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Silver-Catalyzed Reduction of Quinolines in Water

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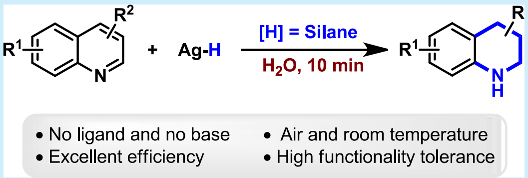
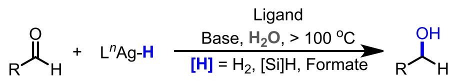
Supporting Information

ABSTRACT: A ligand- and base-free silver-catalyzed reduction of quinolines and electron-deficient aromatic *N*-heteroarenes in water has been described. Mechanistic studies revealed that the effective reducing species was Ag−H. This versatile catalytic protocol provided facile, environmentally friendly, and practical access to a variety of 1,2,3,4-tetrahydroquinoline derivatives at room temperature.



Transition metal−hydride complexes have attracted a great deal of attention in recent years, due to their efficient and unique performance observed in hydrogenation of organic compounds.[1] A vast number of transition metal−hydride complexes, such as rhodium,[2] ruthenium,[3] palladium,[4] iridium,[5] iron,[6] and cobalt,[7] have shown excellent activity in homogeneous hydrogenation. However, the hydrogenations with silver−hydride (Ag−H) complexes have rarely been explored. Only a few examples have concerned the utilization of Ag−H sources in the reduction of aldehydes (Figure 1a).[8] In addition, a ligand and a base were necessary for these works. Herein, we report a ligand- and base-free reduction of quinolines with Ag−H as the reducing species (Figure 1b). Remarkably, the reduction proceeds smoothly in water under air.

(a) The reduction of aldehyde in water with Ag-H as reducing species (***Li et al.***)



(b) The reduction of quinolines in water with Ag-H as reducing species (***This work***)

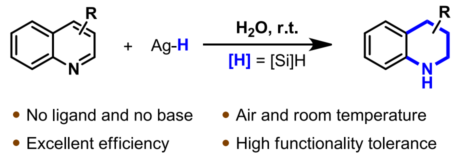


Figure 1. Reduction in water with Ag−H as the reducing species.

Water is one of the most ideal solvents for organic reactions, and great advances have been made with respect to conducting metal-catalyzed organic reactions in water.[9] Because of the unique physical and chemical properties, reactions proceeding in water commonly result in unexpected reactivity and selectivity in comparison with those performed in organic solvents. Silver-catalyzed transformations in water have witnessed increasing popularity due to the mild nature of silver in many processes.[8a,b,9i,10] These significant advances inspired us to explore the reduction of *N*-heteroarenes by using Ag−H as the reducing species in water.

We initiated our investigation with the reduction of 2-methylquinoline (**1a**) using $PhSiH_3$ as the reducing reagent with a silver catalyst. Only a trace amount of hydrogenated product 2-methyl-1,2,3,4-tetrahydroquinoline (**2a**) was observed in the presence of 10 mol % AgOTf in toluene at room temperature (Table 1, entry 1). Other solvents, such as hexane, dichloroethane (DCE), and $CHCl_3$, were also found to be ineffective (entries 2−4, respectively). When the reaction was carried out in ethanol or water at room temperature for 10 min, excellent yields were obtained (entry 5 or 6, respectively). Decreasing the load of AgOTf to 5 mol % resulted in a 97% isolated yield of the desired product (entry 7). Importantly, no product was detected in the absence of the silver catalyst (entry 8). Among the SiH sources examined, $PhSiH_3$ and Ph_2SiH_2 gave a similar result, but the reaction was completely shut down while using PMHS, DEMS, and Ph_3SiH (entries 9−12). In addition, AgOAc and Ag_3PO_4 also provided the reduction product in good yields (entries 13 and 14, respectively).

