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Homogeneous Catalysis | Hot Paper

Silver-Catalyzed Hydrogenation of Aldehydes in Water**

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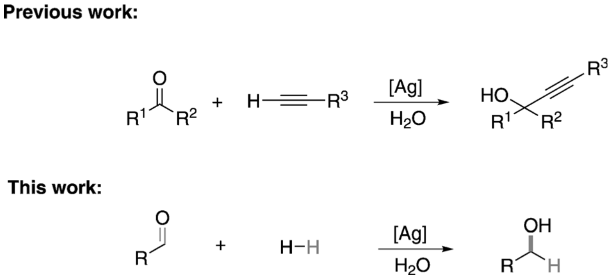
The hydrogenation of organic compounds is one of the most important classes of reactions for the synthesis of biorenewable chemicals and fuels, commodity chemicals, fine chemicals, and pharmaceuticals.[1] Since the widely known Wilkinson catalyst was prepared and used for the hydrogenation of alkenes in the 1960s, a vast number of rhodium,[2] ruthenium,[3] palladium,[4] and iridium[5] catalysts have shown excellent activity in homogeneous hydrogenation. Recently, there has also been significant progress in hydrogenation by using cheaper and more abundant metals (Fe, Co etc.) as catalysts,[6] as well as frustrated Lewis pairs in metal-free systems.[7] Surprisingly, homogeneous complexes of silver, one of the most important metals throughout history, have never shown any practical catalytic organotransformation through activating molecular hydrogen,[8] even though Halpern and Webster reported that inorganic substrates such as $[Cr_2O_7]^{2-}$ and Fe^{3+} could be reduced through catalytic hydrogenation in aqueous solution.[9] One problem is that silver cannot easily undergo oxidative addition like other transition metals do (e.g. $+1$ to $+3$). Traditional catalytic hydrogenations proceed through the homolytic oxidative addition of H_2 across a metal catalyst. The ground-breaking work of Noyori on heterolytic H–H breaking through ruthenium catalysis led to highly efficient hydrogenations for carbonyls, especially in the context of asymmetric synthesis[1e]. Heterolytic cleavage of the H−H bond also allows hydrogenation without changing the oxidation state of the metal.

In the course of our continuing efforts in developing metal-mediated or metal-catalyzed reactions in water, we have discovered that a silver catalyst could activate the C−H bond of terminal alkynes, and the resulting intermediates could further react with carbonyls in water to produce the corresponding addition product. [10] Furthermore, as reported by Halpern and Webster, it is feasible that molecular hydrogen could be activated by silver salts in aqueous media.[9] We hypothesized that the organic transformation of aldehydes into alcohols could be realized by using silver complexes as catalysts. Herein, we report the first silver-catalyzed hydrogenation of aldehydes in water, revealing an unprecedented reactivity for silver (Scheme 1).



Scheme 1. Silver-catalyzed reduction of aldehydes in water.

We began our research by using benzaldehyde (**1a**) as a model substrate (Table 1). Given the importance of bidentate ligands with wide bite angles, bidentate phosphine ligands were examined first. Under H_2 (10 bar), 1,1′-bis(diphenylphosphino)ferrocene (dppf) was tested in water at 100 °C with 20 % diisopropylethylamine (DIPEA) as a base additive; to our frustration, benzyl alcohol (**2a**) was not detected after 24 h (Table 1, entry 1). Other bidentate ligands were screened, and the desired product was generated in 5 % yield by using QUINAP as the ligand (Table 1, entries 2–6). We then turned our attention to the electron-rich monophosphine ligands because they have been proven to enhance the nucleophilicity of nucleophiles.[10b] To our delight, in the presence of AgCl and XPhos (L^7), the expected product was detected in 11 % yield (Table 1, entry 7). Further screening of monophosphine ligands revealed that the Buchwald ligands XPhos (L^7) and RuPhos (L^{12}) were more effective than the others (Table 1, entries 8–12). A series of silver catalysts was then tested by using XPhos (L^7) as the ligand (see the Supporting Information). Among these, $AgPF_6$ was the most promising and delivered the desired product in 56 % yield (Table 1, entry 13). The use of the structurally similar ligand RuPhos (L^{12}) gave a slightly lower yield (Table 1, entry 14). We realized that the pressure of H_2 may be not sufficient to achieve complete conversion. Subsequently, efforts were made to increase the H_2 pressure to further enhance the catalytic efficiency. Under 20 bar of H_2, we obtained **2a** in 65 % yield (Table 1, entry 15). We also obtained **2a** in 83 % yield under 30 bar of H_2 (Table 1, entry 16). When the H_2 pressure was increased to 40 bar, an almost quantitative yield was generated (Table 1, entry 17). However, lowering the reaction temperature to 80 °C resulted in lower efficiency (Table 1, entry 18).

