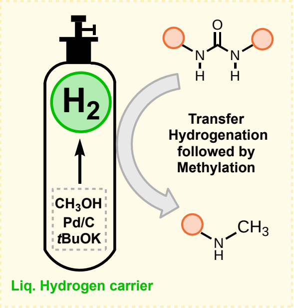
“Liq. Hydrogen carrier and C1 source – Methanol” mediated Selective *N*-Methylation of Urea *via* Transfer Hydrogenation catalyzed by Pd/C

Kiruthigadevi Kamaraj,[a] Pierre H. Dixneuf,[b] Joost N. H. Reek*,[c] and Charles Beromeo Bheeter*,[a]

[a] School of Advanced Sciences, Department of Chemistry, Vellore Institute of Technology, Vellore-632014, TamilNadu, India. (charles-bheeter@vit.ac.in)
[b] University of Rennes, CNRS, ISCR, UMR 6226, F-35000 Rennes, France.
[c] Homogeneous, Supramolecular and Bio-inspired Catalysis group, Van’t Hoff Institute for Molecular Science (HIMS), University of Amsterdam (UvA), Science Park 904, 1098 XH Amsterdam, The Netherlands. (J.N.H.Reek@uva.nl)

KEYWORDS: Green H_2 and C1 source, Methanol, Urea, transfer hydrogenation, Methylation, Pd/C

ABSTRACT: We report the catalytic transfer hydrogenation of urea derivatives using green hydrogen from methanol, which is the most ambitious effort in this hydrogenation world. On enlarging this methodology, selective *N*-methylated amines achieved from urea which are widely featured in drugs, natural products, paints etc. Moreover, this methodology making a sustainable alternative pathway for the synthesis of selective methylated derivative from CO_2 derived compound. The key to the success of this transformation is the use of a commercially available Pd/C heterogenous catalyst and Methanol which act as both H_2 and C1 sources. In addition, several control experiments with the plausible intermediates were performed to analyze this novel pathway. This transformation proceeds in an environmentally friendly greener protocol and high atom-economy.



The Future is towards “Hydrogen economy” where hydrogen can help to obtain a secure and affordable energy. The Hydrogen enormously utilized in the field of oil refining, ammonia production, power generation and fuel cells.[1, 2] In case of Organic transformation, the reduction of organic compounds[3] depends on the stoichiometric use of $LiAlH_4$, $NaBH_4$ or other hydride reagents. On the other hand, for the hydrogenation of chemical compounds where molecular hydrogen is essential.[4] Since Hydrogen is not a natural energy source it must be generate from fossil fuels,[5] biomass,[6] natural gas[7] and from water.[8] The traditional process requires harsh conditions which greatly obstruct the development of environmentally friendly hydrogen production. This provokes the researchers to develop the novel ‘Green hydrogen production’ strategies.[9]

Among all the alternative ways, methanol attracts the research focus on the production of green hydrogen because it is the essential chemical building blocks and emerging energy source.[10-12] Traditionally, methanol release hydrogen by steam reforming method. [13-16] The production of methanol is from renewable sources[17] in large-scale where approximately 160 million metric tons of methanol produced worldwide in 2021.[18] It is widely used in the chemical industry as raw material,[19] solvents, even in everyday products including paints, plastics and fuels. Though methanol is water-soluble and readily biodegradable, its usage makes the process greener. Moreover, methanol has high H/C ratio, sustainability and flexibility which turns methanol as green Liquid hydrogen carrier.[20, 21] In order to find the hydrogen production efficiency from methanol we targeted the difficult functional group hydrogenation reactions.

