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Pd/C-catalyzed transfer hydrogenation of aromatic nitro compounds using methanol as a hydrogen source

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A B S T R A C T

We describe the selective transfer hydrogenation of aromatic nitro compounds to anilines using Pd/C as a heterogeneous catalyst with methanol as a green reductant. Nitroarenes bearing both electron-releasing and electron-deficient groups are amenable to this method and enable the synthesis of corresponding arylamines in moderate to good selectivities including the synthesis of butamben, a local anesthictic drug molecule. This new concise protocol is simple, ligand-free and does not require the supply of external molecular hydrogen.

1. Introduction

Transfer hydrogenation has been regarded as one of the most attractive chemical transformations in organic synthesis. This is due to its inherent advantages, such as ready availability of hydrogen donors, ease of handling and avoidance of high-pressure equipment [1,2]. Also, the transportation and distribution of molecular hydrogen cylinders might sometimes result in increase of costs for small-scale industries and research laboratories [3]. Considering safety obstacles and easy operability, a variety of transfer hydrogen sources were identified on laboratory scale [1]. For instance, formic acid [4], hydrazine hydrate [5], formates [6], silanes [7], ammonia borane [8], and many other common hydrogen donors that can supply hydrogen atom(s) to reduce various suitable functional moieties [1]. However, these hydrogen donors are relatively expensive and also generates significant waste or by products. In the last two years, alcohols [9,10], especially simple methanol have evolved as an attractive transfer hydrogen source [11–13]. Methanol is produced abundantly from both fossil and renewable sources and serves as an outstanding C_1 building block for the manufacture of important bulk and fine chemicals [14–17]. Also, methanol can be utilized as an excellent liquid organic hydrogen carrier (LOHC) for fuel cell applications [18].

Aniline bearing functional compounds are extensively used as key industrial intermediates in chemical sector [19]. The majority of aniline derivatives are produced on industrial-scale *via* direct hydrogenation of nitroarenes [3], especially in the fields like pharmaceuticals, agricultural products, fragrances, and polymers (Fig. 1) [19–21]. In comparison to the direct hydrogenation process, catalytic transfer hydrogenation could be very interesting in both lab-scale and industrial usage if environmental and sustainability are shown to be superior to the status quo.

Due to the presence of high hydrogen content in methanol i.e., 12.5 wt% [22–24], the utilization of methanol as a hydrogen source for organic reactions has become the subject of intense research as well. Quite recently, Rueping [25], Li [11], Xiao [12], and Sunderraju [13] have developed interesting methodologies for the reduction of various functional groups using methanol as hydrogen donor. However, catalytic-transfer hydrogenation of nitroarenes using methanol is still underdeveloped [26,27].

Palladium is among the most active and versatile catalytic element for a variety of organic reactions such as cross-coupling, hydrogenolysis, hydrogenation, hydrodehalogenation and C–H activation reactions [28,29]. Among various palladium catalysts, Pd/C is simple, ligand-free and commercially available in ample quantities [30,31]. Indeed, Pd/C is a promising catalyst for the transfer hydrogenation of nitroarenes and a few reports are available with sodium formate and hydrazine hydrate as hydrogen donors [6,32]. However, methanol as a hydrogen source is seldom reported [26,27]. In this paper, we report our new results on Pd/C-catalyzed transfer hydrogenation of nitroarenes using methanol as a green hydrogen source. The desired anilines were obtained in good to excellent selectivities. Additionally, local anesthictic drug molecule butamben and a key oxazolidinone antibiotic intermediate of Linezolid were successfully synthesized.

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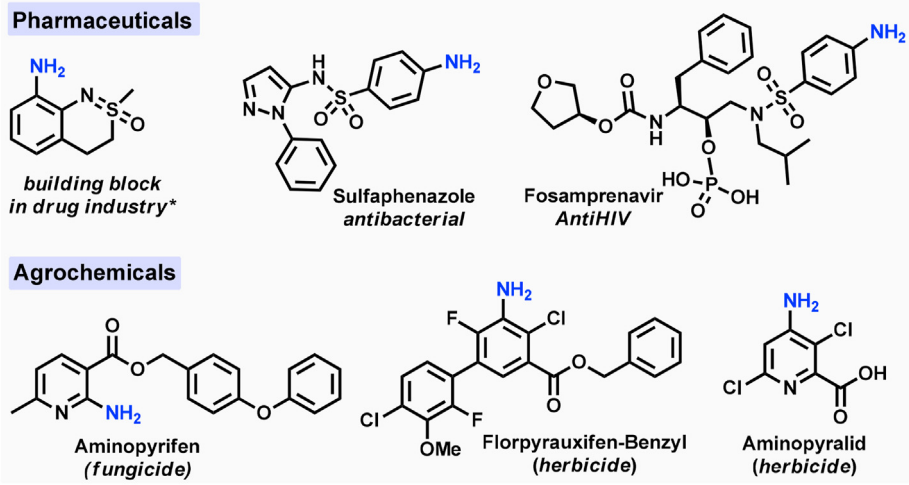


