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Enhanced reactivity of silver- and gold-catalysed hydrogenations using silver(I) salts

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ABSTRACT

A novel application of silver(I) salt promoters in silver- and gold-catalysed hydrogenations was applied to the chemoselective reduction of halonitrobenzenes resulting in excellent conversions and selectivities. This reactivity, coupled with the low cost of silver relative to more expensive precious metal counterparts, demonstrates this catalytic system as an attractive alternative for challenging chemoselective transformations.

1. Introduction

Silver, gold and copper form a group in the periodic table traditionally known as the coinage metals. Silver and gold are relatively inert metals allowing for many of the applications we associate with them today. Their uses have ranged from jewellery and coins to electrical conductors. Silver is also used in mirrors and until recently, in photographic films and plates. However, with the advent of digital cameras the enormous reduction in the use of silver halide-based films has seen the price of silver decrease and remain low in comparison to other precious metals (Table 1).

It was not until the mid 20th century that silver was first identified as a metal for catalytic reactions, with the oxidation of carbon monoxide[1] and the decomposition of formic acid.[2] Since then, its application as a catalyst has been widely reported as illustrated by the oxidation of methanol,[3] the epoxidation of ethylene,[4] and more recently, as a potential alternative to the more expensive platinum used in catalytic converters for diesel engines.[5]

The use of gold in catalysis was initially reported in the early 1970s when Bond described the hydrogenation of olefins over supported gold catalysts.[6] Hutchings and Haruta et al. continued to make breakthroughs with their work around polyvinyl chloride (PVC) manufacture[7] and the use of gold nano-particles in carbon monoxide oxidation,[8] respectively.

The first report of using silver to catalyse hydrogenation reactions was described by Nagase et al.[9] However, it was not until the work by Claus, investigating the reduction of α,β-unsaturated aldehydes,[10] and Qui, with the reduction of chloronitrobenzenes,[11] that the chemoselective properties of supported silver catalysts were first illustrated. The use of gold catalysts for chemoselective reductions of aromatic nitro compounds[12] and the highly selective hydrogenation of α,β-unsaturated aldehydes[13] have provided new and exciting possibilities for gold-catalysed hydrogenation reactions. Although excellent progress has been made in this field one drawback is the high temperatures and pressures required to achieve high conversions.

This Letter describes the design of a chemoselective hydrogenation of synthetically useful substrates using a novel combination of a silver on alumina catalyst, or a range of gold catalysts, coupled with a silver(I) salt promoter. This key combination of catalyst and additive is shown to facilitate low temperature and pressure hydrogenation reactions amenable to large scale manufacture using an inexpensive metal and support.

The reduction of chloronitrobenzenes to their respective chloroanilines is an important transformation in the production of pharmaceutical and agricultural products.[14] Iron in acidic reaction media[15] is routinely used in academia and small scale process research; however, disposal issues associated with the iron residues render the process undesirable for larger scale manufacturing. Alternative methodologies have also been reported using a range of precious metals including platinum,[16] palladium[17] and more recently gold,[18] as catalysts for the hydrogenation of chloronitrobenzenes. Although progress has been made, chemoselectivity can still be a problem with the hydrodehalogenated side product often observed (Fig. 1).

Table 1
Comparison of metal prices

Metal	$/Troy ounce [a]
Gold	1119
Silver	18
Platinum	1668
Palladium	490

[a] Metal prices provided by http://www.metalmarkets.org.uk/ 2nd April 2010.