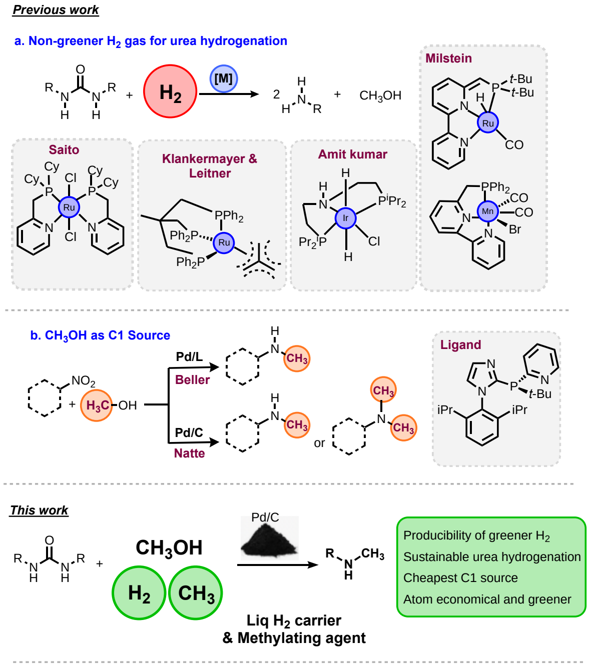


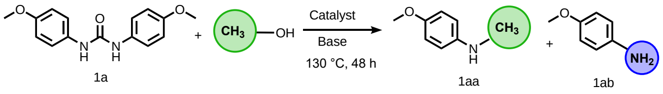
Fig. 1: a, Urea hydrogenation using Non-greener H_2 gas. b, Methylation of nitroarenes using CH_3OH and the present work to hydrogenate and methylate the urea derivatives consecutively.

In that row, the urea hydrogenation is the most challenging of all polar carbonyl bonds due to their low polarizability. Since these carbonic acid derivatives has lower electrophilicity owing to resonance effect of the nitrogen in urea,[22] only few groups overcome these challenges. Firstly, Milstein group have been reported the catalytic hydrogenation of urea derivatives using Bipyridyl- based PNN Ru(II) pincer complex.[23] Then Saito,[24] Leitner, Klankermayer groups,[25] utilized their Ruthenium complexes for urea hydrogenation.[26] Later Milstein developed the first Mn-[PNN] catalyst for the hydrogenation of carbamates and urea derivatives.[27] Finally, in 2021 Amit Kumar group presented the catalytic hydrogenation of urea and polyureas based on a ruthenium or an iridium pincer complex.[28] In all these cases, high pressure of molecular hydrogen gas plays the vital role for hydrogenation. But the demand for molecular hydrogen has grown more than threefold and continues to rise.[29] Considering the significance and difficulty level associated with the production of hydrogen gas and other hydrogenating agent, it is important to explore new methodology to produce green hydrogen from methanol for the sustainable hydrogenation of urea derivatives to corresponding amines.

Nevertheless, contrary to the resulted amine compounds through hydrogenation, *N*-methylation process are highly desired in view of the fact that *N*-methylated amines plays the important role in the production of biological compounds, pharmaceuticals, surfactants and dyes. In addition, *N*-methylated moieties greatly contribute in biomedical research and in drug discovery.[30-33] Moreover, *N*-methylated drugs are in top selling which implements their enormous activity.[34] In general, these *N*-methylamines are produced by using highly active methylating agents which are toxic,[35, 36] or by using formaldehyde which serve as carcinogen. By considering these facts, we are greedy to achieve the selective *N*-methylation of urea by using “Methanol” where methanol itself serves as a sustainable C1 source apart from the hydrogen source.[37-40] Remarkably, methanol is an abundant, renewable feedstock and cheapest C1 source among all. Although methanol mediated *N*-methylation reactions are based on homogeneous catalyst but it requires complicated ligands/complexes and even it is difficult to recycle and reuse.[41-47] In contrast heterogenous catalysts are preferable because of their recycling and reusability fact.[48-50] Thus, heterogenous catalyst are of great importance for reduction process and in the dehydrogenation of methanol too. Moreover, heterogenous material mediated catalysis are easily accessible and convenient. In this array, commercially available heterogeneous catalysts are favorable.