Fig. 1. Selected primary anilines in commercial pharmaceuticals and agrochemicals. *Reference 21.

2. Experimental section

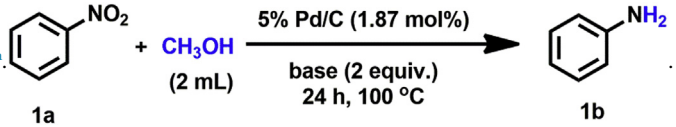
General Information. All chemicals were purchased from Sigma-Aldrich or TCI and were used as received unless stated otherwise. 5% Pd/C was procured from Sigma-Aldrich (product number 75992-10G). The reactions were monitored by thin-layer chromatography (TLC) using silica gel plates (TLC Silica gel 60 F254) and compounds were monitored/visualized with UV light. Gas chromatography mass spectrometry (GCMS) analysis was performed using 5977A MSD attached to a 7890B, an Agilent GC system equipped with a 30 m × 0.32 mm id and 0.25 me mid-polarity capillary column (DB35MS, 35% phenyl/65% dimethylpolysiloxane).

General procedure for transfer hydrogenation of nitroarenes. An oven dried 20 mL ACE® pressure tube was charged with 5% Pd/C (1.87 mol%), KOtBu (2 equiv., 112 mg), nitroarene (0.5 mmol), and MeOH (2 mL). The pressure tube was then sealed and allowed to stir at 100 °C in oil bath for 24 h. After completion of the reaction, the pressure tube was cooled to room temperature, and then the pressure build-up in the tube has been released slowly by losing the screw cap. The solid catalyst was separated from the reaction mixture by filtration through filter paper and washed with 3 mL of ethyl acetate. After evaporating the solvent through rotary evaporator, the crude was submitted for GCMS analysis.

3. Results and discussions

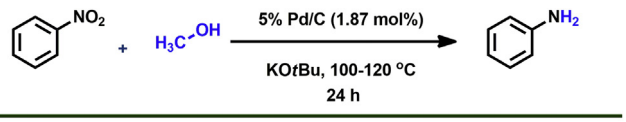
Very recently, Natte and co-workers reported Pd/C-catalyzed *N*-methylation of nitroarenes using methanol as both one-carbon and hydrogen source [33]. During the course of this reaction, very low amounts of anilines as byproduct was observed. This result motivated us to explore selective transfer hydrogenation of nitroarenes using methanol as hydrogen donor by employing 5% Pd/C as a catalyst. Initially, we have chosen simple nitrobenzene (1a) as a benchmark reaction with methanol as both reductant and solvent by employing commercially available 5% Pd/C (1.87 mol%) as catalyst, 2.0 equivalents of KO*t*Bu at 100 °C and 24 h: these reaction conditions enabled the desired aniline (1b) in 90% GCMS selectivity (Table 1, entry 1). We also examined various bases (entries 2–4), nevertheless K_3PO_4, K_2CO_3, NaOH and KOH

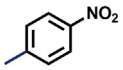
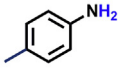
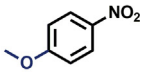
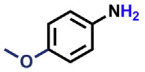
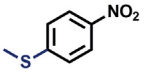
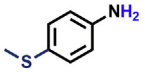
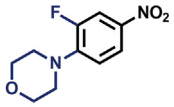
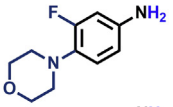
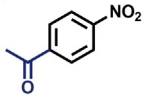
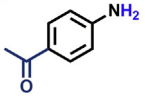
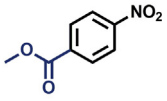
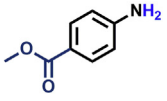
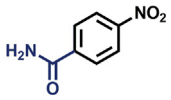
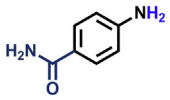
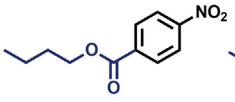
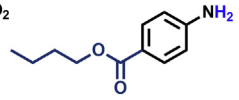
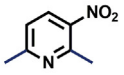
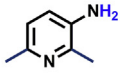
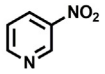
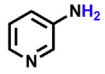
Table 1
Reaction optimization for transfer hydrogenation of nitroarenes using MeOH as hydrogen donor[a].



