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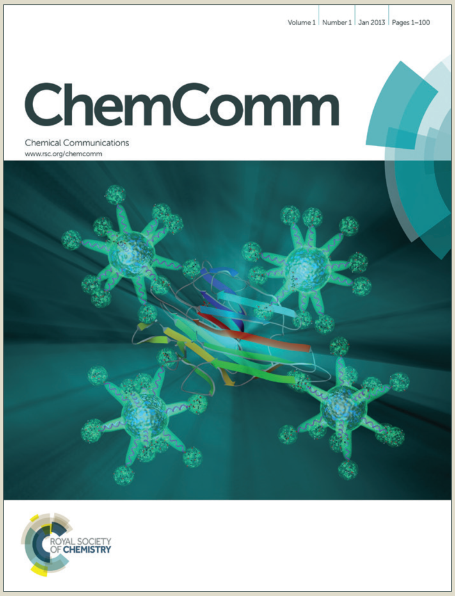

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ARTICLE TYPE

Selective Synthesis of Secondary Amines from Nitriles using Pt Nanowires as a Catalyst

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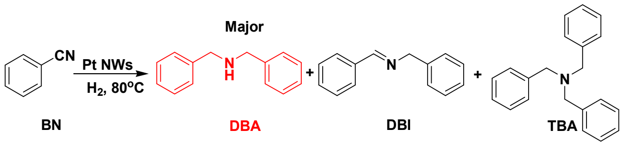
A new one-pot method has been developed for the selective synthesis of secondary amines via the reductive amination of the corresponding nitriles using Pt nanowires as a catalyst. This method allows for the synthesis of both unsymmetrical and symmetrical secondary amines in excellent yields (up to 95%) in the presence or absence of additional amines, respectively. Furthermore, the reaction proceeds under mild conditions and is environmentally benign.

Secondary amines are an important functional group in organic chemistry and examples belonging to this group can be found in an extensive range of natural products, bioactive molecules and industrial materials.[1] Despite their numerous applications and presence in a wide variety of different materials, the development of methods allowing for the selective synthesis of secondary amines represents a long standing problem in organic chemistry, and considerable research efforts have been focused[2] on exploring new synthetic methods in this particular area. Three conventional routes have been reported for the synthesis of these important synthetic targets, including (1) direct base-promoted mono-*N*-alkylation[3], (2) reductive amination[4], and (3) alkylative amination[5]. To date, however, there have been no reports in the literature describing the development of truly efficient and environmentally benign methods for the selective *N*-alkylation of primary amines to form secondary amines. With this in mind, considerable opportunities therefore still exist to improve these methods, in terms of avoiding the generation of wasteful salts[6] and developing more facile processes to enhance the selectivity of these methods for the formation of secondary amines.

We previously reported the development of a method for the formation of C-N bonds via the coupling of aldehydes with an amine[7], as well as a method for the reductive amination of aldehydes and ketones in the presence of ammonia to give secondary amine in a good yield[8]. The direct use of nitriles as alkylating agents for the preparation of secondary amines represents a feasible alternative to the strategies commonly used for amine alkylation, because of their bioavailability in nature and generally commercial availability. Sabo-Etienne et al.[9] investigated the mechanism of the ruthenium-catalyzed hydrogenation of nitriles for the preparation of primary amines, and Srimani et al.[10] selectively prepared a series of imines in high yields via the hydrogenation of nitriles. Sajiki et al.[11] reported the Pd/C catalyzed synthesis of secondary and tertiary amines using simple aliphatic nitriles. It is worth mentioning that aromatic and aliphatic primary amines could also be used as added amines in this particular case. Sharma[12] described the use of a continuous flow multichannel microreactor for the reductive amination of nitriles in the presence of a Pt/C catalyst.

Herein, we report an entirely new Pt nanowire (Pt NW) synthesized from Platinum bis(acetylacetonate)[13] catalyzed reductive amination process for the preparation of both symmetric and unsymmetrical secondary amines from the corresponding nitriles.



Scheme 1 Symmetrical Secondary Amine Formation from the Hydrogenation Reaction of Benzonitrile

At the beginning of this study, we evaluated the possibility of hydrogenating nitriles as a method for accessing symmetrical secondary amines (Scheme 1). Under the optimized reaction conditions (i.e., reaction temperature of 80 °C in methanol under an atmosphere of H_2, See Supporting Information), benzonitrile was efficiently hydrogenated to afford dibenzylamine in an isolated yield of 95.4%. Furthermore, only a trace amount of the corresponding tribenzylamine was detected during the reaction (Figure 1).

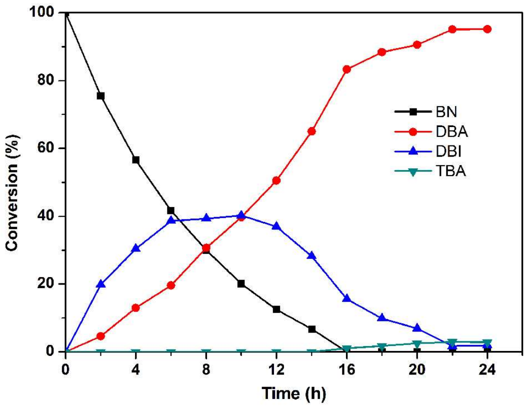


Figure 1. Time-conversion plot for DBA formation from the hydrogenation of benzonitrile using Pt NWs as the catalyst.