With the optimized reaction conditions established, we first studied the scope of C2-substituted quinolines, and the results are listed in Scheme 1. Alkyl-substituted quinolines gave the corresponding 1,2,3,4-tetrahydroquinolines in high yields (**2b**−**2e**). Aryl-substituted quinolines and their derivatives featuring electron-withdrawing as well as electron-donating groups afforded the corresponding products in good to excellent yields (**2f**−**2p**). Notably, functional groups such as methoxy, fluoride, chloride, bromide, trifluoromethyl, and dimethylamino on the aryl ring were well tolerated in the reaction. The alkenyl groups, which are not directly attached to the quinoline ring, were retained in the products (**2d** and **2n**). Moreover, compound **2e** is a key intermediate in the synthesis of (±)-galipinine, a natural product with multiple biological activities.[11] The reduction of quinolines containing a naphthyl

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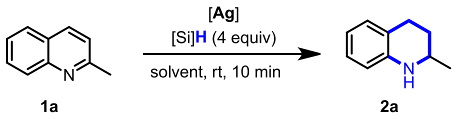
Table 1. Optimization of the Reaction Conditions[a]



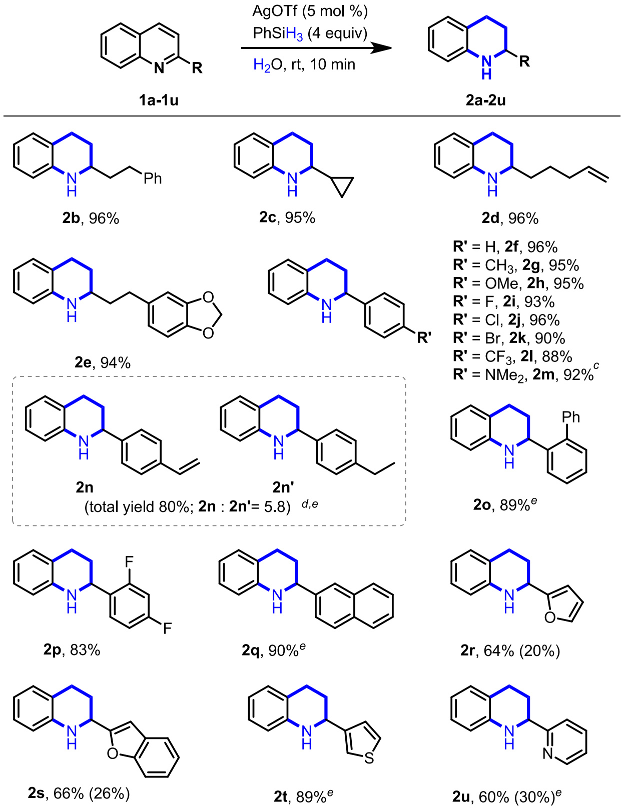
entry	[Ag]	[Si]H	solvent	yield of **2a** (%)[b]
1[c]	AgOTf (10 mol %)	$PhSiH_3$	toluene	trace
2[c]	AgOTf (10 mol %)	$PhSiH_3$	hexane	trace
3[c]	AgOTf (10 mol %)	$PhSiH_3$	DCE	nd
4[c]	AgOTf (10 mol %)	$PhSiH_3$	$CHCl_3$	nd
5	AgOTf (10 mol %)	$PhSiH_3$	EtOH	98
6	AgOTf (10 mol %)	$PhSiH_3$	H_2O	98
7	AgOTf (5 mol %)	$PhSiH_3$	H_2O	97
8	–	$PhSiH_3$	H_2O	nd
9	AgOTf (5 mol %)	Ph_2SiH_2	H_2O	89
10	AgOTf (5 mol %)	Ph_3SiH	H_2O	nd
11	AgOTf (5 mol %)	PMHS	H_2O	nd
12	AgOTf (5 mol %)	DEMS	H_2O	nd
13	AgOAc (5 mol %)	$PhSiH_3$	H_2O	95
14	Ag_3PO_4 (5 mol %)	$PhSiH_3$	H_2O	93

[a] Reaction conditions: **1a** (0.25 mmol), [Ag] (10 mol %), [Si]H (1.0 mmol), in solvent (1 mL) at room temperature for 10 min under air. Abbreviations: nd, not detected; PMHS, polymethylhydrosiloxane; DEMS, diethoxymethylsilane. [b] Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] At room temperature for 2 h under air.

group as well as heteroaromatic groups proceeded smoothly to give the corresponding products in 60–89% yields (**2q**–**2u**). The quinoline was selectively reduced when employing a pyridyl-substituted quinoline, and **2u** was obtained in 60% yield, although a higher reaction temperature was required.

