ChemComm

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Fe$_2$O$_3$-supported nano-gold catalyzed one-pot synthesis of *N*-alkylated anilines from nitroarenes and alcohols†

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Here, we show the one-step synthesis of *N*-alkylated anilines from nitrobenzenes and alcohols catalyzed by nano-gold catalyst. The yields to *N*-alkylated anilines were ~90% under mild conditions. The mechanism of this reaction was explored. It shows promise for clean and simple synthesis of *N*-alkylated anilines.

Aromatic amines are extensively found in biologically active natural products, pharmaceuticals, dyes and ligands for transition-metal-catalyzed reactions.[1] Much effort has been spent for more than a century on methods to prepare aromatic amines. In industry, nevertheless, the catalytic hydrogenation of nitroarenes serves as the key technology.[2] Meanwhile, the anilines need to be further functionalized to get more valuable compounds. Besides the well-known non-catalytic *N*-alkylations of anilines with alkyl halides in the presence of stoichiometric amounts of inorganic bases,[3] various catalytic reactions have been developed because the use of alkyl halides is undesirable from an environmental point of view and causes handling problems as well as significant waste generation. In the last decades, modern transition-metal-catalyzed processes, *i.e.* reaction of amine with amines or aryl halides,[4] reductive amination,[5] hydroaminations[6] and hydroaminomethylations,[7] *etc.*, were successfully employed and elegant results were obtained. Excepting the methods mentioned above, the *N*-alkylation of anilines with alcohol, in which water was produced as the only byproduct, could be a good choice for the development of an environmentally benign method for *N*-functionalized anilines synthesis. In the former reports, extensive attention has been focused upon Ni, Ru, Ir, Pd, Au, Cu, and Fe as effective catalysts.[8] However, the usage of organic ligand and additional base as cocatalyst makes the catalyst system complicated and not practical. Moreover, the anilines need to be firstly synthesized through the reduction of nitrobenzenes.[2] Recently, it was reported that *N*-alkylated anilines could be synthesized in one step using nitrobenzenes as starting materials with alcohol as alkylation reagent.[9] However, it also needs the usage of complicated organic ligand and additional base as cocatalyst. It would be highly desirable if a heterogeneous

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† Electronic supplementary information (ESI) available: Experimental details on the catalyst preparation, reaction procedure and product characterization. See DOI: 10.1039/c1cc11057h
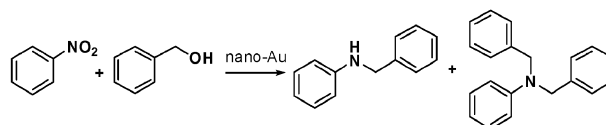
Scheme 1 An illustration for the synthesis of anilines.

catalyst could be used in this reaction without additional organic ligand and base.

The unique activity of supported nano-gold catalyst has been reported in many reactions.[10] Recently, it was found that nano-gold could be a good catalyst in selective oxidation[11] and selective hydrogenation reactions.[12] Inspired by these interesting results, we speculate that supported nano-gold may be applied in the reductive benzylation of nitrobenzene with alcohol, in which the key steps are the oxidation of alcohol and the reduction of imine intermediate.[13] Herein, we want to present our new results on the alkylation of nitrobenzene derivatives catalyzed by iron oxide immobilized nano-gold catalyst, Scheme 1. *N*-monobenzylated or *N*,*N′*-dibenzylated aniline could be obtained by tuning the reaction conditions finely.

A series of metal oxide immobilized nano-gold catalysts were prepared by a co-precipitation method. For the physicochemical properties of the catalysts, see Table S2. The BET surface area of all the catalysts was ~100 m^2 g^{-1}. HR-TEM, XPS and XRD characterization confirmed the formation of metal oxide immobilized nano-catalyst. For a typical sample, *i.e.* 9.1 wt% Au/Fe$_2$O$_3$, the particle size of the nano-gold was ~3 nm and the crystal lattice Au (200) on the iron oxide could be observed clearly (2002 JCPDS 65-2870), Fig. 1, Fig. S2–4.

