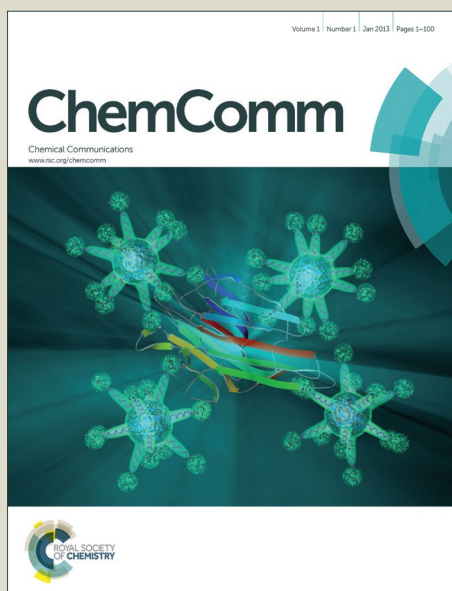


ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



Journal Name

COMMUNICATION

Novel Synthesis of N-alkyl amines from tandem Coupling of either Methylamine or Nitroalkane with Aldehyde

Received 00th January 20xx,
Accepted 00th January 20xx

Shuanglong Lu, Jie Peng, Junjie Wu, Chao Li, Xueqin Cao and Hongwei Gu*

DOI: 10.1039/x0xx00000x

www.rsc.org/

A novel tandem strategy for coupling of either methylamine or nitroalkane with aldehyde has been developed. This is the first demonstration that methylamine or nitroalkane is used as methylation reagent, fabricating N-alkyl amines. The active Pt NWs allows for the selective preparation of a series of N-alkyl amines with good to excellent yield under mild and environmentally friendly conditions.

Tertiary N-alkyl amines are key structural motifs in various biologically active natural compounds and also an irreplaceable class of industrially compounds such as pharmaceuticals, pesticides and dyes.¹ Traditional methods to obtain N-methylamines mainly take advantage of methyl halides like methyl iodine or methyl triflate or dimethyl sulphate.² All of these reagents there used, however, are pollution-carrying resources, always toxic and hardly handled up, which are unfavourable for the sustainable development. Another pathway is through a reductive amination process,³ among which, Eschweiler-Clark reaction⁴ is a well-known route where both primary and secondary amines can be used as starting methylating reagents, yet, therein, excess of formic acid or formaldehyde should be used. Therefore, it is an enormous challenge for us to come up with alternative new catalytic pathways to prepare N-alkyl amines in the view of green chemistry. Beller and co-workers⁵ designed a single Ru complex that is able to convert CO₂ and amines into various kinds of N-methylated products. The similar research was later developed by Beydoun that they described ruthenium-catalyzed reductive methylation of both aromatic amines⁶ and imines⁷ using CO₂ and molecular hydrogen. Obviously, CO₂ is an excellent renewable methylating reagent. However, organometallic catalysts including rhodium, iridium, and

ruthenium complexes should be precisely synthesized to facilitate the transformation. Sortais et al. demonstrated that dimethyl carbonate (DMC) as a useful electrophilic methylation reagent can effectively proceed the reaction under mild conditions.⁸ Another alternative catalytic pathway was put forward by Saito's group using methanol and amines as the starting material.⁹ Their silver loaded titanium dioxide photocatalyst allowed the formation of a series of N-methylamines at room temperature with simplified purification process. Even though all of these methods mentioned above have been investigated in depth and most of them have proved to be greener alternatives to produce N-alkyl amines, developing one pot, tandem reactions starting from more available raw materials and highly active catalytic pathway is still of great important practical significance.

Inspired by our previous work that ammonia gas was used as the nitrogen source and coupled with two equivalent aldehydes,¹⁰ we would like to develop a method for the synthesis of N-alkyl amines by utilizing methylamine (CH₃NH₂) substituted for ammonia gas. Ultrathin platinum nanowire (Pt NW) is used here as superior catalyst over organometallic and other supported heterogeneous catalysts. It has been proved by our previous investigations that Pt NW shows outstanding catalytic activity in C-N coupling reactions¹¹ and selectively hydrogenation reaction of nitriles.¹² Notably, in this paper, we also demonstrated that nitromethane (CH₃NO₂), a much more available and greener raw material¹³ can be used as the very beginning reactant to prepare N-alkyl amines. So herein, a novel, one pot and tandem reaction pathway to synthesize N-methylamine has been developed with both CH₃NH₂ and CH₃NO₂ under mild reaction conditions for the first time.