Entry	Base	Catalyst	Selectivity of 1b (%)
1	KO*t*Bu	Pd/C	90
2	K_3PO_4	Pd/C	59
3	K_2CO_3	Pd/C	68
4	NaOH	Pd/C	70
5	KOH	Pd/C	69
6	KO*t*Bu	Ru/C	45
7	KO*t*Bu	$Pd(OAc)_2$	33
8	.	Pd/C	–
9	KO*t*Bu	.	–

[a] Reaction conditions: nitrobenzene 1a (0.5 mmol), 5% Pd/C (1.87 mol%), base (2 equiv.), MeOH (2 mL), 100 °C, 24 h. Selectivity of 1b (major compound) was determined using GCMS.



Entry	Substrate	Product	Selectivity (%)
1[a]			70
2[a]			65
3[a]			50
4[a]			67
5[a]			45
6[a]			51
7[a]			76
8[a]			85
9[b]			50
10[b]			30

Scheme 1. Transfer hydrogenation of various nitroarenes using MeOH as hydrogen donor.[a]
[a] Reaction conditions: nitroarene (0.5 mmol), 5% Pd/C (1.87 mol%), KO*t*Bu (2 equiv.), MeOH (2 mL), 100 °C, 24 h, GCMS selectivity with respect to major compound; [b] 120 °C; Compound 4: Key intermediate of linezolid; Compound 8: butamben.

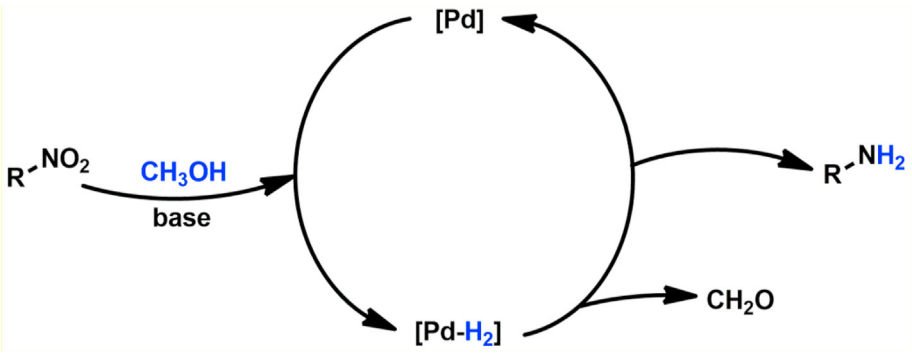
gave moderate selectivities (entries 2–5). Next, Ru/C and homogeneous $Pd(OAc)_2$ catalysts known for transfer hydrogenation reactions did not show any major improvements in the selectivities (entries 6–7). Control experiments revealed that the reaction does not proceed in the absence of a base or catalyst (entries 8–9).

After having optimal conditions in hand, we investigated substrate scope with various nitro derivatives (Scheme 1). Nitroarenes substituted with electron-donating groups like, -Me, -OMe, and –SMe furnished desired anilines in moderate to good selectivities (entries 1–3). However, when 1-chloro-4-nitrobenzene and 1-bromo-4-nitrobenzene were applied, removal of halogens (chloro and bromo) or various side reactions occurred. This may be due to the oxidative addition of aryl halides with palladium [34]. Notably, 4-(2-Fluoro-4-nitrophenyl)morpholine was transfer hydrogenated to its corresponding 3-Fluoro-4-morpholinoaniline in good selectivity by keeping the fluorine group intact (entry 4). Interestingly, the obtained product is a key intermediate for the production of antibacterial drug linezolid [20,35]. Then, nitroarenes substituted with electron-withdrawing groups such as ketone, ester and amide gave corresponding anilines in low to good selectivities (entries 5–7). Delightfully, we directly synthesized pain-killer drug molecule butamben in 85% selectivity from the corresponding starting material (entry 8). Remarkably, nitropyridines also underwent transfer hydrogenation in low to good selectivities (entries 9–10). These results indicate the robustness of Pd/C as a catalyst and methanol as a green hydrogen source to access functional anilines that are widely useful in drug discovery and agrochemical industries. A few of the nitroarenes showed reduced conversion to anilines. This may be attributed to kinetic reaction control and competition between transfer hydrogenation of nitroarene and *N*-methylation of aniline.

