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Hydrogenation of Sulfoxides to Sulfides under Mild Conditions Using Ruthenium Nanoparticle Catalysts[**]

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Abstract: *The first demonstration of the hydrogenation of sulfoxides under atmospheric H_2 pressure is reported. The highly efficient reaction is facilitated by a heterogeneous Ru nanoparticle catalyst. The mild reaction conditions enable the selective hydrogenation of a wide range of functionalized sulfoxides to the corresponding sulfides. The high redox ability of RuO_x nanoparticles plays a key role in the hydrogenation.*

The deoxygenation of sulfoxides to sulfides represents a fundamental and significant process within organic synthesis[1] and biochemistry.[2] For example, during the asymmetric synthesis of carbinols, chiral sulfoxides are introduced to carbonyl compounds as a chiral auxiliary. Subsequent to the asymmetric transformation of the carbonyl group to the carbinol, the sulfoxide moiety is removed from the parent molecule through deoxygenation followed by desulfidation.[3] Deoxygenation is also useful in the one-carbon homologation reaction of carbonyl compounds using active α-methylene sulfoxides as carbon sources.[4] The stoichiometric deoxygenation of sulfoxides has typically been carried out with excess amounts of sacrificial agents such as metal hydrides,[5] gaseous halogens,[6] hydrogen halides,[7] thiols,[8] and phosphines.[9] These reaction systems, however, have significant drawbacks, including the use of highly toxic reagents, the production of large quantities of waste and low yields of sulfides.[3] To date, many different catalytic sulfoxide deoxygenation reactions have been reported, in which low-valent metals are combined with reducing reagents such as PPh_3,[10] silanes,[11] BH_3,[12] organosulfur compounds,[8c] and alcohols.[13] Although these newer systems represent improvements, fundamental problems in terms of low atom-efficiency and difficulties in separating catalysts from the reaction mixtures remain challenges that have not yet been addressed.

The deoxygenation of sulfoxides to sulfides using molecular hydrogen (H_2) is a promising method which offers high atom-efficiency since water is the sole by-product. However, in early research on the hydrogenation of sulfoxides, the use of $RhCl_3$ for the hydrogenation of dimethyl sulfoxide (DMSO) resulted in low yields of dimethyl sulfide in the order of 0.4 % together with low catalytic activity (turnover numbers of 2) and an evidently limited range of applicable substrates.[14] Pd/C[4] and MoO_2Cl_2[15] exhibited moderate catalytic activities for several sulfoxides but required harsh reaction conditions including high H_2 pressure (> 50 atm). These severe conditions also preclude the use of these catalysts for the selective hydrogenation of functionalized sulfoxides containing other reducible or thermally labile functional groups. As a result, the applicability of these processes to different kinds of sulfoxide substrates is greatly restricted. Therefore, the development of an efficient catalytic system for the hydrogenation of diverse sulfoxides to sulfides under mild conditions would represent a significant advance.

Herein we report the first demonstration of the efficient catalytic hydrogenation of sulfoxides under atmospheric H_2 pressure, facilitated by a Ru nanoparticle catalyst. Even under mild conditions, the catalytic activity of the Ru nanoparticle catalyst is much greater than those of previously reported catalyst systems requiring high H_2 pressures. In addition, this new process works under mild conditions and enables the selective hydrogenation of a wide range of functionalized sulfoxides while leaving other reducible or thermally labile functional groups intact.

We initially screened various metal nanoparticle catalysts supported on TiO_2 (anatase) by evaluating the hydrogenation of diphenyl sulfoxide (**1**) as a model substrate at 100 °C under an atmospheric H_2 pressure (Table 1). Among the examined TiO_2-supported metal nanoparticles, Ru nanoparticles with a mean diameter of 1.6 nm exhibited the highest catalytic activity, affording diphenyl sulfide (**2**) in > 99 % yield (entry 1). The activity of Ru nanoparticles was significantly higher than that of other metal nanoparticles; Rh, Pt, and Pd nanoparticles showed very low activities (entries 2–4) while Ni, Cu, Ag, and Au nanoparticles did not show any catalytic activity at all (entries 5–8). The catalytic activity of Ru nanoparticles was affected by the support material: TiO_2 gave the highest activity and SiO_2 was also effective but inferior to TiO_2 (entry 1 versus 9), whereas the use of hydroxyapatite (HAP) and Al_2O_3 supports resulted in moderate to low yields of **2** (entries 10 and 11). The order of efficiency of the supports was consistent with the size of the Ru nanoparticles formed thereon (entries 1 and 9–11). The effect of the size of

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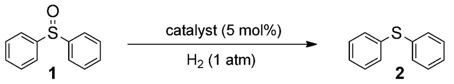
Table 1: Hydrogenation of diphenyl sulfoxide using various supported metal nanoparticle catalysts.[a]