The ultrathin Pt NWs were synthesized through acid acting of FePt NWs¹⁴ under air followed by multiple times methanol washing and redispersed in hexane. The TEM image in Figure 1a and high-resolution TEM image in 1b indicate that the diameter of Pt NW is approximately 1.5 nm and several micrometres in length. Selected area electron diffraction (SAED) (Figure 1c) indicates that the Pt NW has a face-centered cubic (FCC) phase.

Address: Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science & Collaborative Innovation Center of Suzhou Nano Science and Technology, Soochow University, Suzhou, China 215123.

E-mail: hongwei@suda.edu.cn

Electronic Supplementary Information (ESI) available. Experimental procedures include a synthetic protocol for the construction of the Pt NWs, optimization of the reaction conditions. And also, catalytic stability of the Pt NW and NMR spectroscopy data for compounds are provided. See DOI: 10.1039/x0xx00000x

ChemComm Accepted Manuscript

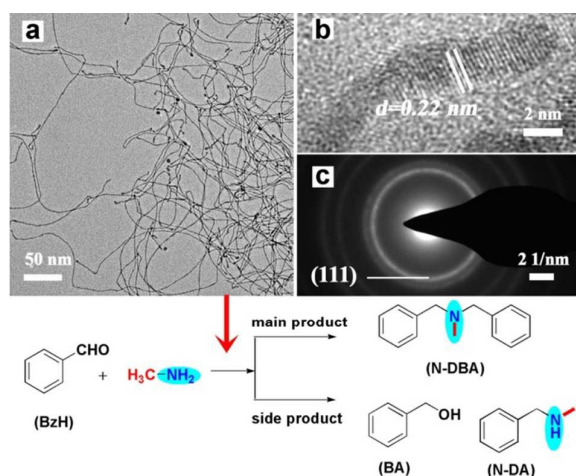


Figure 1 Coupling of benzaldehyde with methylamine catalysed by ultrathin Pt NWs. (a) and (b) are the TEM and high-resolution TEM image of the Pt NW; (c) is the selected area electron diffraction (SAED) pattern of the Pt NW.

Initially, the benzaldehyde (BzH) was chosen as the model reactant and the amination was conducted with methylamine alcohol solution (33 wt %). Faithful to our expectation, N-methyl-dibenzylamine (N-DBA) can be detected by gas chromatography (GC) (Figure S1) and the structure was verified by GC-MS and NMR spectrum (shown in S1). Meanwhile, both the benzyl alcohol (BA) and mono-coupling product N-methylbenzylamine (N-BA) can be found as side products (Figure 1).

Table 1 optimization of the reaction conditions where benzaldehyde is coupling with methylamine^a

Entry	Solvent	T/°C	Conv./% ^d	Sel./% ^d		
				N-DBA	BA	D-BA
1	methanol	40	100	47.8	25.0	23.0
2	THF	40	100	6.4	29.9	63.7
3	CH ₃ CN	80	100	62.4	--	11.5
4	ethanol	80	100	37.6	15.2	47.3
5	toluene	100	100	78.3	6.9	7.4
6	DMF	100	100	93.5	1.4	5.1
7	<i>o</i> -xylene	100	100	73.0	10.1	14.1
8	heptane	100	100	75.5	11.0	9.3
9	DMF	80	100	84.1	11.9	4.0
10	DMF	60	100	71.0	15.1	13.8
11	DMF ^b	100	100	8.3	78.4	13.3
12	DMF ^c	100	100	10.7	76.2	13.1

^a Reaction conditions: 2 mmol benzaldehyde, 1 mmol CH₃NH₂, 0.5 mol% Pt NW, 1 bar H₂ balloon, 2 ml solvent at corresponding temperature for 24 h; ^b 0.5 mol% Pt nanoparticle as catalyst; ^c 0.5 mol% Pt nanorod as catalyst; ^d GC yield.

The solvent and the reaction temperature were firstly optimized and several commonly used solvents were screened

(entry 1-10, table 1). As we can see, the Pt NW catalyst did not exhibit a strong dependence on the polarity of the solvents, but the reaction temperature had notable impact on the yield of our desired product. Higher temperature was proved to be favourable for the formation of N-DBA, which can be confirmed by comparing entry 1-4 with 5-9 and also entry 6, 10, 11. Finally, DMF, in which the yield of N-DBA could reach up to 93.5%, was selected as the best solvent for further studies. We also investigated the catalytic performance of other Pt based nanomaterials, such as Pt nanoparticle¹⁵(entry 12) and Pt nanorod¹⁶(entry 13). It is clear that the Pt nanowire shows superior catalytic activity and regioselectivity, which is the crucial factor for the successful transformation of BzH with CH₃NH₂ to N-DBA. Impressively, the Pt NW catalysts can be easily recycled and reused. The conversion and selectivity were almost constant around 90% over 6 cycles (Figure S2) and no leached Pt was detected by atomic absorption spectroscopy (AAS) and ICP-MS.