The results for the benzylation of nitrobenzene with benzyl alcohol using different immobilized nano-catalysts are shown in Table 1. Only *N*-benzylideneaniline was observed if using
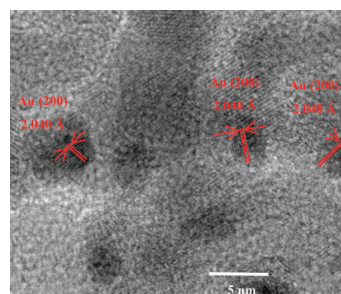

Fig. 1 HR-TEM picture of 9.1 wt% Au/Fe$_2$O$_3$.

Table 1 *N*-benzylaniline synthesis from nitrobenzene[a]

Entry	Catalyst	Au mol (%)	Conv. (%)[b]	Sel. (%)[c]	P.S. (nm)[d]
1	Fe$_2$O$_3$	—	51	0	—
2	1.8 wt% Au/Fe$_2$O$_3$	0.18%	>98	25	∼3
3	4.3 wt% Au/Fe$_2$O$_3$	0.44%	>98	53	∼3
4	6.3 wt% Au/Fe$_2$O$_3$	0.64%	>98	66	∼3
5	9.1 wt% Au/Fe$_2$O$_3$	0.92%	>98	96	∼3
6	4.6 wt% Au/CeO$_2$	0.47%	89	6	—[e]
7	2.8 wt% Au/Co$_3$O$_4$	0.28%	97	6	∼6
8	2.5 wt% Au/NiO	0.25%	95	60	∼4
9	3.6 wt% Pd/Fe$_2$O$_3$	0.37%	63	5	—[e]
10	2.9 wt% Ru/Fe$_2$O$_3$	0.29%	59	8	—[e]
11[f]	11.5 wt% Au/Fe$_2$O$_3$	1.17%	>99	78	∼4.5

[a] 5 mmol (0.615 g) nitrobenzene, 50 mmol (5.400 g) benzyl alcohol, 0.1 g catalyst, 160 °C, 8 h, 20 mL pressure tube, Ar. [b] Conversion of nitrobenzene determined by GC-FID. [c] Selectivity to *N*-benzylaniline determined by GC-FID. The major byproduct was *N*-benzylideneaniline. [d] Gold particle size determined by TEM. [e] Difficult to be determined. [f] Catalyst from Prof. Haruta's group. It was prepared by a co-precipitation method and calcined at 400 °C. Prior to usage, the catalyst was activated under flowing air (20 mL min^{-1}) at 300 °C for 1 h. The gold particle was estimated by HR-TEM measurement.

hematite as the catalyst simply although 51% nitrobenzene was reduced, Entry 1. The introduction of gold could remarkably improve the formation of *N*-benzylaniline, *i.e.* the conversion of *N*-benzylideneaniline to *N*-benzylaniline, Entry 2. By increasing the loading of gold from 1.8 wt% to 9.1 wt%, an almost stoichiometric amount of *N*-benzylaniline could be produced, Entries 3–5. The conversion was >98% and the selectivity to *N*-benzylaniline is 96% using catalyst 9.1 wt% Au/Fe$_2$O$_3$, Entry 5. The supports play an extremely important role in order to achieve good activity. By applying catalysts 4.6 wt% Au/CeO$_2$ and 2.8 wt% Au/Co$_3$O$_4$, the selectivities to *N*-benzylaniline are all less than 10%, Entries 6–8. Also, a relatively good result was obtained if 2.5 wt% Au/NiO was used, Entry 8. The iron oxide immobilized Pd and Ru catalysts were also prepared and checked here, Entries 9–10. However, there is almost no improvement if comparing the result using iron oxide solely. Therefore, it is possibly a unique catalytic activity of iron oxide immobilized nano-gold to convert nitrobenzene into *N*-benzylaniline. Another iron oxide supported nano-gold catalyst, *i.e.* 11.5 wt% Au/α-Fe$_2$O$_3$ calcined at 400 °C, which was independently prepared by Haruta *et al.*, was also measured under the same reaction conditions, Entry 11. The conversion of nitrobenzene was almost 100% and the selectivity to *N*-benzylaniline was 78%. This difference in selectivity might be attributed to the difference in the size of Au particles and calcination temperature. When 9.1 wt% Au/Fe$_2$O$_3$ was reused for the second run, unfortunately, the major product was imine intermediate, *i.e.* >80%. ICP analysis showed 4.4 wt% Au was maintained in the used sample and XRD characterization suggested the severe aggregating of nano-gold during the reaction, Fig. S2b, which should be the reasons for the deactivation of the catalyst. Although there is no direct evidence, it could be imagined that the formation of water during the reaction is one of the possible reasons for the aggregation of nano-gold particles.