Interestingly, palladium-based catalyst favored the *N*-methylation of amines using methanol as C1 source. Initially, Pd/TiO_2 catalyst used for *N*-methylation of amines and amino acids using methanol as methyl source.[51] Later on Beller group established the selective mono-*N*-methylation of nitroaromatics using phosphine ligands containing palladium complex with methanol.[52] Natte published *N*-methylation nitroarenes and amine by using commercially available Pd/C with methanol as both a C1 and Hydrogen source.[53] Till now, the hydrogenation of urea is feasible only with homogenous Ru and Mn complexes. Here we reported the first heterogenous Pd/C catalyzed the *N*-methylation of urea derivatives using methanol as hydrogen source for the hydrogenation of urea to aniline derivatives and then as C1 source which methylated the aniline in sequential manner. This tandem reaction is atom economical and greener. 1,3-Bis(4-methoxyphenyl)urea (1a) was selected as a model substrate for the study of hydrogenation followed by methylation of aryl ureas. Our initial optimization was studied using various catalysts (Table 1, entry 1-4) and *t*-buOK (0.6 mmol) in the presence of methanol (2 ml) at 130 °C for 48 h. On screening the catalysts, Rh/C and Ru/C (entry 1,3) resulted in *p*-anisidine 1ab 42% and 38% respectively, hence poor selectivity towards methylated product 1aa. Only 17% of *p*-anisidine 1ab was observed using activated carbon as a catalyst (entry 4). Interestingly, *N*-methylation of 1,3-Bis(4-methoxyphenyl)urea (1a) resulted in 99% yield of methylated product 1aa on using Pd/C (10 mg) (entry 2). Thus, Pd facilitates the methylation reaction rather than other metals. Furthermore, on alternating the base from *t*-buOK to carbonates or acetates (entry 5-7) results in lower yield of 1aa whereas moderate yield occurs in the case of KOH and NaOH (entry 8,9). Surprisingly, the poor nucleophile (*t*-buOK) potassium *tert*-butoxide was enough to facilitate *N*-methylation of urea. Base is required for dehydrogenation of methanol. However, on decreasing the *t*-buOK loading to 0.4 mmol, only 82% of 1aa was observed (entry 11). Whereas on reducing the bath temperature to 100 °C, 55% of desired product was observed (entry 12).

