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# Interfacial hydrogenation and deamination of nitriles to selectively synthesize tertiary amines†

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**A novel one-pot method has been developed for the interfacial hydrogenation of nitriles to synthesize asymmetrical tertiary amines. The active Pt NWs allow for the preparation of a series of tertiary amines in excellent yields (up to 99.0%) and a mixed solvent is vital for the adjustment of the yield. And also, the reaction proceeded under mild conditions and is environmentally friendly.**

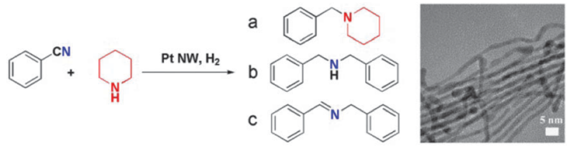
Tertiary amines are an extremely important class of compounds from the drug discovery perspective. Indeed, no less than a quarter of registered drugs contain tertiary amines.[1] They are particularly common in drugs which are active within the central nervous system.[2] Tertiary amines are also important building blocks in organic synthesis and routinely serve as synthons for pharmaceuticals, herbicides, agricultural chemicals, and functionalized materials.[3] A number of catalytic and non-catalytic procedures, for example (1) *N*-alkylation of amines with alkyl halides or alcohols,[4] (2) reductive amination of carbonyl compounds,[5] (3) amination of arylhalides,[6] and (4) hydroamination of unsaturated hydrocarbons with amines[7] have been developed for the synthesis of tertiary amines. However, problems, such as the use of expensive starting materials, tedious workup procedures, low selectivity, and formation of large amounts of wasteful salts may occur here. Also, most of the traditional methods are homogeneous systems and have shortcomings in the catalyst/product separation and recycling of expensive metal catalysts. N. Mizuno *et al.* developed the heterogeneous catalytic *N*-arylation using $Ru(OH)_x$ supported on $TiO_2$ as a catalyst.[8] The Cao group used supported gold nanoparticles[9] to promote the selective synthesis of tertiary amines from alcohol and urea.[10] Both of these methods are novel and efficient. One limitation associated with these systems is that a large excess of relatively expensive alcohols is needed.

Herein, we report an entirely new Pt nanowire (Pt NW) catalyzed reduction amination process for the preparation of a series of tertiary amines from the corresponding nitriles. The ultrathin Pt NWs were synthesized from acidic etching of FePt NW and they can be recycled easily through simple centrifugation, which was reported in our previous work.[11]

Inspired by our last work[12] where secondary amines have been obtained from the reduction of nitriles with additional primary amines, we substituted the primary amine with secondary amine as the additional reagent to get the tertiary amine. Nitriles are easily available and asymmetrical tertiary amines can be prepared without any wasteful salts and it can be a very atom-efficient catalytic transformation (Scheme 1).

As far as we have known, almost no paper has been published in the preparation of a tertiary amine directly from a nitrile[13] for the reason that the cyan group is relatively stable and the selectivity of several products (self-coupling to di- or tri-amines and imines) are hard to be controlled. It seems impossible that an unsymmetrical tertiary amine can be obtained from the hydrogenation of nitriles in the presence of other secondary amines.

At the beginning of the investigation, we evaluated the possibility of hydrogenation of nitriles with piperidine as the added secondary amine for accessing tertiary amines in different solvents. However, the results (shown in Table 1) were not that satisfactory.



Scheme 1 Asymmetrical tertiary amine formation from the hydrogenation reaction of benzonitrile.

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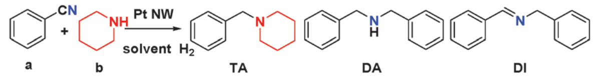
† Electronic supplementary information (ESI) available: Experimental procedures include a synthetic protocol for the construction of the Pt NWs, optimization of the reaction conditions, catalytic activities with different Pt morphologies, and upscaled results for this system. And also, catalytic stability of the Pt NW and full spectroscopy data for all compounds are provided (23 pages). See DOI: 10.1039/c4cc05132g