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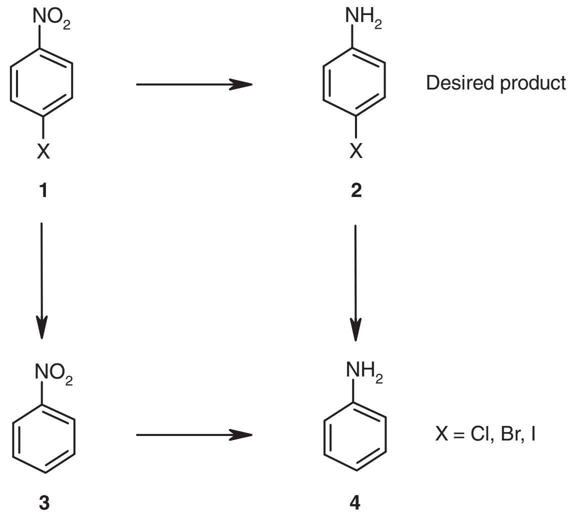
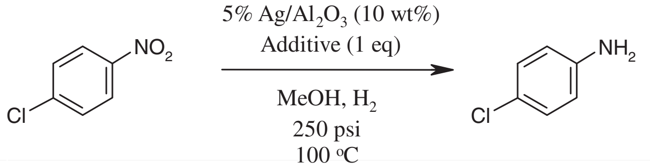


Figure 1. Possible side reactions during the reduction of halonitroaromatics.

We started our investigation by comparing the effect of catalyst on the hydrogenation of *para*-chloronitrobenezene (*p*-CNB). A traditional palladium catalyst, 5% Pd/C 58 was examined in tandem with 5% Ag/Al_2O_3 [both supplied by Johnson Matthey (J.M.)]. When the palladium catalyst was used complete conversion into the aniline **4** was observed even at a low pressure of 40 psi. Gratifyingly, when the 5% Ag/Al_2O_3 catalyst was used, a selective reduction was achieved but with only 15% conversion into the desired *p*-chloroaniline **2** (100 °C, 300 psi H_2). Thus, our next aim was to develop milder reaction conditions for the reduction of halonitrobenzenes whilst increasing the conversion during the hydrogenation. To achieve this goal, we investigated the possibility of enhancing the reactivity with an additive.

Akao et al. identified Rh/C doped with additives, such as $Fe(OAc)_2$ and $Ni(NO_3)_2{\cdot}6H_2O$, as excellent promoters for accelerating the reduction of a range of functionalised nitrobenzenes including 4-chloronitrobenzene under hydrogenation conditions.[19] This approach appeared attractive and so a range of additives was investigated in conjunction with the Ag/Al_2O_3 catalyst for the hydrogenation of *p*-CNB. The results are summarised in Table 2. Whilst excellent selectivity was achieved in all cases with the 5% Ag/Al_2O_3 catalyst, conversion into the desired chloroaniline showed a greater dependence on the additive used. Several metal salts were beneficial with $Zn(OAc)_2$ and $Cu(OAc)_2$ showing some promise, but silver salts clearly had the most beneficial effect.

Table 2
Selective hydrogenation of *p*-CNB with JM 5% Ag/Al_2O_3 catalyst



Additive	Time (h)	Conversion[a] (%)
None	20	15
CF_3SO_3Ag	20	6
Na_2CO_3	20	10
NaOAc	20	11
$CaCO_3$	20	16
$AgBF_4$	20	18
$Ni(NO_3)_2{\cdot}6H_2O$	20	18
$Fe(OAc)_2$	20	20
$Zn(OAc)_2$	20	35
$Cu(OAc)_2$	20	51
Ag_2O	20	54
Ag_2CO_3	23[b]	29
Ag_2CO_3	6	99
AgOAc	21[b]	90
AgOAc	6	99

[a] No hydrodehalogenation observed.
[b] Reactions performed at 100 psi.

In order to achieve both high chemoselectivity and conversion, the presence of a silver cation and a basic anion was shown to be important. AgOAc and Ag_2CO_3 in combination with 5% Ag/Al_2O_3 yielded >99% of the chloroaniline at 100 °C and at a hydrogen pressure of 250 psi. Further investigations showed that the AgOAc and Ag_2CO_3 additives were both effective at a reduced pressure of 100 psi, but with a much slower reaction rate. However, at these lower pressures, the AgOAc additive out-performed Ag_2CO_3 resulting in high conversion and selectivity after 21 h.