Table 1. Optimization of *N*-methylation of urea derivatives

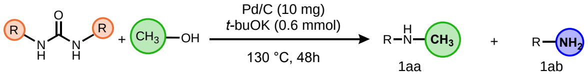


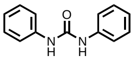
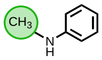
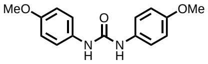
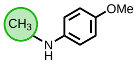
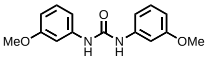
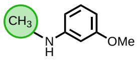
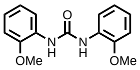
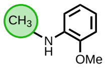
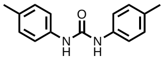
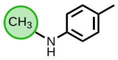
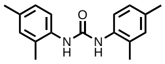
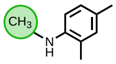
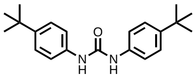
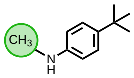
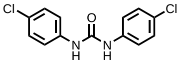
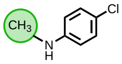
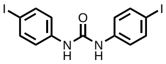
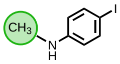
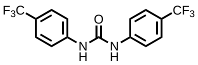
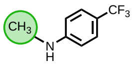
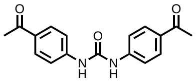
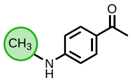
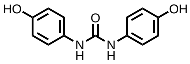
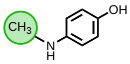
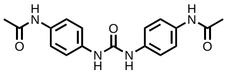
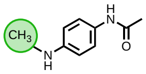
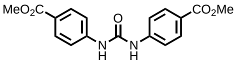
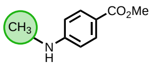
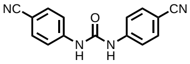
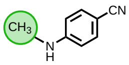
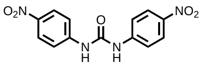
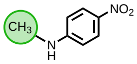
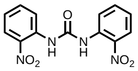
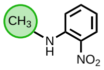
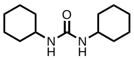
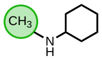
Entry[a]	Catalyst	Base	1aa[b]	1ab[b]
1	Rh/C	*t*-buOK	--	42%
2	Pd/C	*t*-buOK	99%	--
3	Ru/C	*t*-buOK	--	38%
4	Carbon	*t*-buOK	--	17%
5	Pd/C	Na_2CO_3	11%	24%
6	Pd/C	K_2CO_3	30%	54%
7	Pd/C	CH_3CO_2K	36%	15%
8	Pd/C	KOH	78%	--
9	Pd/C	NaOH	70%	--
10	Pd/C	Nil	--	--
[c]11	Pd/C	*t*-buOK	82%	--
[d]12	Pd/C	*t*-buOK	55%	44%
[e]13	Pd/C	*t*-buOK	52%	46%

[a] Conditions: *p*-OMe urea (0.2 mmol), catalyst (10 mg), base (0.6 mmol) and Methanol (2 ml), heated in oil bath at 130 °C for 48 h. [b]Yields and conversions determined by GC analysis using mesitylene as internal standard. [c] *t*-buOK 0.4mmol, [d] temp 100 °C, [e] time 24.

This tandem reaction required 48 h to get methylated 1aa product whereas 24 h reaction resulted in 46% yield of *p*-anisidine 1ab, and 54% yield of methylated product 1aa [entry 13]. Thus, the optimal reaction condition was 0.1 mol % of Pd/C, 0.6 mmol of *t*-BuOK and 2 mL of methanol at 130 °C and 48 h for the selective *N*-methylation of Urea.

Table 2. Pd/C catalyzed hydrogenation followed by methylation of urea derivatives.

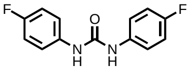
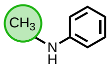
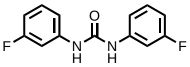
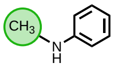


Entry	Urea derivative	N-me aniline	Yields
1			70%
2			95%
3			76%
4			54%
5			92%
6			72%
7			69%
8			82%
9			90%
10			50%
11			52%
12			55%
13			50%
14			nd
15			62%
16			45%
17			30%
18			82%

[a] Conditions: urea derivative (0.2 mmol), catalyst (10 mg), base (0.6 mmol) and Methanol (2 ml), 130 °C, 48 h. Products were detected by the NMR. The conversion and yield were determined by GC.

We next explored the scope of the urea under the optimized conditions (Table 2). An electron-donating group at the *para* position of aromatic substituted urea enhanced the reactivity of the urea substrates (entry 2-7). Among these 1,3-Bis(4-methoxyphenyl)urea shows excellent yield of 95% (entry 2) but *meta* and *ortho* methoxy substituted ureas retarded the reaction and resulted in 76% & 54% due to steric factor (entry 3 and 4). On enhancing the electron donating group in urea, the reactivity decreases where *para*-methyl, dimethyl and *t*-butyl groups gave corresponding methylated product in 92%, 72% and 69% respectively (entry 5-7). Similarly substrates with an electron-withdrawing groups like chloro, iodo and CF$_3$ at *para* position gives good yield of 82%, 90% and 50% (entry 8-10) except 1,3-Bis(4-fluorophenyl)urea. Fluro substituted urea undergoes hydrohalogenation due to the oxidative addition of carbon halogen bond (entry 19 and 20).[54] On the other hand, the functional groups namely alcohol and acetamide bearing ureas were resulted in 55% and 50% yields (entry 11-13) but no reaction occurs in the case of ester functional group (entry 14). Moderate yield was obtained in the case of *p*-ketone, *p*-CN, *p*-NO$_2$ and *m*-NO$_2$ due to the self-hydrogenation of these functional group rather than urea hydrogenation (entries 15-17). On the contrary, urea derivatives bearing aliphatic substituents (entries 18) shows good yield of 82%.