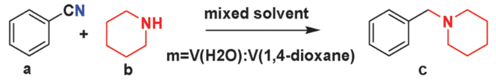
Table 1 Formation of tertiary amines from benzonitrile in a series of reaction conditions[a]



| Entry | $n$(b) : $n$(a) | $T$ (°C) | Solvent | Conv.[b] (%) | Sel.[b] (%) | | |
|---|---|---|---|---|---|---|---|
| | | | | | TA | DA | DI |
| 1 | 2 | 80 | Toluene | 100 | 45.0 | 33.0 | 21.0 |
| 2 | 2 | 100 | Toluene | 100 | 72.2 | 23.0 | 2.4 |
| 3 | 2 | 80 | Xylene | 100 | 16.6 | 74.4 | 9.0 |
| 4 | 2 | 100 | Xylene | 100 | 33.5 | 55.7 | 9.0 |
| 5 | 2 | 80 | 1,4-Dioxane | 100 | 51.6 | 31.1 | 17.3 |
| 6 | 2 | 100 | 1,4-Dioxane | 100 | 41.9 | 36.6 | 21.5 |
| 7 | 2 | 40 | Methanol | 100 | 23.3 | 58.6 | 16.6 |
| 8 | 2 | 40 | Acetic acid | 100 | 36.8 | 25.9 | 30.6 |
| 9 | 2 | 80 | Triethylamine | 98.8 | 38.6 | 44.5 | 16.8 |
| 10 | 2 | 80 | Heptane | 100 | 13.3 | 1.9 | 83.4 |
| 11 | 2 | 80 | Ethanol | 100 | 64.4 | 32.2 | 3.4 |
| 12 | 2 | 60 | Ethanol | 100 | 74.3 | 23.0 | 2.6 |
| 13 | 2 | 80 | Water | 100 | 62.9 | 3.0 | 4.8 |
| 14 | 2 | 100 | Water | 100 | 84.8 | 1.3 | 8.1 |

[a] Reaction conditions: 0.005 mmol Pt NWs, 1 bar $H_2$ pressure in corresponding temperature and solvent (2.0 mL). [b] GC yield.

Table 2 Formation of tertiary amine in a series of reaction conditions[a]



| Entry | Catalyst | $H_2$(bar) | $n$(a)/$n$(b) | $M$ | $T$ (°C) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | Pt NW | 1 | 1.1 | 1 | 100 | 92.6 |
| 2 | Pt NW | 1 | 1.1 | 1 | 80 | 65.8 |
| 3 | Pt NW | 1 | 1.1 | 1 | 60 | 75.1 |
| 4 | Pt NW | 1 | 1.1 | 1 | 40 | 40.5 |
| 5 | Pt NW | 1 | 1.1 | 2 | 100 | 95.3 |
| 6 | Pt NW | 1 | 1.1 | 3 | 100 | 96.1 |
| 7 | Pt NW | 1 | 1.1 | 5 | 100 | 95.5 |
| 8 | Pt NW | 1 | 1.1 | 7 | 100 | 94.2 |
| 9 | Pt NW | 1 | 1.1 | 9 | 100 | 77.6 |
| 10 | Pt NW | 1 | 1.1 | 1/3 | 100 | 91.5 |
| 11 | Pt NW | 1 | 1.1 | 1/7 | 100 | 78.3 |
| 12 | Pt NW | 1 | 2 | 1 | 100 | 97.7 |
| 13 | Pt NW | 1 | 5 | 1 | 100 | 98.5 |
| 14 | — | 1 | 1.1 | 3 | 100 | N.D.[c] |
| 15 | Pt NW | — | 1.1 | 3 | 100 | N.D.[c] |

[a] All Reactions were carried out with 0.005 mmol Pt NW at the appropriate temperature, mixed solvent (2.0 mL), 1 bar $H_2$ pressure for 24 h. [b] GC yield. [c] Not detected.