Entry	Catalyst	Particle size [nm]	Conv. of **1** [%][b]	Yield of **2** [%][b]
1	Ru/TiO_2	1.6	>99	>99
2	Rh/TiO_2	–[c]	18	16
3	Pt/TiO_2	–[c]	12	11
4	Pd/TiO_2	–[c]	12	10
5	Cu/TiO_2	–[c]	2	2
6	Ni/TiO_2	–[c]	2	2
7	Ag/TiO_2	–[c]	<1	<1
8	Au/TiO_2	–[c]	<1	<1
9	Ru/SiO_2	2.1	73	72
10	Ru/HAP	3.0	51	50
11	Ru/Al_2O_3	4.2	26	23
12	Ru/TiO_2	2.0	86	85
13	Ru/TiO_2	2.7	69	69

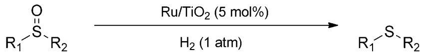
[a] Reaction conditions: catalyst (0.05 g), **1** (0.5 mmol), 1,4-dioxane (5 mL), 100°C, 1 h. [b] Determined by GC using an internal standard. [c] Not determined.

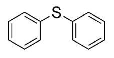
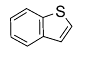
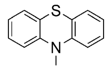
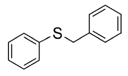
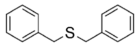
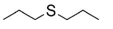
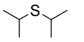
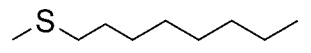
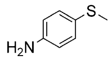
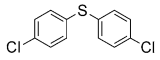
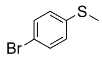
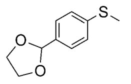
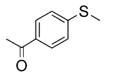
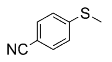
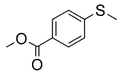
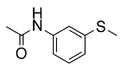
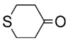
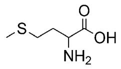
Ru nanoparticles on the catalytic activity was investigated using Ru/TiO_2 with varying sizes of Ru nanoparticles.[16] It was shown that the catalytic activity of the nanoparticles increases with decreasing size (entry 1 versus 12 and 13). These results demonstrate that a combination of small Ru nanoparticles with a TiO_2 support produces an effective catalytic system, which allows the highly efficient hydrogenation of **1**.

Ru/TiO_2 was found to be capable of showing high catalytic activity for the selective hydrogenation of various sulfoxides to sulfides (Table 2). A number of aromatic and benzylic sulfoxides were efficiently converted to the corresponding sulfides with excellent yields (entries 1, 3–6) and aliphatic sulfoxides were also successfully hydrogenated, giving the desired sulfides (entries 7–9). Due to the high activity of the Ru/TiO_2 catalyst under these mild reaction conditions, the chemoselective hydrogenation of sulfoxides without affecting other reducible functional groups such as halogen, acetal, carbonyl, cyano, ester, and amide groups was possible (entries 11–18). Notably, Ru/TiO_2 was also applicable to the deoxygenation of methionine sulfoxides in aqueous medium, which naturally occurs in metabolic systems, e.g. in animal livers or plant cells.[2b,d] Ru/TiO_2 exhibited excellent chemoselectivity, giving methionine as the sole product with high yield (entry 19).

To further probe the utility of the Ru/TiO_2-catalyzed hydrogenation of sulfoxides, we explored the use of Ru/TiO_2 in the asymmetric synthesis of a carbinol (Scheme 1 a) and in the one-carbon homologation reaction of a carbonyl compound (Scheme 1 b). In both cases, the sulfoxide hydrogenation step proceeded efficiently under mild reaction conditions, affording the desired products in excellent yields. These results demonstrate the high efficiency and versatility of the Ru/TiO_2 system.

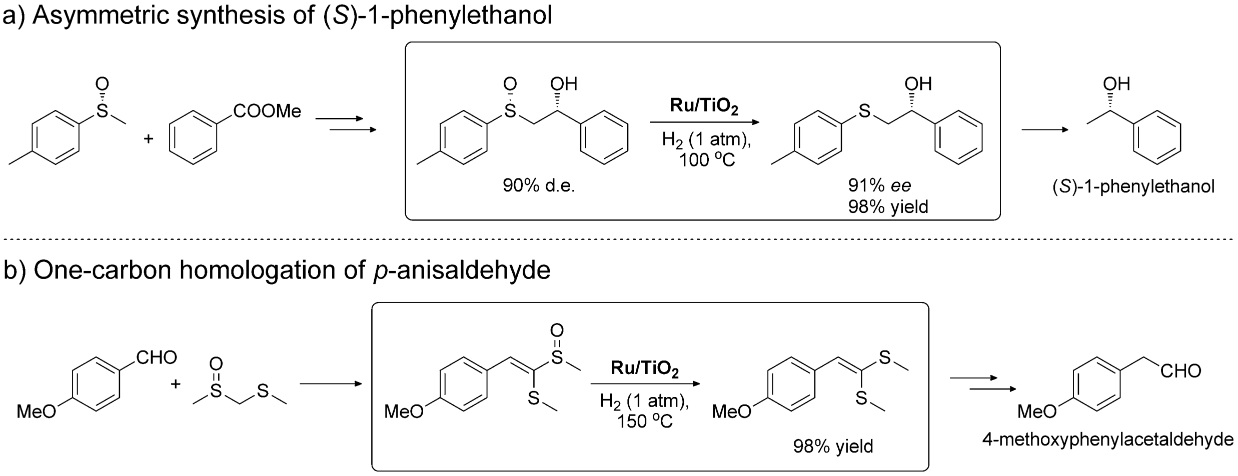
Table 2: Hydrogenation of various sulfoxides using Ru/TiO_2.[a]