When we subjected the C3-substituted quinolines to the standard reaction conditions, only moderate conversions of the starting material were observed. Moreover, quinolines with other substitution patterns also gave similar results under the conditions described above. We postulated that the inferior reactivity of C3-substituted quinolines was caused by strong coordination of the nitrogen atom to the Lewis acid silver(I) center, effectively deactivating the catalyst. Such strong coordination is hindered by bulky substituents in the C2 position on the quinoline ring, which prevents deactivation of the catalyst.[10a] To our delight, further screening showed that both increasing the reaction temperature and extending the reaction time greatly enhanced the reactivity (for details of these studies, see the Supporting Information). In this way, the yield of **2w** could be increased to 78% with an increase in the reaction time to 10 h (at room temperature) and to 95% with an increase in the reaction temperature to 95 °C (for a 5 h reaction time, under an argon atmosphere). Subsequently, a number of substituted quinolines were subjected to these two sets of reaction conditions as shown in Scheme 2. With C3-substituted quinolines, various substituents were well tolerated, affording the desired products in moderate to good yields (**2v**–**2ab**). Quinolines with other substitution patterns, such as quinoline itself and 4-methylquinoline, also gave the corresponding 1,2,3,4-tetrahydroquinolines in good yields (**2ac** and **2aj**). In the case of 6-substituted and 8-substituted quinolines, methyl, chloride, and bromide groups were well tolerated, and the corresponding products were isolated in good yields (**2ae**–**2ai**). Although the presence of a hydroxyl group dramatically decreased the conversion at room temperature, desired product **2af** was obtained in 64% yield at 95 °C.

Scheme 1. Reduction of C2-Substituted Quinolines[a,b]

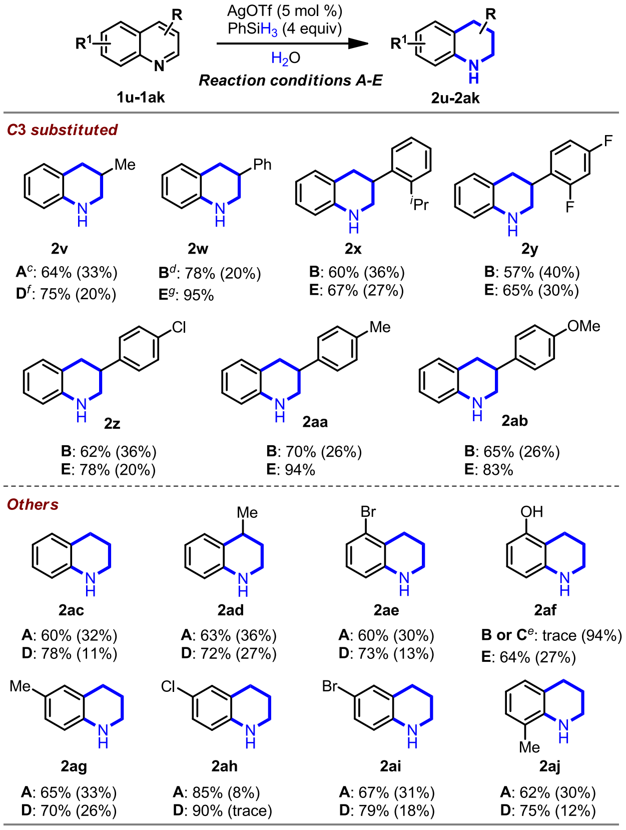


[a] Reaction conditions: substrate (0.25 mmol), AgOTf (5 mol %), $PhSiH_3$ (1.0 mmol), in H_2O (1 mL) at room temperature for 10 min under air. [b] Isolated yields; recovered substrates are given in parentheses. [c] For 10 h. [d] The ratio was determined by ^1H NMR spectroscopy. [e] At 50 °C for 30 min.