Both the aprotic (heptane, toluene, xylene, 1,4-dioxane, *etc.*) and protic (water, ethanol, methanol, *etc.*) solvents cannot afford high selectivity for the tertiary amine. And also, acidic and basic conditions are applied to run the model reaction (entries 8 and 9). Obviously, the yield of tertiary amine was not enhanced much. Therein, the main problem was the side reaction where the nitriles tend to interact with themselves instead of with the added piperidines, which was consistent with the fact that the hydrogenation of nitriles under vigorous hydrogenation conditions over platinum metal catalysts is favorable for self-hydrogenation.[14]

However, one interesting point we noted was that even though water is a poor solvent for benzonitrile (10 mg $mL^{-1}$ in 100 °C), the selectivity of the tertiary amine in it was surprisingly higher than those which dissolved nitriles well. Because of the nature of benzonitrile's solubility in water, the reaction mixtures were always in emulsion (shown in Fig. 1). The two corresponding sides may contribute to the selectivity of the tertiary amine in water. For one thing, due to the interaction of cyan groups with water, the orientation of these functional groups was towards water molecules, which decreased the chance for nitriles to couple with each other and it became easier for the piperidine to approach the nitrile. For another, a part of nitrile molecules was concealed inside the droplet, restricting a further increase in the selectivity.

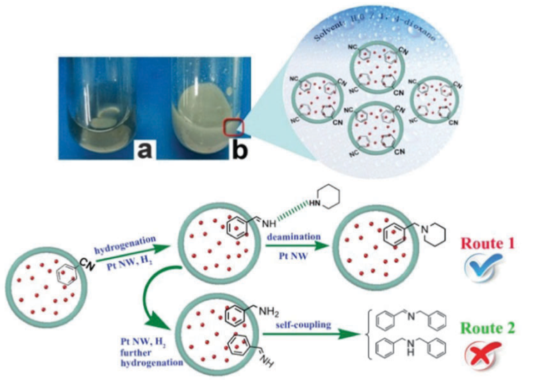


Fig. 1 Proposed mechanism (the solvent for reaction mixture a is dioxane, the solvents for reaction mixture b are water and dioxane).

To further enhance the yield of tertiary amines, 1,4-dioxane was chosen as the additional reagent to form a mixed solvent. 1,4-Dioxane is miscible with water and it can dissolve the hydrophobic part well.

In accordance with our conjecture, the mixed solvent shows excellent performance in the selective synthesis of tertiary amines from hydrogenation of nitriles (Table 2, entry 1). Further investigation of different proportions of the two different solvents used (entries 5–11 in Table 2) revealed that when the volume ratio of water and 1,4-dioxane was 3, a balance was reached and the highest yield of tertiary amine was obtained. The reaction temperature also had a noticeable impact on the selectivity of the reaction, and a higher temperature was found to exhibit better selectivity for the generation of tertiary amines.

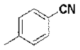
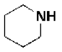
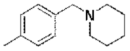
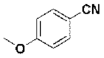
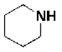
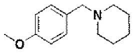
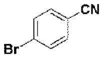
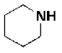
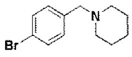
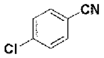
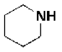
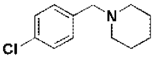
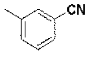
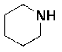
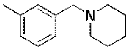
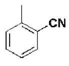
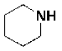
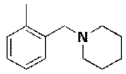
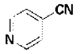
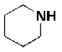
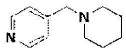
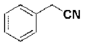
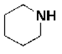
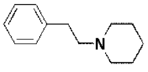
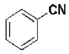
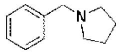
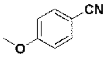
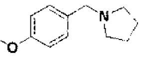
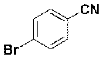
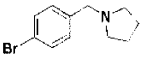
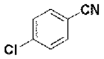
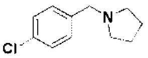
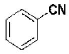
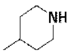
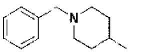
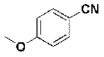
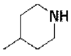
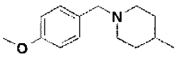
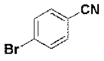
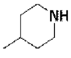
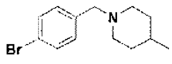
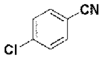
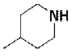
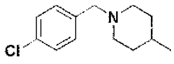
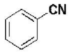
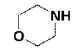
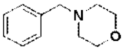
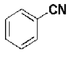
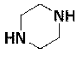
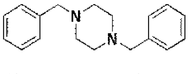
Besides, more additional amine contributed to a higher yield of the desired products. Also, when the reaction was conducted in the absence of the catalyst or hydrogen, the tertiary amine could not be detected, which indicates that the Pt NW and hydrogen gas were critical to the success of this transformation.