Further on, the reactions of different nitrobenzene and alcohol derivatives were employed with catalyst 9.1 wt%
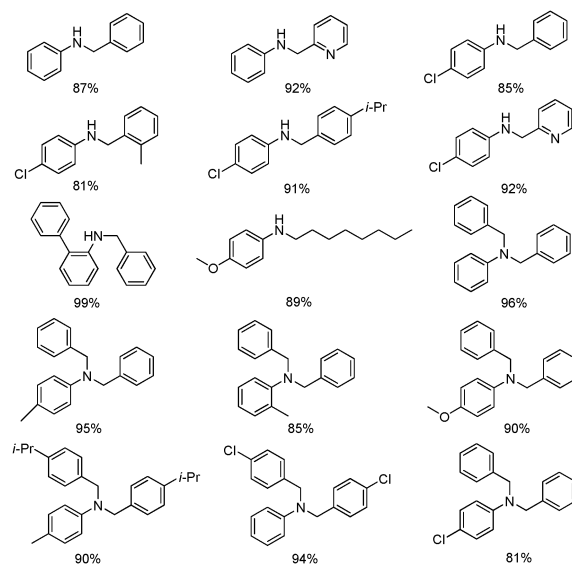
Scheme 2 Results of the reductive alkylation of nitrobenzenes.

Au/Fe$_2$O$_3$, Scheme 2. For the reaction of nitrobenzene and benzyl alcohol, 87% yield was obtained. If performing the reaction with 2-pyridine methanol as alkylation reagent, 92% yield could also be gotten. That means the presence of a heterocyclic group doesn't affect the catalytic activity of the nano-gold. Then, the reaction of 4-chloronitrobenzene with benzyl alcohol, 2-methyl-benzyl alcohol, 4-isopropylbenzyl alcohol and 2-pyridine methanol gave 81–92% yields. Interestingly, 99% yield was achieved using 2-phenylnitrobenzene and benzyl alcohol as starting materials. Importantly, the reaction could also progress with aliphatic alcohol as starting material. The yield to *N*-octyl-4-methoxyaniline was 89%.

Thus, our nano-gold catalyst could activate both aromatic and aliphatic alcohols. Also, the product from aliphatic alcohol was different from those from aromatic alcohol. As was mentioned above, the major product with aromatic alcohol as starting material was benzaldehyde. For aliphatic alcohol, *i.e.* 1-octanol, octyl octanoate and coupling products from octanal were detectable by GC-MS. However, this nano-gold catalyst is not active for the amination of methanol and secondary alcohols such as isopropanol and phenethyl alcohol. Only ∼20% aniline was formed in the presence of methanol and no reaction occurred with isopropanol and phenethyl alcohol as starting materials.