Having established the optimized parameters (H₂ balloon, 2 ml DMF, 100 °C, 24 h), we proceeded to investigate the scope of the reaction using a range of substituted aldehydes. The results are summarized in Figure S3. Obviously, almost all of the substrates give the desired tertiary amines in good to excellent yields. Neither the electron withdrawing groups nor donating groups appear to have a notable influence on the outcome of the reaction yield (entry 1, 2, 4 and 5 in Figure S3). Further investigation reveals that substrate bearing heterocyclic ring can also be utilized as starting aldehyde, where the yield is good enough (entry 3 in Figure S3). α -branched aliphatic aldehyde is also an applicable reactant with a high yield of 94.7%, while the aldehyde with aliphatic chain can only get a yield of 68.4% (entry 6, 7 in Figure S3). If the steric hindrance of the aliphatic aldehyde increases, the result becomes even worse (entry 8 in Figure S3).

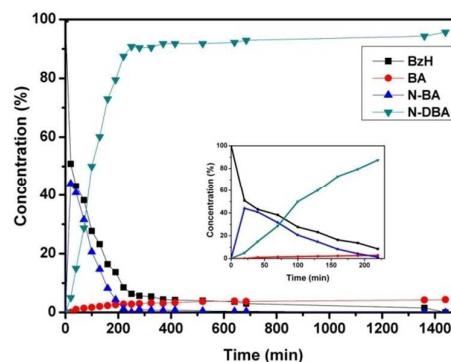


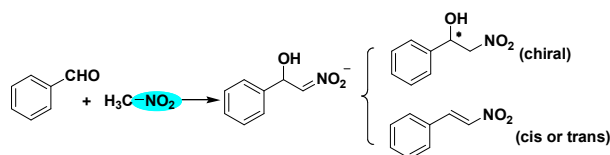
Figure 2 Time-conversion plot for the model reaction between the benzaldehyde and methylamine with Pt NWs (insert: the first three hour results).

To have a deep understanding of the reaction process, real time GC data were recorded to trace the evolution of the reactant. As shown in Figure 2, at the beginning of the reaction, BzH was quickly consumed with the concentration of N-BA increasing to a maximum of 47.4%. Meanwhile, there was a steady enhancement of the yield for desired product N-DBA.

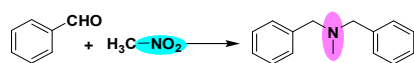
At this stage, due to the higher concentration of the initial reactants, the reaction rate of BzH with CH_3NH_2 is much larger than the rate of BzH with N-BA, as a result of which, the intermediate N-BA accumulates (clear to be seen in the insert diagram of Figure 2). Afterwards, with further enhanced the concentration of the intermediate N-BA, prime elementary reaction becomes to be the coupling of N-BA with BzH. N-BA was gradually converted to N-DBA until all the BzH and intermediate N-BA was exhausted. Of the whole process, BA, as the main side product, can be detected with a low concentration.

Till now, we have developed a facile and efficient Pt NW-catalyzed coupling of CH_3NH_2 with aldehyde to prepare N-alkylamines. Nevertheless, one problem remains that CH_3NH_2 is easy to evaporate so that additional reagent (water or alcohol) is needed to store it. Nitromethane, a commonly used solvent, however, is much more available and stable than methylamine. We set out to access the possibility of the tandem reaction using nitromethane as the very starting material. In previous researches,¹⁷ many efforts have been devoted to exploring the nitroaldol reaction of nitromethane, where the reactive site is located on the methyl group adjacent to the nitro group.

Previous work: Catalyzed by various metal organic complexes or well-designed heterogeneous materials.