Hydrohalogenation

19			95%
20			95%

In addition, we performed the direct *N*-methylation of 1,3-Bis(4-methoxyphenyl)urea (1a) on a gram scale where 70% of the desired product obtained (Fig 2). We also demonstrated the recycling and reusability of the Pd/C for the *N*-methylation of 1,3-Bis(4-methoxyphenyl)urea *via* transfer hydrogenation under standard conditions. Due to Pd-leaching factor, we observed the yield of the desired product was dropped in second and third cycles which shows the loss in catalytic activity (Fig 2).[55]

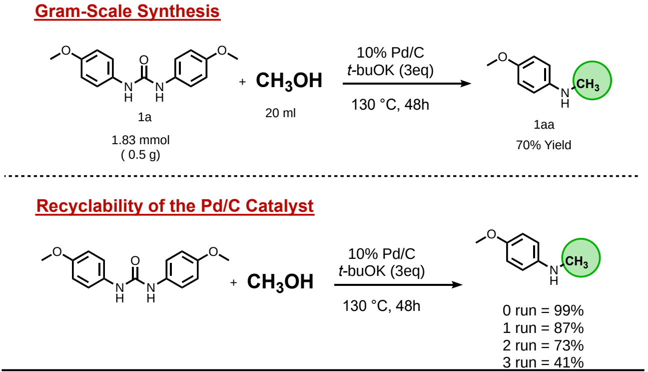


Fig 2: Gram scale synthesis and Recyclability of the Pd/C

A series of control experiments were explored to evaluate the protocol of selective *N*-methylation of urea derivatives. First and foremost, the generation of hydrogen gas was confirmed by the dehydrogenation of methanol under the standard condition without the substrate which is detected by GC (See SI). On deuterated studies, we concluded methanol act as hydrogen and C1 source and confirmed the selective *N*-methylated product through NMR and HRMS (See SI). In order to analyze the intermediates of this reaction the time course experiments were conducted. After 3h, 48% of unreacted urea was observed but within 6h, 30% of aniline (1ab) and 17% of *N*-methylaniline (1aa) was obtained. On increasing the reaction time, gradually aniline (1ab) converted to *N*-methylaniline (1aa). Accordingly, within 24h 46% of methylated product and 54% of aniline product were observed in crude NMR (See SI). In this regard, selectivity of *N*-methylaniline (1aa) was observed at 48h. This reaction time experiments shows that aniline (1ab) act as a one of the intermediate in this transformation. Moreover, we conducted the control studies to understand the urea hydrogenation pathway in which the presence of *N*-phenylformamide was observed by the HRMS in the deduction of *t*-buOK (0.1 mmol) and reaction time (16h).