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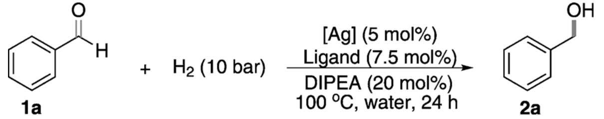
Table 1: Optimization of the silver-catalyzed hydrogenation in water.



Entry	[Ag]	Ligand	Yield [%][a]
1	$AgPF_6$	L^1	N. R.
2	$AgPF_6$	L^2	trace
3	$AgPF_6$	L^3	5
4	$AgPF_6$	L^4	N. R.
5	$AgPF_6$	L^5	N. R.
6	$AgPF_6$	L^6	trace
7	AgCl	L^7	11
8	AgCl	L^8	7
9	AgCl	L^9	trace
10	AgCl	L^{10}	N. R.
11	AgCl	L^{11}	N. R.
12	AgCl	L^{12}	9
13	$AgPF_6$	L^7	56
14	$AgPF_6$	L^{12}	47
15	$AgPF_6$	L^7	65[b]
16	$AgPF_6$	L^7	83[c]
17	**$AgPF_6$**	**L^7**	**99[d]**
18	$AgPF_6$	L^7	81[e]

[a] Yield based on **1a** and was determined by ^1H NMR analysis by using mesitylene as an internal standard. [b] Reaction was conducted under 20 bar of H_2. [c] Reaction was conducted under 30 bar of H_2. [d] Reaction was conducted under 40 bar of H_2. [e] Reaction was conducted at 80 °C.

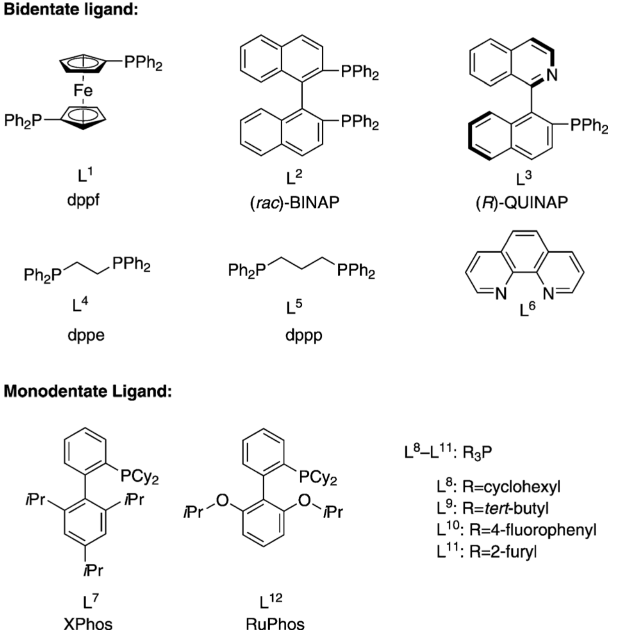
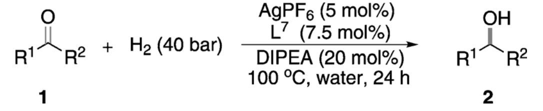
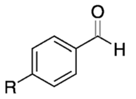
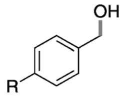
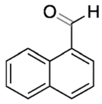
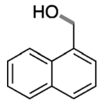
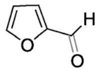
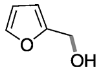
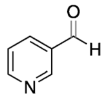
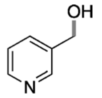
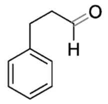
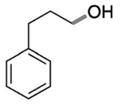
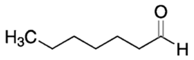
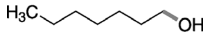
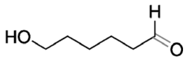
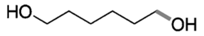
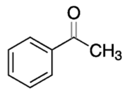
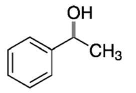
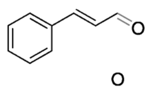
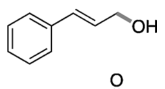
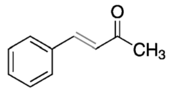
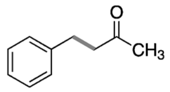