Throughout the studies no hydrodechlorination of *p*-CNB or the chloroaniline was observed in any of the reactions. Furthermore, *p*-chloroaniline was not reduced to the undesired aniline when subjected to the Ag/Al_2O_3 and AgOAc system for 40 h at 250 psi and 100 °C.

Next, we attempted to apply the reaction conditions to a range of functionalised halonitrobenzenes. Table 3 illustrates that all the halo-substituted nitrobenzenes were reduced selectively into the corresponding halo-substituted anilines with the exception of iodonitrobenzene where significant deiodination was observed. In general, in situ yields of >95% could be achieved at a temperature of 100 °C at 150 psi for the chloro and fluoronitrobenzenes. It was noted that the position of the halide had very little effect on the hydrogenation process. However, the electronic effect of the halogen did appear to have an important influence on the rate of hydrogenation as illustrated in Table 3.

The conversion data illustrates that the rate of hydrogenation decreases moving down group VII of the periodic table. Fluoronitrobenzene can be reduced selectively within 1 h whereas reduction of the corresponding iodonitrobenzene was incomplete after 30 h at the same temperature and pressure.

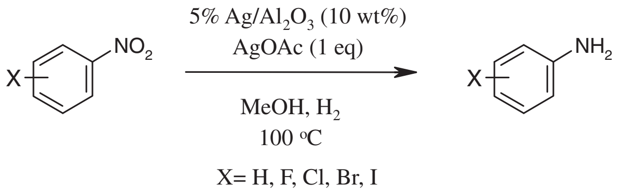
Table 4 shows that a combination of AgOAc and Al_2O_3 alone can also catalyse the selective hydrogenation of *p*-CNB to chloroaniline in yields of up to 39% with no hydrodehalogenation.

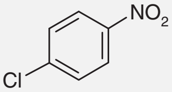
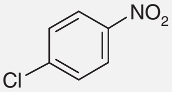
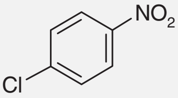
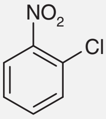
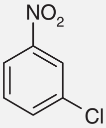
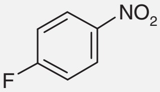
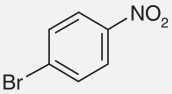
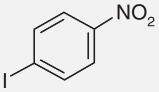
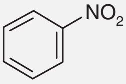
Interestingly, in all reactions containing AgOAc a thin silver film was observed. The silver film indicates the formation of silver particles from AgOAc during the hydrogenation process and this could be, in part, responsible for the enhanced conversion observed on addition of silver(I) salts to the reactions. The formation of these silver particles could provide an alternative catalytic site for the reaction to take place. However, Table 4 also suggests that it is only when all three components are combined, Ag catalyst, Al_2O_3 and AgOAc, that high yields are observed at the temperatures and pressures stated.

We also studied the effect of additives on the gold-catalysed hydrogenations. Hence, the same selection of additives was investigated in conjunction with a 5% Au/Al_2O_3 catalyst provided by Johnson Matthey. Table 5 lists the excellent selectivities obtained in all reactions with no hydrodehalogenation products observed. Once more the choice of additive had an important effect on the conversion. Without an additive the reaction was very slow under the conditions studied, but enhanced reaction rates were achieved using silver salts. With Ag_2CO_3 and AgOAc the reaction was complete within 6 h at 100 °C and 250 psi. This evidence supports the importance of both a silver cation and a basic anion.