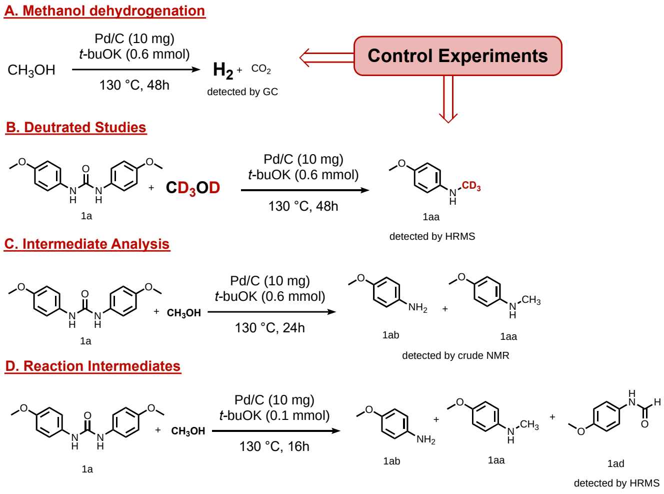


Fig. 3: **Control experiments**: A, Methanol dehydrogenation B, Deuterated Studies C, Intermediate Analysis D, Reaction Intermediates

Based on the control experiments, a proposed pathway for the selective *N*-methylation of urea derivatives has been outlined in Fig 4. Initially, hydrogen and formaldehyde are produced through the methanol dehydrogenation[56-58] in the presence of Pd/C and *t*-buOK. This hydrogen interacts with Pd/C and the active species Pd-H will generate. Then, this Pd-H react with urea to give corresponding aniline (II) and *N*-phenylformamide (III). Followed by hydrogenation, condensation occurs between formaldehyde and aniline (II) from urea with the help of base resulted in imine formation (IV).[59] Then, imine is hydrogenated by Pd-H species to give desired product *N*-methylaniline and regenerates the Pd metal sites on the catalyst surface.

In conclusion, selective *N*-methylation *via* the occasional hydrogenation of urea derivatives using methanol in the presence of Pd/C has been accomplished. We have developed this greener methodology by avoiding the use of high pressure of molecular hydrogen. This is the first demonstration of Pd/C heterogenous catalyzed transfer hydrogenation followed by *N*-methylation of organic urea using sustainable methanol. Remarkably, 1) the commercial Pd/C is easily recycled and reused 2) Methanol is the sustainable liquid hydrogen carrier. 3) Indirect conversion of CO_2 to C1 source through transfer hydrogenation of Urea derivatives. These above factors facilitate this atom economical approach in future industrial scale.

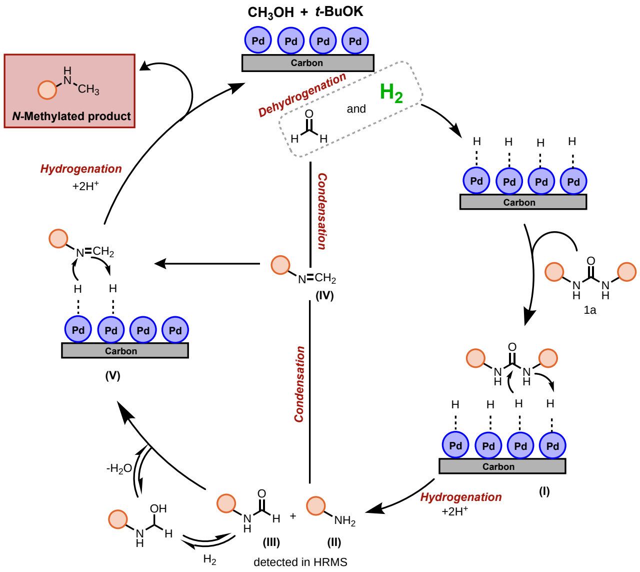


Fig. 4: Plausible reaction mechanism for the Pd/C catalyzed *N*-methylation of Urea.

AUTHOR INFORMATION

CORRESPONDING AUTHOURS

*Charles Beromeo Bheeter (charlesbheeter@vit.ac.in)

* Joost N.H. Reek (j.n.h.reek@uva.nl)

Author Contributions

C.B.B. guided the research. J.N.H.R. co-guided the research. C.B.B. and K.D. designed the project, performed the experiments, wrote the manuscript and edited. P.H.D and J.N.H.R. edited the manuscript.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at.(….). Complete experimental procedures including general considerations and characterization data, NMR spectra, HRMS data, are available as PDF.

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