We then proceeded to explore the scope of this catalytic

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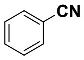
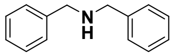
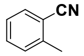
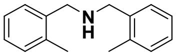
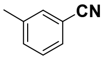
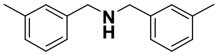
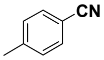
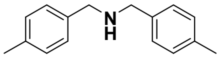
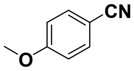
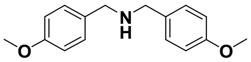
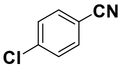
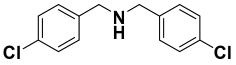
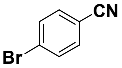
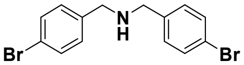
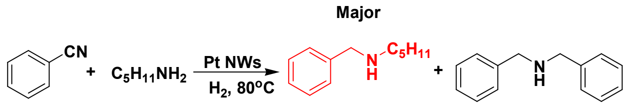
transformation using a range of *para*, *meta*, and *ortho*-substituted aromatic nitrile substrates. The results of these scoping experiments are summarized in the Supporting Information and Table 1. It is noteworthy that the use of higher pressures led to increases in the yield and shorter reaction times. Steric hindrance from the substituents of the phenyl ring of the nitrile also had a noticeable impact on the reaction (Table 1, entry 2). For example, the yields of the symmetrical secondary amines decreased from 96.6% to 91.8% on going from the *para*-methylbenzonitrile to the *ortho*-methylbenzonitrile, (Table 1, entries 2 and 4). In addition, the optimized reaction conditions were found to be highly compatible with several other functional groups on the aromatic nitriles. For example, electron-deficient substrates were well tolerated, and afforded relatively high yields of the corresponding symmetrical secondary amine products (Table 1 entries 5–7).

Table 1 Formation of Symmetrical Secondary Amines from Different Nitriles.[a]

entry	substrate	product	Yield (%)[b]	Yield (%)[c]
1			95.4	>99
2			78.2	91.8
3			88.9	95.6
4			93	96.6
5			70.8	87.6
6			84.1	89.9
7			76	91.3

[a]Reaction condition: 80 °C, ethanol (2.0 mL), 1 bar H_2 pressure for 24 h; [b]GC yield; [c]4 bar H_2.

Given the highly efficient nature of this reaction for the generation of symmetrical secondary amines via the hydrogenation of nitriles, we proceeded to examine the catalytic capability of our system for the preparation of unsymmetrical secondary amines by conducting the reaction in the presence of an additional amine[14].

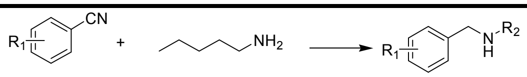


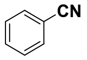
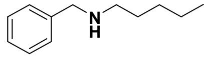
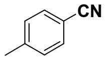
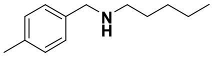
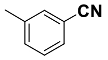
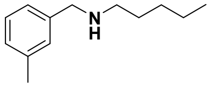
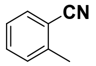
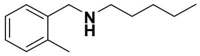
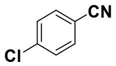
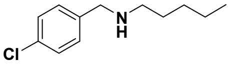
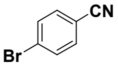
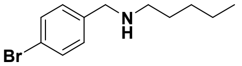
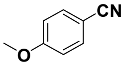
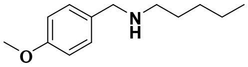
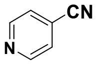
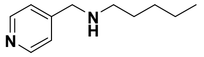
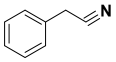
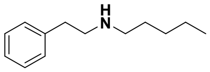
Scheme 2 Asymmetrical Secondary Amine Formation from the Hydrogenation Reaction of Benzonitrile with Pentylamine

To begin with, the reaction was screened in seven different solvents under 1 bar of hydrogen pressure. In ethanol, dioxane and toluene, the Pt NW catalyst did not exhibit a strong dependence on the polarity of the solvent and showed excellent catalytic activity towards the reaction between benzonitrile and pentylamine, with the *N*-benzylpentan-1-amine product being formed in yields of up to 90%. However, when water and heptane were used as the solvent, the desired secondary amine products were formed in much lower yields, with significant quantities of the imine being formed instead. Based on these results, toluene was selected as the best solvent for further studies. The reaction temperature also had a noticeable impact on the selectivity of the reaction, and the reaction system was found to exhibit its highest selectivity for the generation of unsymmetrical secondary amines at 80 °C in toluene. In addition, when the reaction was conducted in the absence of the catalyst or hydrogen, the conversion of the benzonitrile was relatively low, which indicated that the Pt NW and hydrogen were critical to the success of this transformation.