To obtain a greater understanding of the factors influencing the hydrogenation process this investigation was continued with the exploration of a diverse range of gold-supported catalysts. The hydrogenation of *p*-CNB was again used as the test reaction at 100 °C and 150 psi. The results shown in Table 6 illustrate that

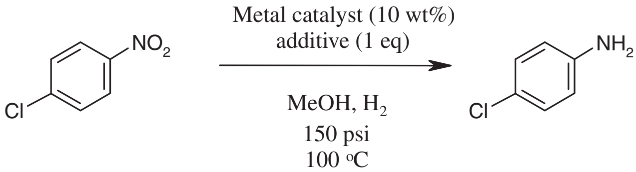
Table 3
Selective hydrogenation of a range of halonitroaromatics with JM 5% Ag/Al_2O_3 catalyst



Substrate	Pressure (psi)	Time (h)	Conversion (%)	%Hydrodehalogenation
	250	8	99	0
	150	11	99	0
	150	21	10[a]	0
	150	14.5	99	0
	150	14	99	0
	150	0.5	100	0
	150	24	70	0
	150	30	42[b]	19
	150	24	100	n/a

[a] Reaction carried out at 50 °C.
[b] 10% of nitrobenzene also formed.

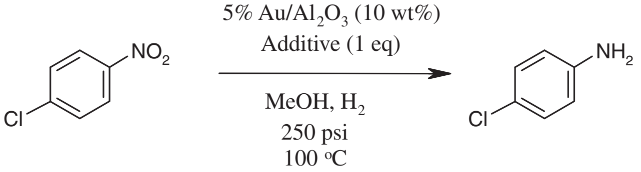
Table 4
Selective hydrogenation of *p*-CNB



Catalyst	Additive	Time (h)	Conversion[a] (%)
Ag/Al_2O_3	AgOAc	6	99
None	AgOAc	20	3
None	Al_2O_3	20	4
None	Al_2O_3 and AgOAc	17	39

[a] No hydrodehalogenation observed.

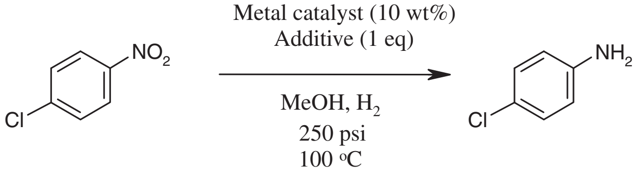
Table 5
Selective hydrogenation of *p*-CNB with JM 5% Au/Al_2O_3 catalyst



Additive	Time (h)	Conversion (%)[a]
No additive	20	11
$Fe(OAc)_2$	20	2
$Ni(NO_3)_2{\cdot}6H_2O$	20	3
$Zn(OAc)_2$	20	3
CF_3SO_3Ag	20	3
NaOAc	20	3
$AgBF_4$	20	7
$Cu(OAc)_2$	20	10
$CaCO_3$	20	12
Na_2CO_3	20	12
Ag_2O	20	37
AgOAc	6	99
Ag_2CO_3	4	99

[a] No hydrodehalogenation observed.

Table 6
Comparison of catalyst supports for the hydrogenation of *p*-CNB after 20 h



Catalyst	Additive	Conversion[a] (%)
Ag/Al_2O_3	None	10
Ag/Al_2O_3	AgOAc	100
Au/Al_2O_3	None	11
Au/Al_2O_3	AgOAc	77
Au/SiO_2	None	6
Au/SiO_2	AgOAc	63
Au/TiO_2	None	22
Au/TiO_2	AgOAc	52
Au/C	None	13
Au/C	AgOAc	2

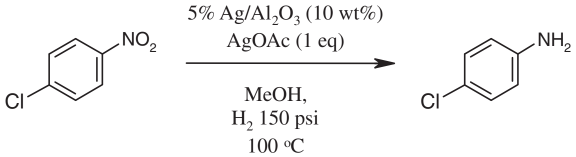
[a] No hydrodehalogenation observed.

the solid support does have a large effect on the hydrogenation process.

It was found that a metallic oxide support was required to enhance reaction rates for the selective reduction of *p*-CNB. For example, when the Au/SiO_2 catalyst was doped with AgOAc, a 10-fold increase in conversion was observed when compared to the system without the additive. The corresponding reaction when carbon was used as a support, resulted in retardation of the rate when AgOAc was added, thus illustrating the importance of a metal support for this reaction.