Next, based on the literature [33], a plausible catalytic cycle was proposed and shown in Scheme 2. Initially, methanol undergoes dehydrogenation to release dihydrogen and formaldehyde in presence of Pd/C and base. Next, Pd abstracts hydrogen and produces Pd–H_2 species, which participates in hydrogenation of nitroarene to yield the desired corresponding aniline (Scheme 2).

4. Conclusions

We have developed an operationally simple and environmentally friendly palladium-catalyzed transfer hydrogenation of nitroarenes using methanol as green reductant. This concise catalytic protocol features the use of commercially available Pd/C as catalyst and does not require the use of ligands. Various nitroarene bearing functional groups have been tolerated and gave selectivites up to 90%. Notably, the developed approach is also applicable for the synthesis of butamben, a local anesthictic drug molecule and a key pharmaceutical intermediate of linezolid.



Scheme 2. Plausible catalytic cycle for Pd/C-catalyzed transfer hydrogenation of nitroarenes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jics.2021.100014.

References

[1] Wang D, Astruc D. The golden age of transfer hydrogenation. Chem. Rev. 2015;115:6621–86.
[2] Johnstone RAW, Wilby AH, Entwistle ID. Heterogeneous catalytic transfer hydrogenation and its relation to other methods for reduction of organic compounds. Chem. Rev. 1985;85:129–70.
[3] Formenti D, Ferretti F, Scharnagl FK, Beller M. Reduction of nitro compounds using 3d-non-noble metal catalysts. Chem. Rev. 2019;119:2611–80.
[4] Jagadeesh RV, Natte K, Junge H, Beller M. Nitrogen-doped graphene-activated iron-oxide-based nanocatalysts for selective transfer hydrogenation of nitroarenes. ACS Catal. 2015;5:1526–9.
[5] Zhang C, Lu J, Li M, Wang Y, Zhang Z, Chen H, Wang F. Transfer hydrogenation of nitroarenes with hydrazine at near-room temperature catalysed by a MoO_2 catalyst. Green Chem. 2016;18:2435–42.
[6] Zoran A, Sasson Y, Blum J. Catalytic transfer hydrogenation of unsaturated compounds by solid sodium formate in the presence of palladium on carbon. J. Mol. Catal. 1984;26:321–6.
[7] Natte K, Dumrath A, Neumann H, Beller M. Palladium-catalyzed carbonylations of aryl bromides using paraformaldehyde: synthesis of aldehydes and esters. Angew. Chem. Int. Ed. 2014;53:10090–4.
[8] Wang F, Planas O, Cornella J. Bi(I)-Catalyzed transfer-hydrogenation with ammonia-borane. J. Am. Chem. Soc. 2019;141:4235–40.
[9] Zellner G, Winter J. Secondary alcohols as hydrogen donors for CO_2-reduction by methanogens. FEMS Microbiol. Lett. 1987;44:323–8.
[10] Alshakova ID, Gabidullin B, Nikonov GI. Ru-catalyzed transfer hydrogenation of nitriles, aromatics, olefins, alkynes and esters. ChemCatChem 2018;10:4860–9.
[11] Wang R, Han X, Xu J, Liu P, Li F. Transfer hydrogenation of ketones and imines with methanol under base-free conditions catalyzed by an anionic metal–ligand bifunctional iridium catalyst. J. Org. Chem. 2020;85:2242–9.
[12] Aboo AH, Bennett EL, Deeprose M, Robertson CM, Iggo JA, Xiao J. Methanol as hydrogen source: transfer hydrogenation of aromatic aldehydes with a rhodacycle. Chem. Commun. 2018;54:11805–8.
[13] Garg N, Paira S, Sundararaju B. Efficient transfer hydrogenation of ketones using methanol as liquid organic hydrogen carrier. ChemCatChem 2020;12:3472–6.
[14] Roode-Gutzmer QI, Kaiser D, Bertau M. Renewable methanol synthesis. ChemBioEng Rev 2019;6:209–36.
[15] Bos MJ, Kersten SRA, Brilman DWF. Wind power to methanol: renewable methanol production using electricity, electrolysis of water and CO_2 air capture. Appl. Energy 2020;264:114672.