Entry	Product	T [°C]	t [h]	Yield [%][b]
1		100	1	>99 (93)
2[c]		160	36	>99 (96)
3		100	1	>99 (95)
4		100	1	>99 (94)
5[d]		80	12	98 (90)
6[d]		60	12	98 (94)
7		100	1	>99 (84)
8		100	1	>99 (81)
9		100	1	>99 (90)
10		100	2	>99 (92)
11		100	1	>99 (95)
12		80	3	99 (93)
13		100	5	>99 (95)
14		100	1	99 (97)
15		100	8	>99 (96)
16		100	2	>99 (97)
17		100	3	>99 (94)
18		100	8	>99 (91)
19[d,e,f]		100	12	(90)

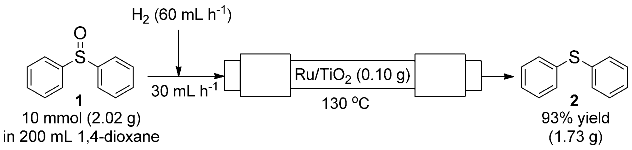
[a] Reaction conditions: Ru/TiO_2 (0.10 g), sulfoxide (1.0 mmol), 1,4-dioxane (5 mL). The conversion for all entries was >99% as determined by GC with an internal standard. [b] Determined by GC with an internal standard. Values in the parentheses are isolated yields. [c] Catalyst (0.20 g), diphenylsulfoxide (50 mmol), mesitylene (100 mL). [d] Catalyst (0.20 g). [e] H_2O was used as the solvent. [f] Conversion was determined by NMR.

A further advantage of this catalyst system is the ease of the subsequent work-up, because water is the sole byproduct after the hydrogenation. For example, after a 50 mmol-scale reaction of **1**, the product **2** was readily isolated in 96% yield by simple filtration of the catalyst followed by evaporation of the filtrate (Table 2, entry 2). During the hydrogenation reaction, a turnover number as high as 500 was achieved, a value which is significantly larger than those obtained with previously reported catalyst systems requiring high H_2



Scheme 1. a) Efficient asymmetric synthesis of a carbinol. b) One-carbon homologation reactions through the Ru/TiO$_2$-catalyzed hydrogenation of sulfoxides. Diastereomeric excess (% d.e.) is calculated by $(R_SR_C - R_SS_C)/(R_SR_C + R_SS_C) \times 100$.

pressure (Pd/C: TON 50;[4] MoOCl$_2$: TON 50[15]). In addition, inductively coupled plasma (ICP) analysis of the filtrate showed no leaching of the Ru species into the reaction mixture, demonstrating the high durability of the Ru/TiO$_2$. The simple work-up and high durability of the Ru/TiO$_2$ system prompted us to explore the feasibility of incorporating the present catalyst system into a column flow reactor. When **1** (10 mmol, 2.02 g) in 1,4-dioxane (0.050 M) was passed through a Ru/TiO$_2$-packed column reactor at a flow rate of 30 mL h^{-1} along with H$_2$ at atmospheric pressure, **2** was successively obtained in 93% isolated yield (1.73 g) (Scheme 2).



Scheme 2. Continuous flow reactor system for the hydrogenation of **1** containing Ru/TiO$_2$.

To investigate the origin of the superior catalytic activity of Ru/TiO$_2$, an in situ X-ray adsorption fine structure (XAFS) analysis of Ru/TiO$_2$ was performed. Fourier transformation (FT) of the k^3-weighted extended X-ray adsorption fine structure (EXAFS) data obtained for the fresh Ru/TiO$_2$ under argon showed two main peaks at 1.72 and 2.36 Å, attributed to Ru−O and Ru−Ru scattering, respectively (Figure 1 a). Inverse FT of these peaks was well fitted to Ru−O and Ru−Ru shells with coordination numbers of 4.3 and 2.1, respectively (Figure S1 and Table S1). These results indicate that RuO$_x$ nanoparticles with partially reduced surfaces are located on the TiO$_2$.