Table 2: Substrate scope of the silver-catalyzed hydrogenation in water.[a]

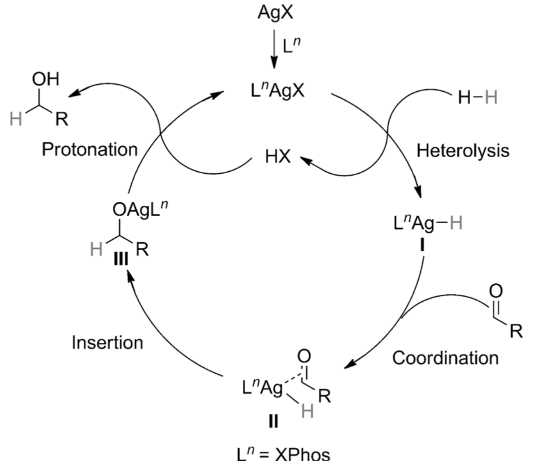


Entry	Substrate	1	Product	2	Yield [%][b]
					
1	R = H	**1a**	R = H	**2a**	93
2	R = Me	**1b**	R = Me	**2b**	99[b,c]
3	R = Br	**1c**	R = Br	**2c**	99[b,c]
4	R = OMe	**1d**	R = OMe	**2d**	99[b,c]
5	R = CF_3	**1e**	R = CF_3	**2e**	85
6	R = OH	**1f**	R = OH	**2f**	95
7	R = *t*Bu	**1g**	R = *t*Bu	**2g**	99[b,c]
8		**1h**		**2h**	90
9		**1i**		**2i**	77
10		**1j**		**2j**	83
11		**1k**		**2k**	91
12		**1l**		**2l**	90
13		**1m**		**2m**	37
14		**1n**		**2n**	trace
15		**1o**		**2o**	45
16		**1p**		**2p**	27

[a] Conditions: The reaction was conducted by using substrate (0.5 mmol), H_2 (40 bar), $AgPF_6$ (5 mol%), XPhos (7.5 mol%), and DIPEA (20 mol%) in H_2O (2 mL) at 100 °C for 24 h. [b] Yield of isolated product. [c] No flash column chromatography.

Having established the optimal conditions, we then converted a variety of commercially available aldehydes into the corresponding alcohols to further explore the scope of this novel silver-catalyzed hydrogenation in water (Table 2). Both electron-donating and electron-withdrawing groups on the aromatic ring were well tolerated, providing the corresponding products in excellent yields (Table 2, entries 1–5). Electron-withdrawing groups such as trifluoromethyl retarded the corresponding reaction slightly (Table 2, entry 5). 4-Hydroxybenzaldehyde was observed to give the corresponding 4-hydroxymethylphenol in 95 % yield (Table 2, entry 6). The substrate **1g**, which has a bulky *tert*-butyl group, was reduced to give the corresponding product **2g** in quantitative yield, even without additional purification by flash column chromatography (Table 2, entry 7). 1-Naphthaldehyde was reduced to 1-naphthylmethanol in 90 % yield (Table 2, entry 8). Heterocyclic aldehydes, such as furfural and 3-pyridinecarboxaldehyde, were also suitable substrates for this reductive process, affording the corresponding products in 77 % and 83 % yields (Table 2, entries 9 and 10). Subsequently, we also examined the reactivity of aliphatic aldehydes. Gratifyingly, these reactions proceeded smoothly, providing an attractive route for the synthesis of aliphatic alcohols. Under the optimized conditions, we obtained 3-phenyl-1-propanol and 1-heptanol in 91 % and 90 % yields respectively (Table 2, entries 11 and 12). Interestingly, the introduction of a hydroxy group on the aliphatic chain was found to decrease the reactivity (Table 2, entry 13). For a general aromatic ketone such as acetophenone **1n**, only a trace amount of the desired product was detected under the optimal reaction conditions (Table 2, entry 14). For substrates with multiple functional groups, a unique chemoselectivity was observed during the hydrogenation process. Cinnamaldehyde **1o**, which bears a C=C double bond, was reduced to the corresponding unsaturated alcohol in moderate yield (Table 2, entry 15). To our surprise, the C=C double bond of benzalacetone **1p** was reduced with preservation of the carbonyl group.