[16] Jiang X, Nie X, Guo X, Song C, Chen JG. Recent advances in carbon dioxide hydrogenation to methanol via heterogeneous catalysis. Chem. Rev. 2020;120:7984–8034.
[17] Natte K, Neumann H, Beller M, Jagadeesh RV. Transition-metal-catalyzed utilization of methanol as a C_1Source in organic synthesis. Angew. Chem. Int. Ed. 2017;56:6384–94.
[18] Simon Araya S, Liso V, Cui X, Li N, Zhu J, Sahlin SL, Jensen SH, Nielsen MP, Kær SK. A review of the methanol economy: the fuel cell route. Energies 2020;13:596.
[19] Murugesan K, Senthamarai T, Chandrashekhar VG, Natte K, Kamer PCJ, Beller M, Jagadeesh RV. Catalytic reductive aminations using molecular hydrogen for synthesis of different kinds of amines. Chem. Soc. Rev. 2020;49:6273–328.
[20] Goyal V, Sarki N, Singh B, Ray A, Poddar M, Bordoloi A, Narani A, Natte K. Carbon-supported cobalt nanoparticles as catalysts for the selective hydrogenation of nitroarenes to arylamines and pharmaceuticals. ACS Applied Nano Materials 2020;3:11070–9.
[21] Blakemore DC, Castro L, Churcher I, Rees DC, Thomas AW, Wilson DM, Wood A. Organic synthesis provides opportunities to transform drug discovery. Nat. Chem. 2018;10:383–94.
[22] Kothandaraman J, Goeppert A, Czaun M, Olah GA, Prakash GKS. Conversion of CO_2 from air into methanol using a polyamine and a homogeneous ruthenium catalyst. J. Am. Chem. Soc. 2016;138:778–81.
[23] Trincado M, Banerjee D, Grützmacher H. Molecular catalysts for hydrogen production from alcohols. Energy Environ. Sci. 2014;7:2464–503.
[24] Nielsen M, Alberico E, Baumann W, Drexler H-J, Junge H, Gladiali S, Beller M. Low-temperature aqueous-phase methanol dehydrogenation to hydrogen and carbon dioxide. Nature 2013;495:85–9.
[25] Sklyaruk J, Zubar V, Borghs JC, Rueping M. Methanol as the hydrogen source in the selective transfer hydrogenation of alkynes enabled by a manganese pincer complex. Org. Lett. 2020;22:6067–71.
[26] Zhao G, Chen H, Yuan Y, Li X, Zhu Z. New process of 2-nitrotoluene into 2-methylaniline by transfer hydrogenation with methanol over X zeolite catalyst. Catal. Lett. 2016;146:174–9.
[27] Xiang Y, Li X, Lu C, Ma L, Zhang Q. Water-improved heterogeneous transfer hydrogenation using methanol as hydrogen donor over Pd-based catalyst. Appl. Catal. Gen. 2010;375:289–94.
[28] Biffis A, Centomo P, Del Zotto A, Zecca M. Pd metal catalysts for cross-couplings and related reactions in the 21st century: a critical review. Chem. Rev. 2018;118:2249–95.
[29] He J, Wasa M, Chan KSL, Shao Q, Yu J-Q. Palladium-catalyzed transformations of alkyl C–H bonds. Chem. Rev. 2017;117:8754–86.
[30] Mironenko RM, Belskaya OB, Likholobov VA. Approaches to the synthesis of Pd/C catalysts with controllable activity and selectivity in hydrogenation reactions. Catal. Today 2020;357:152–65.
[31] Liu X, Astruc D. Development of the applications of palladium on charcoal in organic synthesis. Adv. Synth. Catal. 2018;360:3426–59.
[32] Chen X, Zhou X-Y, Wu H, Lei Y-Z, Li J-H. Highly efficient reduction of nitro compounds: recyclable Pd/C-catalyzed transfer hydrogenation with ammonium formate or hydrazine hydrate as hydrogen source. Synth. Commun. 2018;48:2475–84.
[33] Goyal V, Gahtori J, Narani A, Gupta P, Bordoloi A, Natte K. Commercial Pd/C-catalyzed N-methylation of nitroarenes and amines using methanol as both C_1 and H_2 source. J. Org. Chem. 2019;84:15389–98.
[34] Senn HM, Ziegler T. Oxidative addition of aryl halides to palladium(0) Complexes: A density-functional study including solvation. Organometallics 2004;23:2980–8.
[35] Russell MG, Jamison TF. Seven-step continuous flow synthesis of linezolid without intermediate purification. Angew. Chem. Int. Ed. 2019;58:7678–81.