitriles with Carbon Dioxide and Molecular hydrogen. *Chem. Sci.* **2014,** *5*, 649-655.

(7) Cui, X.; Zhang, Y.; Shi, F.; Deng, Y. Ruthenium-Catalyzed Nitro and Nitrile Compounds Coupling with Alcohols: Alternative Route for N-Substituted Amine Synthesis. *Chem. Eur. J.* **2011**, *17*, 2587-2591.

(8) Paul, B.; Shee, S.; Chakrabarti, K.; Kundu, S. Tandem Transformation of Nitro Compounds to N-methylated Amines: Greener Strategy for the Utilization of Methanol as a Methylating Agent. *ChemSusChem* **2017**, *10*, 2370-2374.

(9) (a) Zhou, P.; Zhang, Z.; Jiang, L.; Yu, C.; Lv, K.; Sun, J.; Wang, S. A Versatile Cobalt Catalyst for the Reductive Amination of Carbonyl Compounds with Nitro Compounds by

Transfer Hydrogenation. *Appl. Catal. B: Environ.* **2017**, *210*, 522-532. (b) Zhou, P.; Zhang, Z. One-pot Reductive Amination of Carbonyl Compounds with Nitro Compounds by Transfer Hydrogenation over Co-Nx as Catalyst. *ChemSusChem* **2017**, *10*, 1892-1897. (c) Zhang, Q.; Li, S.-S.; Zhu, M.-M.; Liu, Y.-M.; He, H.-Y.; Cao, Y. Direct Reductive Amination of Aldehydes with Nitroarenes Using Bio-renewable Formic Acid as a Hydrogen Source. *Green Chem.* **2016**, *18*, 2507-2513. (d) Zhou, X.; Li, X.; Jiao, L.; Huo, H.; Li, R. Programmed Synthesis Palladium Supported on Fe3O4@C: An Efficient and Heterogeneous Recyclable Catalyst for One-Pot Reductive Amination of Aldehydes with Nitroarenes in Aqueous Reaction Medium. *Catal. Lett.* **2015**, *145*, 1591-1599. (e) Pisiewicz, S.; Stemmler, T.; Surkus, A.-E.; Junge, K.; Beller, M. Synthesis of Amines by Reductive Amination of Aldehydes and Ketones using Co_3O_4/NGr@C Catalyst. *ChemCatChem* **2015**, *7*, 62-64. (f) Park, J. W.; Chung, Y. K. Hydrogen-Free Cobalt−Rhodium Heterobimetallic NanoparticleCatalyzed Reductive Amination of Aldehydes and Ketones with Amines and Nitroarenes in the Presence of Carbon Monoxide and Water. *ACS Catal.* **2015**, *5*, 4846-4850. (g) Artiukha, E. A.; Nuzhdin, A. L.; Bukhtiyarova, G. A.; Zaytsev, S. Y.; Plyusnin, P. E.; Shubin, Y. V.; Bukhtiyarov, V. I. One-pot Reductive Amination of Aldehydes with Nitroarenes over an Au/Al_2O_3 Catalyst in a Continuous Flow Reactor. *Catal. Sci. Technol.* **2015**, *5*, 4741-4745. (h) Stemmler, T.; Westerhaus, F. A.; Surkus, A.-E.; Pohl, M.-M.; Junge, K.; Beller, M. General and Selective Reductive Amination of Carbonyl Compounds Using a Core–shell Structured Co_3O_4/NGr@C Catalys. *Green Chem.* **2014**, *16*, 4535-4540. (i) Nasrollahzadeh, M. Green Synthesis and Catalytic Properties of Palladium Nanoparticles for the Direct Reductive Amination of Aldehydes and Hydrogenation of Unsaturated Ketones. *New J. Chem.* **2014**, *38*, 5544-5550. (j) Wei, S.; Dong, Z.; Ma, Z.; Sun, J.; Ma, J. Palladium Supported on Magnetic Nanoparticles as Recoverable Catalyst for One-pot Reductive Amination of