The 2,3-disubstituted quinoline derivatives were then surveyed, and the results are listed in Scheme 3. All the 2,3-disubstituted quinolines reacted smoothly in 10 min at room temperature, providing the corresponding disubstituted hydrogenated products in good yields, with moderate to excellent diastereoselectivities (Scheme 3, **4a**–**4f**). Notably, the reactions of 2-phenyl-3-alkyl-disubstituted quinolines (**4a** and **4b**) afforded single *trans*-disubstituted products in high yields. In addition, the high reactivity indicates that the presence of bulky C3 substituents helped to prevent deactivation of the catalyst. Gratifyingly, the reaction can be conducted on a gram scale with 0.08 mol % loading of the catalyst, forming **2a** in 72% yield with a turnover number of 900 (Figure S1).

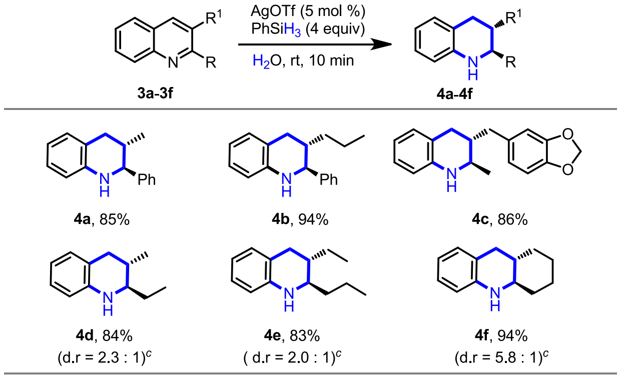
A number of other *N*-heteroarenes were examined (Scheme 4). The protocol can be successfully applied to the reduction of several aromatic heterocycles such as naphthyridine (**5a**), 1,10-phenanthroline (**5b**), acridine (**5c**), and 2,3-dimethylquinoxaline (**5d**); albeit higher reaction temperatures and longer reaction times are required. Surprisingly, the catalytic system presented here was not able to facilitate the reduction of isoquinoline to the hydrogenated *N*-heteroarene (**6e**), which could be attributed to the strong coordination of isoquinoline to Ag(I) (because the nitrogen is more accessible than in the quinolines and C2-substituted quinolines) or the difficult addition of the Ag–H species to isoquinoline. In addition,

Scheme 2. Reduction of Quinolines with Various Substitution Patterns[a,b]



[a] Reaction conditions: substrate (0.25 mmol), AgOTf (5 mol %), $PhSiH_3$ (1.0 mmol), in H_2O (1 mL) at room temperature for 10 min under air. [b] Isolated yields; recovered substrates are given in parentheses. [c] A. The reaction was performed at room temperature for 10 min under air. [d] B. The reaction was performed at room temperature for 10 h under air. [e] C. The reaction was performed at 50 °C for 30 min under air. [f] D. The reaction was performed at 95 °C for 10 min under Ar. [g] E. The reaction was performed at 95 °C for 5 h under Ar.

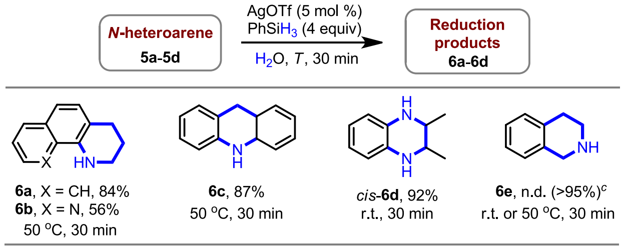
Scheme 3. Reduction of Disubstituted Quinolines[a,b]



[a] Reaction conditions: substrate (0.25 mmol), AgOTf (5 mol %), $PhSiH_3$ (1.0 mmol), in H_2O (1 mL) at room temperature for 10 min under air. [b] Isolated yields. [c] The diastereomeric ratio (d.r) values were determined by ^1H NMR spectroscopic analysis.

pyridine also failed to give the desired hydrogenated product, which may be for similar reasons.

Scheme 4. Reduction of *N*-Heteroarenes[a,b]



[a] Reaction conditions: substrate (0.25 mmol), AgOTf (5 mol %), $PhSiH_3$ (1.0 mmol), in H_2O (1 mL) at the noted temperature for 30 min under air. [b] Isolated yields. [c] Recovered substrate **5d** is given in parentheses.