During this investigation, silver and gold catalysts have been shown to be activated in the presence of a range of different additives and catalyse the hydrogenation of aromatic nitro compounds in excellent yields and selectivity. The best system utilised silver acetate and the procedure was optimised to more commercially advantageous temperatures and pressures without compromising chemical performance. The results described herein highlight the potential of supported silver and gold catalysts activated by AgOAc as excellent hydrogenation catalysts for selective synthesis of haloanilines.

2. Typical experimental procedure for the Ag/Al_2O_3 and AgOAc-mediated hydrogenation of chloronitrobenzene



To a GC vial was added chloronitrobenzene (50 mg, 0.313 mmol) in MeOH (0.5 ml) along with a micromagnetic stirrer bar and the contents agitated for 5 min. The 5% Ag/Al_2O_3 catalyst (5 mg, 10 wt %) was then charged into the vial together with AgOAc (52.2 mg, 0.313 mmol). The vial was then capped and crimped, and the septum was pierced with a needle to allow H_2 ingress. The hydrogenation was performed at 100 °C under H_2 (150 psi) in a HEL CAT18 autoclave. Using an Eppendorf pipette the reaction was sampled every 1 h for 24 h. The extent of conversion was determined by reverse phase HPLC using an Agilent Zorbax RRHT 1.8 μm column.

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References and notes

1. Benton, A. F.; Bell, R. T. *J. Am. Chem. Soc.* **1934**, *56*, 501–505.
2. Lawson, A. *J. Catal.* **1968**, *11*, 295–304.
3. Guo, D. J.; Li, H. L. *Carbon* **2005**, *43*, 1259–1264.
4. Bal'zhinimaev, B. S. *Kinet. Catal.* **1999**, *40*, 795–810.
5. Lindfors, L. E.; Eränen, K.; Klingstedt, F.; Murzin, D. Y. *Top. Catal.* **2004**, *28*, 185–189.
6. Bond, G. C.; Sermon, P. A.; Webb, D.; Buchanan, A.; Wells, P. B. *J. Chem. Soc., Chem. Commun.* **1973**, 444–445.
7. Hutchings, G. J. *J. Catal.* **1985**, *96*, 292–295.
8. Haruta, M.; Kobayashi, T.; Sano, H.; Yamada, N. *Chem. Lett.* **1987**, 405–408.
9. Nagase, Y.; Hattori, H.; Tanabe, K. *Chem. Lett.* **1983**, 1615–1618.
10. Volckmar, C. E.; Bron, M.; Bentrup, U.; Martin, A.; Claus, P. *J. Catal.* **2009**, *261*, 1–8.
11. Chen, Y.; Wang, C.; Liu, H.; Qiu, J.; Bao, X. *Chem. Commun.* **2005**, 5298–5300.
12. Corma, A.; Serna, P. *Science* **2006**, *313*, 332–334.
13. Claus, P. *Appl. Catal., A.* **2005**, *291*, 222–229.
14. Kratky, V.; Kralik, M.; Mecarova, M.; Stolcova, M.; Zalibera, L.; Hronec, M. *Appl. Catal.* **2002**, *235*, 225–231.
15. Werner, J. *Ind. Eng. Chem.* **1949**, *41*, 1841–1846.
16. Strutz, J.; Hopf, E. *Chem. Ing. Tech.* **1988**, *60*, 297–298.
17. Liu, M.; Gao, F.; Liu, J. *Hecheng Huaxue* **2008**, *16*, 252–255.
18. Chen, Y.; Qiu, J.; Wang, X.; Xiu, J. *J. Catal.* **2006**, *242*, 227–230.
19. Akao, A.; Sato, K.; Nonoyama, N.; Mase, T.; Yasuda, N. *Org. Process Res. Dev.* **2006**, *10*, 1178–1183.