A tentative mechanism that rationalizes the product formation is illustrated in Scheme 2. Note that any comment on the specific details of the mechanism is speculative at this stage. First, the active silver catalyst is generated through complexation of the ligand with the silver precursor, because silver(I) cannot undergo oxidative addition easily as other transition metals do (although a few special silver(III) compounds[11] do exist). Furthermore, the high temperature and basic conditions favor a heterolytic process in the form of a concerted action by the central metal cation and the coordinated ligand or anion, as reported by Halpern and Webster.[9b,c] However, the possibility of a homolytic process could not be excluded at this stage. Following this assumption, the heterolytic splitting of H_2 catalyzed by the silver complex forms the intermediate **I** and liberates the corresponding acid HX. Coordination of the aldehyde to the catalytic silver center affords intermediate **II**, followed by insertion of the C=O double bond into the Ag–H bond to give intermediate **III**. Finally, protonation of the resulting intermediate **III** by HX, which is produced in the heterolysis step, releases the product and closes the catalytic cycle.



Scheme 2. Proposed mechanism for the silver-catalyzed reduction of aldehydes in water.

In summary, we have discovered an unprecedented chemical property of silver complexes. The first silver-catalyzed hydrogenation of aldehydes in water was developed. This protocol provides an expeditious and simple way to access alchohols in water. Further mechanistic studies related to this silver-catalyzed reduction and its enantioselective potential are currently underway.

Experimental Section

A stainless steel autoclave reactor with a magnetic stirring bar was charged with Ag catalyst ($AgPF_6$-XPhos; 0.025 mmol), substrate benzaldehyde (**1a**; 50.8 μL, 0.5 mmol), DIPEA (0.1 mmol), and H_2O (2 mL). Under 40 bar of H_2, the reaction mixture was stirred for 24 h at 100 °C, then cooled to room temperature. After carefully releasing the hydrogen, the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was concentrated in vacuo and purified by flash column chromatography on silica gel to give the desired product.

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[1] a) P. N. Rylander, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, New York, **1967**, p. 21; b) B. R. James, *Homogeneous Hydrogenation*, Wiley, New York, **1973**; c) J. G. De Vries, C. J. Elsevier, *Handbook of Homogeneous Hydrogenation*, Wiley-VCH, Weinheim, **2007**; d) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393; e) W. S. Knowles, R. Noyori, *Acc. Chem. Res.* **2007**, *40*, 1238; f) A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007**, *107*, 2411; g) N. B. Johnson, I. C. Lennon, P. H. Moran, J. A. Ramsden, *Acc. Chem. Res.* **2007**, *40*, 1291.

[2] a) D. Evans, J. A. Osborn, G. J. Wilkinson, *Nature* **1965**, *208*, 1203; b) J. A. Osborn, F. H. Jardine, J. F. Young, G. J. Wilkinson, *J. Chem. Soc. A* **1966**, 1711; c) M. C. Baird, J. T. Mague, J. A. Osborn, G. J. Wilkinson, *J. Chem. Soc. A* **1967**, 1347; d) P. S. Hallman, D. Evans, J. A. Osborn, G. J. Wilkinson, *J. Chem. Soc. Chem. Commun.* **1967**, 305; e) J. A. Osborn, G. J. Wilkinson, *Inorg. Synth.* **1990**, *28*, 77; f) R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 2134; g) R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 2143; h) R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 4450; i) J. M. Brown, *Angew. Chem.* **1987**, *99*, 169; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 190; j) D. A. Evans, M. M. Morrissey, *J. Am. Chem. Soc.* **1984**, *106*, 3866.

[3] a) J. Halpern, J. F. Harrod, B. R. James, *J. Am. Chem. Soc.* **1961**, *83*, 753; b) J. Chatt, R. G. Hayter, *J. Chem. Soc.* **1961**, 2605; c) R. A. Grey, G. P. Pez, A. Wallo, *J. Am. Chem. Soc.* **1980**, *102*, 5948; d) R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1987**, *109*, 5856.

[4] a) K. Nagayama, I. Shimizu, A. Yamamoto, *Chem. Lett.* **1998**, 1143; b) K. Nagayama, I. Shimizu, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1803; c) M. W. van Laren, C. J. Elsevier, *Angew. Chem.* **1999**, *111*, 3926; *Angew. Chem. Int. Ed.* **1999**, *38*, 3715; d) P. Hauwert, G. Maestri, J. W. Sprengers, M. Catellani, C. J. Elsevier, *Angew. Chem.* **2008**, *120*, 3267; *Angew. Chem. Int. Ed.* **2008**, *47*, 3223.