Aldehydes with Nitroarenes under Ambient Conditions. *Catal. Commun.* **2013**, *30*, 40-44. (k) Li, L.; Niu, Z.; Cai, S.; Zhi, Y.; Li, H.; Rong, H.; Liu, L.; Liu, L.; He, W.; Li, Y. A PdAg Bimetallic Nanocatalyst for Selective Reductive Amination of Nitroarenes. *Chem. Commun.* **2013**, *49*, 6843-6845. (l) Sreedhar, B.; Rawat, V. S. Mild and Efficient PtO_2-catalyzed One-pot Reductive Mono-N-alkylation of Nitroarenes. *Synth. Commun.* **2012**, *42*, 2490-2502. (m) Hu, L.; Cao, X.; Ge, D.; Hong, H.; Guo, Z.; Chen, L.; Sun, X.; Tang, J.; Zheng, J.; Lu, J.; Gu, H. Ultrathin Platinum Nanowire Catalysts for Direct C-N Coupling of Carbonyls with Aromatic Nitro Compounds under 1 Bar of Hydrogen. *Chem. Eur. J.* **2011**, *17*, 14283-14287. (n) Dell'Anna, M. M.; Mastrorilli, P.; Rizzuti, A.; Leonelli, C. One-pot Synthesis of Aniline Derivatives from Nitroarenes under Mild Conditions Promoted by a Recyclable Polymer-supported Palladium catalyst. *Appl. Catal. A.* **2011**, *401*, 134-140. (o) Sreedhar, B.; Reddy, P. S.; Devi, D. K. Direct One-Pot Reductive Amination of Aldehydes with Nitroarenes in a Domino Fashion: Catalysis by Gum-Acacia-Stabilized Palladium Nanoparticles. *J. Org. Chem.* **2009**, *74*, 8806-8809. (p) Sydnes, M. O.; Kuse, M.; Isobe, M. Reductive Monoalkylation of Nitro Aryls in One-pot. *Tetrahedron* **2008**, *64*, 6406-6414. (q) Bae, J. W.; Cho, Y. J.; Lee, S. H.; Yoon, C.-O. M.; Yoon, C. M. A One-pot Synthesis of N-alkylaminobenzenes from Nitroaromatics: Reduction Followed by Reductive Amination Using $B_{10}H_{14}$. *Chem. Commun.* **2000**, 1857-1858.

(10) (a) Byun, E.; Hong, B.; De Castro, K. A.; Lim, M.; Rhee, H. One-Pot Reductive Mono-N-alkylation of Aniline and Nitroarene Derivatives Using Aldehydes. *J. Org. Chem.* **2007**, *72*, 9815-9817. (b) Sydnes, M. O.; Isobe, M. One-pot Reductive Monoalkylation of Nitro Aryls with Hydrogen over Pd/C. *Tetrahedron Lett.* **2008**, *49*, 1199-1202.

(11) Tsyganenko, A. A.; Pozdnyakov, D. V.; Filimonov, V. N. Infred Study of Surface Species Arising from ammonia adsorption on Oxide surfaces. *J. Mol. Struct.* **1975**, *29*, 299-318.

(12) Elliott, W. J.; Ram, C. V. S. Calcium Channel Blockers. *J. Clin. Hypertens.* **2011**, *13*, 687–689.

(13) Traversa, G.; Bianchi, C.; Da Cas, R.; Abraha, I.; Menniti-Ippolito, F.;Venegoni. M. Cohort Study of Hepatotoxicity Associated with Nimesulide and Other Non-steroidal Anti-inflammatory Drugs. *BMJ* **2003**, *327*, 18–22.

(14) Schmidt, R. M.; Rosenkranz, H. S. Antimicrobial Activity of Local Anesthetics: Lidocaine and Procaine. *J Infect Dis* **1970**, *121*, 597-607.

(15) Sriram, D.; Yogeeswari, P.; Thirumurugan, R. Antituberculous Activity of Some Aryl Semicarbazone Derivatives. *Bioorg. Med. Chem. Lett,* **2004**, *14*, 3923-3924

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