Control experiments were performed to understand the reaction mechanism (Table S2 and Figure S2). As shown in Table S2, no ligand effect was found in the reduction. The hydrosilylation products were not observed in the reaction system regardless of whether the water was replaced with aprotic solvents (Figure S2a) or the amount of $PhSiH_3$ was decreased (Figure S2b). In addition, 3-silylated tetrahydroquinolines gave only a trace amount of the desired products under the standard conditions (Figure S2c). From these results, we concluded that the reduction process was entirely different from the Lewis acid-catalyzed reduction with silane as a reductant, which usually undergoes a hydrosilylation process,[8f,13] and also recognized that water or alcohol was necessary to initiate the reaction. When the reaction was conducted in ethanol, $PhSiH_3$ was converted to $Ph(EtO)SiH_2$ or $Ph(EtO)_2SiH$, each of which was identified by NMR analysis of the final reaction mixture (Figure S2g). The result suggests that alcohol acts as a ligand to promote the formation of silver hydride[12] along with a hydrogen source. The reaction of **1a** and **1v** in d_6-ethanol or D_2O led to the product bearing 100% and 91% deuterium at the third position, respectively (Figure S2d,e). These observations suggest that the quinoline may be reduced through a stepwise 1,4/1,2-addition of Ag−H species to quinolines.[8a−e] Also, the addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) had no obvious influence on the conversion (Figure S 2f), confirming the silver-catalyzed radical reduction process should be excluded.

On the basis of the observations described above and previous reports,[13] an outer-sphere catalytic pathway involving a stepwise 1,4/1,2-addition of the Ag−H species to quinoline, which was activated by the Lewis acid Ag(I), was proposed (Figure 2a, path B). Theoretically, in addition to pathway B as described in Figure 2a, another possible pathway is a 1,2-hydride addition followed by a 3,4-hydride addition (Figure 2a, path A). To further clarify the active hydrogenation pathway, the reductions of reaction intermediates **7a** and **7c** and their analogue **7b** were conducted under the standard conditions (Figure 2b,c). The corresponding results suggest that the latter process is most likely to be active in our catalytic system (for the overall reaction mechanism, see Figure S3).

In summary, we have developed a practical silver-catalyzed reduction of quinolines and electron-deficient *N*-heteroarenes with hydrosilanes in water. The current protocol operates under mild conditions and enables the reduction of quinolines in good yields and selectivity in the absence of both a ligand and a base. A high reaction efficiency (10 min) and ≤900 turnovers were achieved. Mechanistic studies indicate that the reaction most likely proceeds through a stepwise 1,4/1,2-

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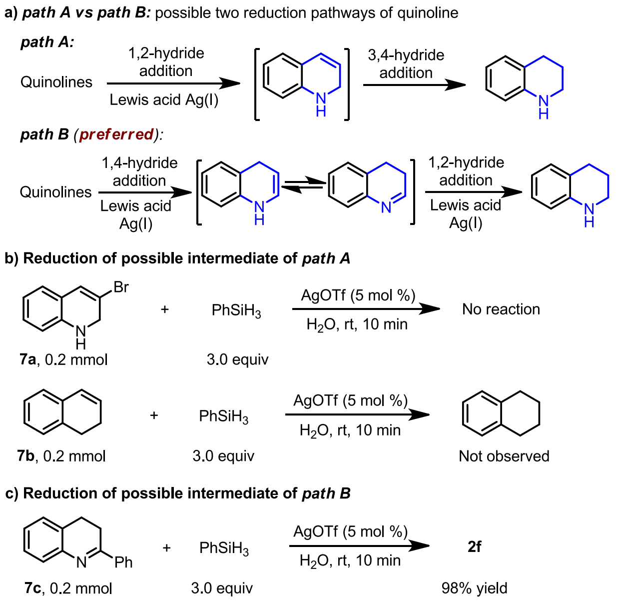

Figure 2. Two possible pathways for the reduction of quinolines.

addition of the Ag–H species to the quinoline activated by Lewis acid Ag(I). Further studies of the application of Ag–H sources in other reductions are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01055.

Experimental procedures along with characterization data and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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