[5] a) R. H. Crabtree, H. Felkin, G. E. Morris, *J. Organomet. Chem.* **1977**, *141*, 205; b) R. H. Crabtree, H. Felkin, T. Fillebeenkhan, G. E. Morris, *J. Organomet. Chem.* **1979**, *168*, 183; c) R. H.

Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331; d) B. Wüstenberg, A. Pfaltz, *Adv. Synth. Catal.* **2008**, *350*, 174; e) S. P. Smidt, N. Zimmermann, M. Studer, A. Pfaltz, *Chem. Eur. J.* **2004**, *10*, 4685; f) J. W. Suggs, S. D. Cox, R. H. Crabtree, J. M. Quirk, *Tetrahedron Lett.* **1981**, *22*, 303.

[6] a) C. P. Casey, H. Guan, *J. Am. Chem. Soc.* **2007**, *129*, 5816; b) R. Langer, G. Leitus, Y. B. David, D. Milstein, *Angew. Chem.* **2011**, *123*, 2168; *Angew. Chem. Int. Ed.* **2011**, *50*, 2120; c) S. C. Bart, E. Lobkovsky, P. J. Chirik, *J. Am. Chem. Soc.* **2004**, *126*, 13794; d) E. J. Daida, J. C. Peters, *Inorg. Chem.* **2004**, *43*, 7474; e) G. Zhang, B. L. Scott, S. K. Hanson, *Angew. Chem.* **2012**, *124*, 12268; *Angew. Chem. Int. Ed.* **2012**, *51*, 12102.

[7] a) G. C. Welch, R. R. S. Juan, J. D. Masuda, D. W. Stephan, *Science* **2006**, *314*, 1124; b) P. A. Chase, T. Jurca, D. W. Stephan, *Chem. Commun.* **2008**, 1701; c) P. Spies, S. Schwendemann, S. Lange, G. Kehr, R. Fröhlich, G. Erker, *Angew. Chem.* **2008**, *120*, 7654; *Angew. Chem. Int. Ed.* **2008**, *47*, 7543; d) P. A. Chase, G. C. Welch, T. Jurca, D. W. Stephan, *Angew. Chem.* **2007**, *119*, 8196; *Angew. Chem. Int. Ed.* **2007**, *46*, 8050; e) T. Mahdi, Z. M. Heiden, S. Grimme, D. W. Stephan, *J. Am. Chem. Soc.* **2012**, *134*, 4088; f) L. Greb, P. Oña-Burgos, B. Schirmer, S. Grimme, D. W. Stephan, J. Paradies, *Angew. Chem.* **2012**, *124*, 10311; *Angew. Chem. Int. Ed.* **2012**, *51*, 10164.

[8] a) G. N. Khairallah, R. A. J. O'Hair, *Dalton Trans.* **2005**, 2702; b) G. N. Khairallah, R. A. J. O'Hair, *Dalton Trans.* **2007**, 3149; c) R. Mitrić, J. Petersen, A. Kulesza, M. I. S. Rohr, V. Bonacić-Koutecký, C. Brunet, R. Antoine, P. Dugourd, M. Broyer, R. A. J. O'Hair, *J. Phys. Chem. Lett.* **2011**, *2*, 548.

[9] a) J. Halpern, *Q. Rev. Chem. Soc.* **1956**, *10*, 463; b) A. H. Webster, J. Halpern, *J. Phys. Chem.* **1956**, *60*, 280; c) A. H. Webster, J. Halpern, *J. Phys. Chem.* **1957**, *61*, 1239; d) A. H. Webster, J. Halpern, *J. Phys. Chem.* **1957**, *61*, 1245; e) J. Halpern, *J. Phys. Chem.* **1959**, *63*, 398.

[10] a) X. Yao, C.-J. Li, *Org. Lett.* **2005**, *7*, 4395; b) Z. Jia, X. Li, A. C. Chan, C.-J. Li, *Synlett* **2012**, 2758; c) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095; d) for a silver-catalyzed hydrosilation of aldehdyes, see: B. M. Wile, M. Stradiotto, *Chem. Commun.* **2006**, 4104.

[11] J. A. McMillan, *Chem. Rev.* **1962**, *62*, 65.