With the optimal reaction conditions in hand, we proceeded to investigate the scope of the reaction for the synthesis of unsymmetrical secondary amines using a range of different nitriles and amines (Supporting Information). In most of these cases, however, the reaction only afforded a mixture of the secondary amine and the corresponding imine. Pleasingly, the use of a higher reaction pressure led to an increase in the selectivity. Thus, when 4 bar H_2 pressure was used, the imine intermediates were readily converted to the desired secondary amines. Further increases in the pressure, however, led to self-coupling reactions in the aromatic nitriles and the formation of the symmetrical secondary amines (Supporting Information).

Table 2 The formation of Unsymmetrical Secondary Amines from different Nitriles.[a]



entry	substrate	product	Yield (%)[b]
1			93.3
2			96.3
3			95.2
4			77.4
5			91.8
6			88.6
7			90.9
8			89.2
9[c]			91.8

[a]Reaction condition: 80 °C, toluene (2.0 mL), nitrile:amine ratio of 1:2, 10 h in 1 bar H_2 pressure, and then 10 h in 4 bar H_2 pressure; [b]GC yield; [c]100 °C.

Then we divided this process in two steps. Thus, the reaction was initially conducted under an atmosphere of H_2 for the first 10 h, and the whole system was then subjected to 4 bar of H_2 pressure for another 10 h. Under these new conditions, all of the different substrates were converted to the desired unsymmetrical secondary amine products in yields of up to 90% (Table 2).

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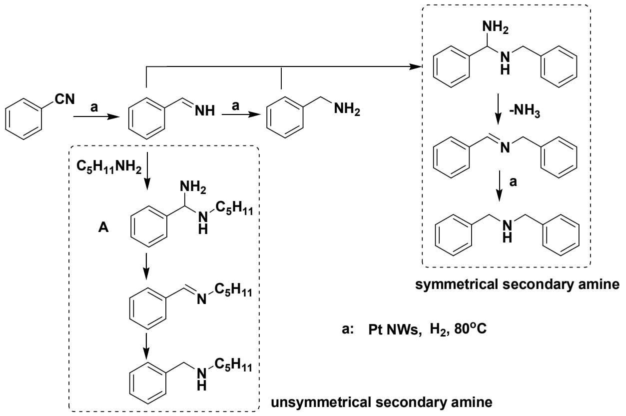
Furthermore, the substituents on the phenyl rings of the substrates did not appear to have a significant influence on the outcome of the reaction, and steric hindrance only exerted a minor influence on the reaction yield. Overall, the current transformation is both simple and effective, and satisfies the requirements of a green chemical process. It is noteworthy that the reaction still afforded a satisfactory yield of the desired secondary amine product when the substrate was changed to 2-phenylacetonitrile and the temperature was increased to 100 °C. This result therefore demonstrated that the system was valid for aliphatic nitriles.

Real time GC measurements were carried out during the course of the model reaction between benzonitrile and pentylamine in the presence of the Pt NW catalyst to develop a deeper understanding of the mechanism of this catalytic process. The results of these measurements suggested that the intermediate *N*-benzylidenepentan-1-amine was quickly formed with the consumption of benzonitrile. The amount of this intermediate increased steadily up to its highest point around 7 h, and then decreased sharply. During this decrease, there was a steady increase in the amount of *N*-benzylpentan-1-amine. The reaction required a total of 12 h to reach completion, and a small amount of dibenzyl amine could also be detected.

Based on the kinetics, which is mentioned above, we have proposed a plausible mechanism for the reaction shown in Scheme 3. Thus, the partial hydrogenation of benzonitrile would give the corresponding benzyl imine, which would react with the added pentylamine to give intermediate A instead of being further hydrogenated to the corresponding benzyl amine. The subsequent elimination of ammonia from A (either through the unsymmetrical imine or direct interaction with the Pt NW catalyst) would lead to the formation of the unsymmetrical secondary amine product. This mechanism also accounts for the trace amount of dibenzyl amine observed during the reaction, which would be formed from the side reaction between benzyl amine and the benzyl imine.



Scheme 3. Proposed Mechanism for the Synthesis of Symmetrical and Unsymmetrical Secondary Amines

In conclusion, we have successfully developed a one-pot method for the synthesis of both symmetrical and unsymmetrical secondary amines from nitriles using a Pt NW catalyst with excellent yields of up to 96.6 %. This method is attractive because it does not involve alkyl halides or carbonyl compounds and consequently avoids the harsh reaction conditions, poor yields and low levels of chemical selectivity associated with these conventional N-alkylation procedures. Further studies of this catalytic system are currently underway in our laboratory to investigate its wider applications.

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Notes and references

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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, real GC measurements for the formation of asymmetrical secondary amine, catalytic stability of the Pt NW and full spectroscopy data for all compounds (24 pages). See DOI: 10.1039/b000000x/

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