It is worth noting that *N,N*-di-substituted anilines with different functional groups could be synthesized just by varying the amount of catalyst and the ratio between nitrobenzene and alcohol. The yields to *N,N*-dibenzylaniline, *N,N*-dibenzyl-4-methylaniline, *N,N*-dibenzyl-2-methylaniline, *N,N*-dibenzyl-4-methoxyaniline, *N,N*-di-4-isopropylbenzylaniline, *N,N*-di-4-chlorobenzylaniline and *N,N*-dibenzyl-4-chloro-aniline reached 85–96% respectively. Therefore, we can synthesize anilines with different structure with this simple nano-gold catalyst system.
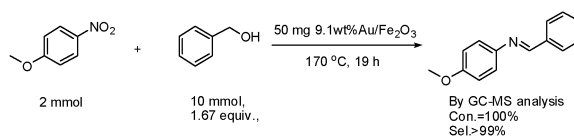
The iron oxide supported nano-gold catalyst could also be used in the synthesis of imine. As an example, N-benzylidene-4-methoxyaniline could be obtained if reducing the amount of catalyst simply.

Moreover, this catalyst offers a method for the synthesis of N,N-disubstituted amine from N-substituted amine. As a model reaction, N-benzyl-N-4-methoxybenzylaniline could be synthesized with 97% yield.
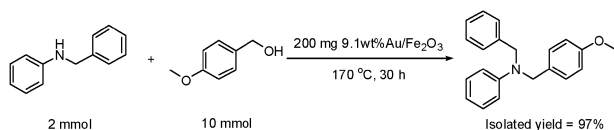
In order to check the possible reaction mechanism, the reaction between nitrobenzene and d_7-benzyl alcohol was performed. Traced by GC-MS, d_6-benzaldehyde, aniline and d_6-N-benzylideneaniline were formed at the initial stage.

Further exploration of the H–D exchange by GC-MS between aniline and D_2O under the same reaction conditions suggested that the ratio of aniline (m/z = 93) to d_1-aniline (m/z = 94) and d_2-aniline (m/z = 95) was 8.6 : 6.2 : 1.
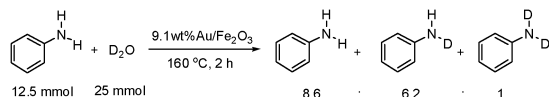
Thus there is an equilibrium in the H–D exchange of aniline and D_2O. However, based on the GC-MS measurement of the reaction using nitrobenzene and d_7-benzyl alcohol, no d_2-aniline could be observed and the ratio of 94 (m/z, d_1-aniline) and 93 (m/z, aniline) by ion selective spectra was less than 5%. This number was almost the same as that observed for pure aniline analysis. Also, only d_6-benzaldehyde could be detected, which suggested that almost all the protons on the hydroxyl groups have been transferred into the aniline. So we can say that the proton on the nitrogen of $PhNH_2$ was totally derived from the proton of the hydroxyl group of benzyl alcohol and one benzylic proton was transferred into water.
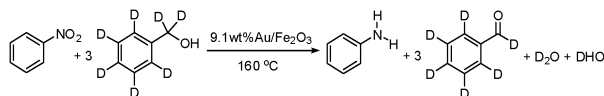
The H–D exchange could be neglected because the concentrations of aniline and D_2O were still very low at the initial stage of the reaction. According to the observation, a possible mechanism is given as follows.
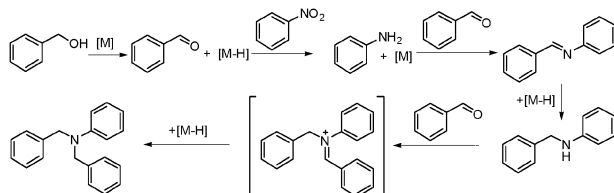
In summary, the one-step syntheses of anilines from nitrobenzenes were successfully realized with supported nano-gold as catalyst. The utilization of organic ligand and additional base was excluded. This reaction was simple and easily operationable. The improvement of the catalyst and reaction is now underway in our laboratory.

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