We proposed the interfacial interaction and organic mechanism in Fig. 1 based on our experiment and previous research.[14,15] Aromatic nitriles formed microdroplets in water and 1,4-dioxane used prevented them from being submerged inside (shown in Fig. 1).

Benzoimine is the most important intermediate got through partial hydrogenation of benzonitrile. It would react with the added piperidine preferentially, subsequent elimination of ammonia from which would lead to tertiary amine as the major product. Benzylamine obtained from further hydrogenation will react with the initial imine to give both symmetrical secondary amine and imine as byproducts, which is unfavorable according to the interfacial interaction shown in Fig. 1. Herein, the Pt NW plays a vital role in the hydrogenation and elimination of $NH_3$.

With the optimal reaction conditions (1 bar $H_2$, 100 °C, mixed solvent 2 mL (1.5 mL water, 0.5 mL 1,4-dioxane), 1 mmol nitrile, 1.1 mmol added secondary amine) in hand, we proceeded to investigate the scope of the reaction using a wide range of nitriles and secondary amines. Obviously, almost all of the substrates gave the desired tertiary amines in good to excellent yields. The substituents on the phenyl rings of the substrates did not appear to have a significant influence on the outcome of the reaction, but steric hindrance exerted an influence on the reaction yield (entries 5 and 6). Also the results in entries 7 and 8 demonstrated that the system was also valid for heterocyclic and aliphatic nitriles. Weaker H-bonding between amines and water contributes to higher selectivity of desired products (entries 9–17, compared with piperidine). Interestingly, when piperazine was used as an added secondary amine, the C–N coupling could be reached on both sides of it (entry 18).

Table 3 Tertiary amines prepared using different nitriles and secondary amines over Pt NWs[a]

| Entry | Nitriles | Amines | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  |  |  | 85.5(83.0) |
| 2 |  |  |  | 94.3(89.0) |
| 3 |  |  |  | 90.1(86.3) |
| 4 |  |  |  | 83.2(79.5) |
| 5 |  |  |  | 75.3 |
| 6 |  |  |  | 42.3 |
| 7 |  |  |  | 73.6(68.8) |
| 8 |  |  |  | 83.8 |
| 9 |  |  |  | 87.9(85.7) |
| 10 |  |  |  | 92.3(90.2) |
| 11 |  |  |  | 89.7(86.3) |
| 12 |  |  |  | 82.0(80.1) |
| 13 |  |  |  | 99.3(96.2) |
| 14 |  |  |  | 99.0(97.2) |
| 15 |  |  |  | 87.3(85.2) |
| 16 |  |  |  | 97.0 |
| 17 |  |  |  | 86.6(84.5) |
| 18[c] |  |  |  | 73.0 |

[a] Reaction conditions: 1 mmol nitrile, 1.1 mmol secondary amine, 0.005 mmol Pt NWs, 100 °C, water (1.5 mL), 1,4-dioxane (0.5 mL), 1 bar $H_2$ pressure for 24 h. [b] GC yield. [c] 2 mmol nitrile, 1 mmol piperazine. The values in the parentheses are the yields of the isolated products.

The reaction can be upscaled successfully and Pt NWs show great superiority in achieving high conversion and selectivity compared with other Pt catalysts with different morphologies (shown in the ESI†) (Table 3).

In conclusion, a series of tertiary amines have been successfully synthesized from the interfacial hydrogenation of nitriles in one pot using highly active and stable Pt NWs as the catalyst. A mixed solvent was applied here to adjust the solubility of aromatic nitriles, as a result of which the yield of tertiary amine could reach up to 99.0%. The idea of this reaction is novel, efficient and environmentally friendly. Further study of this catalytic system for wider application is under investigation in our laboratory.

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## Notes and references

1 A. R. Brown, D. C. Rees, Z. Rankovic and J. R. Morphy, *J. Am. Chem. Soc.*, 1997, **119**, 3288–3295.

2 D. Menche, S. Bohm, J. Li, S. Rudolph and W. Zander, *Tetrahedron Lett.*, 2007, **48**, 365–369.

3 (*a*) K. P. C. Vollhardt and N. E. Schore, *Organic Chemistry: Structure and Function*, W. H. Freeman and Company, USA, 3rd edn, 1999; (*b*) S. A. Lawrence, *Amines: Synthesis Properties, and Applications*, Cambridge University, Cambridge, 2004; (*c*) A. A. NfflÇez Magro, G. R. Eastham and D. J. Cole-Hamilton, *Chem. Commun.*, 2007, 3154–3156.