This work: ultrathin Pt nanowire as catalyst

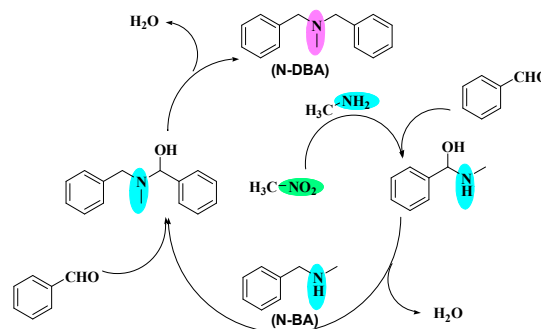


Scheme 1 Different reaction pathway of aldehyde with nitroalkane

As shown in Scheme 1, both chiral isomers and cis-trans isomers were widely reported with the coupling of BzH and CH_3NO_2 under different reaction conditions. However, when the reaction was carried out under the catalysis of our highly active Pt NW, an unexpected compound, N-DBA, was detected by the GC-MS analysis, as the main product. Conditions like solvent, temperature and molar ratio (Table S1) were filtered to find out the best parameters. A yield of 84.3% for the desired product is obtained in toluene at 100 °C when the molar ratio of CH_3NO_2 over BzH is 2.5. Notably, when we used triethylamine as an additive, the yield of the N-DBA reached up to 91.3%. Also, the H_2 gas and Pt NW are proved to be indispensable to achieve the desired product (Table S2).

Given the feasibility of directly coupling of BzH with CH_3NO_2 , CH_3NH_2 is likely to be the intermediate of the first stage. After taking the real time GC measurement (Figure 2) of BzH with CH_3NH_2 into consideration, the N-BA may be another crucial intermediate. Scheme S2 illustrates the control experiment

using BzH and N-BA as starting materials and Pt NW as catalyst. Compared with previous reports,¹⁸ it can still present a better result (a yield of 96.7% for N-DBA), which also provides evidence for our assumption. Based on the kinetics and control experiment mentioned above, we have proposed a plausible mechanism for the reaction of BzH with CH_3NO_2 shown in Scheme 2.



Scheme 2 Proposed mechanism

Due to the superior active, Pt NW works as dual catalyst both in the reduction of nitro group in CH_3NO_2 and C-N coupling in the tandem procedure. CH_3NH_2 , got from the reduction of CH_3NO_2 , reacted with one equivalent of BzH, following which, hydroxyl is eliminated to produce N-BA. Another equivalent of BzH further couples with intermediate N-BA. Finally, N-DBA can be obtained with H_2O as the sole by-product, which is faithful to the demands of green chemistry.

Then, to evaluate the scope of the as-developed catalytic process, a range of substituted aromatic aldehydes were subjected to the hydrogenation amination reaction under ambient hydrogen pressure in toluene (Table S3). As we see, aromatic aldehydes with electron-donating substituents can achieve excellent results (entry 1-2), while the electron-withdrawing group of the substrate seems to be unfavourable for N-alkyl amine formation (entry 3). Additionally, the reaction is sensitive to the steric hindrance (entry 4-5). And also, both α -branched aliphatic aldehyde (entry 6) and heterocyclic aldehyde (entry 7) can be employed as the starting aldehydes with a good yield of corresponding amines. What's more, $\text{CH}_3\text{CH}_2\text{NO}_2$ and $\text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2$ were also applied in place of nitromethane, whose yields of N-alkylamines are 66.8% and 74.7% respectively. Aliphatic aldehydes are applicable and the steric hindrance makes big difference (entry 10, 11).

In conclusion, we have developed a novel method to synthesize N-alkyl amines from the coupling of both methylamine and nitroalkane with aldehyde. This method is attractive because the reaction is firstly reported and the active Pt NW allows for the selective preparation of a series of N-alkyl amines with good to excellent yields. Most importantly, nitroalkane, a commonly used solvent, can work as the very beginning C and N source to manufacture N-alkyl amines under mild and environmentally friendly conditions. It is expected that the Pt NW-catalyzed strategy for preparing N-

alkyl amines can be expanded to be a practical candidate for the greener industrial applications. Currently, the catalytic system is further studied to widen the applications in our laboratory.

Acknowledgements

H.W.G. acknowledges the financial support of the National Natural Science Foundation of China (No. 21003092), the Key Project of Chinese Ministry of Education (No. 211064), and the Priority Academic Program Development of Jiangsu Higher Education Institutions. S.L.L acknowledges financial support from scientific innovation research of college graduate in Jiangsu province (KYLX_1242).