Interestingly, when Ru/TiO$_2$ was treated with **1** in 1,4-dioxane under an Ar atmosphere at 100 °C, the peak intensity of the Ru−Ru scattering significantly decreased (Figure 1 b), indicating that the reduced Ru species on the surfaces of the RuO$_x$ particles were oxidized by **1**. Successive treatment of the Ru/TiO$_2$ with 1 atm of H$_2$ regenerated the Ru−Ru scattering peak (Figure 1 c). The spectral feature of the treated Ru/TiO$_2$ was similar to that of the Ru/TiO$_2$ prior to any treatments (as shown in Figure 1 a), showing that the oxidized surface Ru species were reduced again, thereby regenerating the original nanoparticles. These reversible

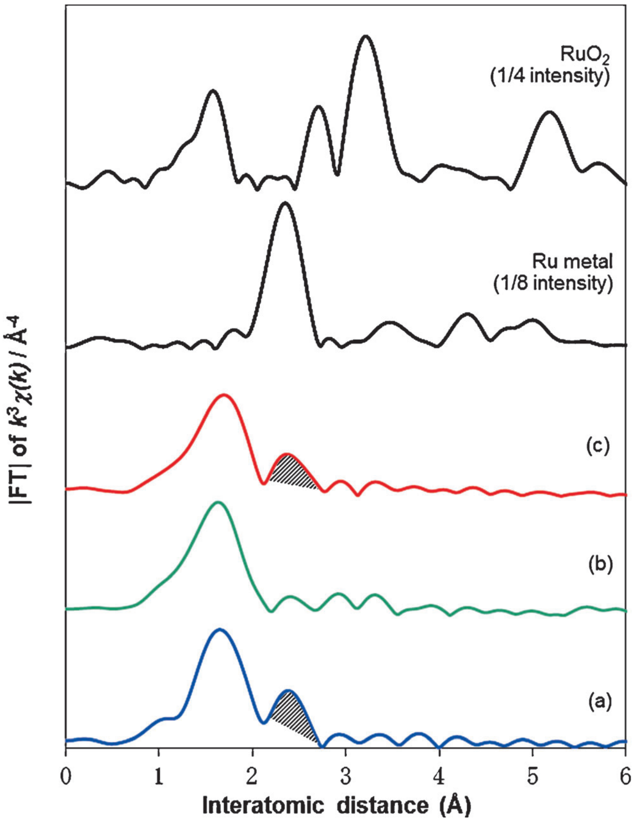


Figure 1. FT spectra of Ru K-edge EXAFS of Ru/TiO$_2$ a) before use (blue line); b) after treatment of (a) with **1** (green line); and c) after treatment of (b) with H$_2$ (red line).

transitions through oxidation by **1** followed by reduction with H_2 were also confirmed by X-ray adsorption near edge structure (XANES) spectra (Figure S2), in which the adsorption energy of the fresh Ru/TiO$_2$ was shifted toward higher values following treatment with **1** (Figure S2 a,b). In a reversible manner, the subsequent treatment with H_2 shifted the peak back to almost the original adsorption energy (Figure S2 c). These results show that the partially reduced Ru species on the surface of RuO$_x$ particles exhibits high redox ability under mild reaction conditions using **1** and H_2. An additional experimental trial was performed using **1** under an Ar atmosphere in the presence of Ru/TiO$_2$. Notably, the disproportionation reaction of **1** occurred to afford diphenyl sulfone together with the formation of **2**, thus demonstrating both the deoxygenation ability of the reduced Ru species and the high oxygenation ability of oxidized Ru species generated in situ. These combined results clearly demonstrate that the reduced Ru species on the surface of RuO$_x$ nanoparticles can directly deoxygenate sulfoxides to sulfides. Afterwards, the oxidized Ru species generated in situ are readily reduced back to the original nanoparticles by H_2. This efficient redox behavior of the reduced Ru species on RuO$_x$ nanoparticles enables the catalytic hydrogenation of various sulfoxides under mild conditions.

In conclusion, the efficient catalytic hydrogenation of sulfoxides was demonstrated using Ru nanoparticles. Notably, this hydrogenation proceeds under mild reaction conditions and greatly broadens the applicability to a wide range of sulfoxides. The Ru/TiO$_2$ catalyst was readily recoverable, highly durable, and also suitable for use in a column flow reactor. Furthermore, spectroscopic analyses demonstrated that the high redox properties of partially reduced Ru species on RuO$_x$ play a crucial role in this hydrogenation.

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[16] See Supporting Information for details of the method to prepare Ru/TiO$_2$ with varying Ru nanoparticle sizes.