4 (*a*) R. N. Salvatore, C. H. Yoon and K. W. Jung, *Tetrahedron*, 2001, **57**, 7785–7811; (*b*) R. N. Salvatore, A. S. Nagle and K. W. Jung, *J. Org. Chem.*, 2002, **67**, 674; (*c*) C. Chiappe, P. Piccioli and D. Pieraccini, *Green Chem.*, 2006, **8**, 277–281; (*d*) C. B. Singh, V. Kavala, A. K. Samal and B. K. Patel, *Eur. J. Org. Chem.*, 2007, 1369–1377; (*e*) M. H. S. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555; (*f*) A. C. Bissember, R. J. Lundgren, S. E. Creutz, J. C. Peters and G. C. Fu, *Angew. Chem., Int. Ed.*, 2013, **52**, 5129–5133.

5 G. Hughes, P. N. Devine, J. R. Naber, P. D. O'Shea, B. S. Foster, D. J. McKay and R. P. Volante, *Angew. Chem.*, 2007, **119**, 1871–1874 (*Angew. Chem., Int. Ed.*, 2007, **46**, 1839–1842).

6 (*a*) J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1158; (*b*) S. Shekhar, P. Ryberg, J. F. Hartwig, J. S. Mathew, D. G. Blackmond, E. R. Strieter and S. L. Buchwald, *J. Am. Chem. Soc.*, 2006, **128**, 3584; (*c*) O. Navarro, N. Marion, J. Mei and S. P. Nolan, *Chem. – Eur. J.*, 2006, **12**, 5142.

7 (*a*) K. C. Hultzsch, D. V. Gribkov and F. Hampel, *J. Organomet. Chem.*, 2005, **690**, 4441–4452; (*b*) A. M. Johns, M. Utsunomiya, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 1828; (*c*) B. D. Stubbert and T. J. Marks, *J. Am. Chem. Soc.*, 2007, **129**, 4253–4271.

8 (*a*) J. L. He, J. W. Kim, K. Yamaguchi and N. Mizuno, *Angew. Chem.*, 2009, **121**, 10072–10076 (*Angew. Chem., Int. Ed.*, 2009, **48**, 9889–9893); (*b*) K. Yamaguchi, J. L. He, T. Oishi and N. Mizuno, *Chem. – Eur. J.*, 2010, **16**, 7199–7207.

9 X. Liu, L. He, Y. M. Liu and Y. Cao, *Acc. Chem. Res.*, 2014, **47**, 793–804.

10 L. He, Y. Qian, R. S. Ding, Y. M. Liu, H. Y. He, K. N. Fan and Y. Cao, *ChemSusChem*, 2012, **5**, 621–624.

11 (*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*) F. Q. Qi, L. Hu, S. L. Lu, X. Q. Cao and H. W. Gu, *Chem. Commun.*, 2012, **48**, 9631–9633; (*c*) L. Y. Shi, L. Hu, J. Q. Wang, X. Q. Cao and H. W. Gu, *Org. Lett.*, 2012, **14**, 1876–1879.

12 S. L. Lu, J. Q. Wang, X. Q. Cao, X. M. Li and H. W. Gu, *Chem. Commun.*, 2014, **50**, 3512–3515.

13 J. Shares, J. Yehl, A. Kowalsick, P. Byers and M. P. Haaf, *Tetrahedron Lett.*, 2012, **53**, 4426–4428.

14 (*a*) H. Sajiki, T. Ikawa and K. Hirota, *Org. Lett.*, 2004, **6**, 4977–4980; (*b*) R. Reguillo, M. Grellier, N. Vautravers, L. Vendier and S. Sabo-Etienne, *J. Am. Chem. Soc.*, 2010, **132**, 7854–7855; (*c*) D. Srimani, M. Feller, Y. Ben-David and D. Milstein, *Chem. Commun.*, 2012, **48**, 11853–11855.

15 S. K. Sharma, J. Lynch, A. M. Sobolewska, P. Plucinski, R. J. Watsonc and J. M. J. Williams, *Catal. Sci. Technol.*, 2013, **3**, 85–88.