Notes and references

- (a) A. Ed. Ricci, *Modern Amination Methods*, Wiley-VCH: Weinheim, Germany, 2000; (b) R. N. Salvatore, C. H. Yoon and K. W. Jung, *Tetrahedron.*, 2001, **57**, 7785.
- (a) T. C. Nugent and M. El-Shazly, *Adv. Synth. Catal.*, 2010, **352**, 753; (b) A. R. Cartolano, G. A. Vedage, *InKirk-Othmer Encyclopedia of Chemical Technology*, John Wiley & Sons, Inc, New York, 2004, **2**, 476; (c) S. Gomez, J. A. Peters and T. Maschmeyer, *Adv. Synth. Catal.*; 2002, **344**, 1037; (d) G. Lamoureux and C. Agüero, *ARKIVOC.*, 2009, 251.
- (a) C. Li, V. B. Marcos and J. Xiao, *J. Am. Chem. Soc.*, 2009, **131**, 6967; (b) D. Steinhuebel, K. Y. Sun, K. Matsumara, N. Sayo and T. Saito, *J. Am. Chem. Soc.*, 2009, **131**, 11316.
- H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *J. Am. Chem. Soc.*, 1933, **55**, 4571.
- Y. H. Li, X. J. Fang, K. Junge and M. Beller, *Angew. Chem.*, 2013, **125**, 9747.
- K. Beydoun, G. Ghattas, K. Thenert, J. Klankermayer and W. Leitner, *Angew. Chem. Int. Ed.*, 2014, **53**, 11010.
- K. Beydoun, T. V. Stein, J. Klankermayer and W. Leitner, *Angew. Chem. Int. Ed.*, 2013, **52**, 9554.
- J. X. Zheng, C. Darcel and J. Sortais, *Chem. Commun.*, 2014, **50**, 14229.
- V. N. Tsarev, Y. Morioka, J. Caner, Q. Wang, R. Ushimaru, A. Kudo, H. Naka and S. Saito, *Org. Lett.*, 2015, **17**, 2530.
- F. Q. Qi, L. Hu, S. L. Lu, X. Q. Cao and H. W. Gu, *Chem. Commun.*, 2012, **48**, 9631.
- (a) L. Hu, X. Q. Cao, D. H. Ge, H. Y. Hong, Z. Q. Guo, L. Chen, X. H. Sun, J. X. Tang, J. W. Zheng, J. M. Lu and H. W. Gu, *Chem. Eur. J.*, 2011, **17**, 14283; (b) L. Y. Shi, L. Hu, J. Q. Wang, X. Q. Cao and H. W. Gu, *Org. Lett.*, 2012, **14**, 1876.
- (a) S. L. Lu, J. Q. Wang, X. Q. Cao, X. M. Li and H. W. Gu, *Chem. Commun.*, 2014, **50**, 3512; (b) S. L. Lu, C. Li, J. Q. Wang, Y. Pan, X. Q. Cao and H. W. Gu, *Chem. Commun.*, 2014, **50**, 11110.
- R. R. Walvoord, S. Berritt and M. C. Kozlowski, *Org. Lett.*, 2012, **14**, 4086.
- C. Wang, Y. Hou, J. Kim and S. Sun, *Angew. Chem., Int. Ed.*, 2007, **46**, 6333.
- C. Wang H. Daimon T. Onodera, O. Koda and S. Sun, *Angew. Chem. Int. Ed.*, 2008, **47**, 3588.
- J. Kim, Y. Lee, S. Sun, *J. Am. Chem. Soc.*, 2010, **132**, 4996.
- (a) H. Y. Huang, H. Zong, G. L. Bian, H. F. Yue and L. Song, *J. Org. Chem.*, 2014, **79**, 9455; (b) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (c) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692; (d) T. Okino, S. Nakamura, T. Furukawa and Y. Takemoto, *Org. Lett.*, 2004, **6**, 625; (e) M. T. Barry and S. C. Y. Vince, *Angew. Chem. Int. Ed.*, 2002, **42**, 861; (e) T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen and H. Hiemstra, *Angew. Chem., Int. Ed.*, 2006, **45**, 929; (f) C. Palomo, M. Oiarbide and A. Mielgo, *Angew. Chem. Int. Ed.*, 2004, **43**, 5442.
- (a) D. Chusov and B. List, *Angew. Chem. Int. Ed.*, 2014, **53**, 5199; (b) Q. Lei, Y. W. Wei, D. Talwar, C. Wang, D. Xue and J. L. Xiao, *Chem. Eur. J.*, 2013, **19**, 4021; (c) V. Kumar, U. Sharma, P. K. Verma, N. Kumar and B. Singh, *Adv. Synth. Catal.*; 2012, **354**, 870.