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A practical procedure for the synthesis of multifunctional aldehydes through the Fukuyama reduction and elucidation of the reaction site and mechanism

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Abstract—A highly efficient heterogeneous Pd/C catalyst **D1** was found to effect the reduction of thiol esters **1** to the corresponding aldehydes **2** with such a low catalyst loading as 0.5–1.0 mol %. The chemical properties of the Pd/C catalysts together with the XRF analysis reveal that the reduction is most likely to proceed on the solid surface of the Pd/C catalyst rather than in the solution phase outside the pores. A reaction mechanism through oxidative addition of Pd to the thiol esters **1** was postulated by detection of the oxidative addition intermediate by React IR analysis. A practical purification of **2** was accomplished by conversion to water-soluble bisulfite adducts **7**.

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Multifunctional aldehydes have received considerable attention as useful intermediates for drugs and natural products. Various synthetic methods[1] of the aldehydes involving reduction of activated or nonactivated carboxylic acid derivatives have been reported. However, they generally suffer from either one of the following drawbacks: functional group intolerance, the need for quite low temperature and/or expensive reagents. A two-step procedure involving prior reduction of carboxylic acids to alcohols followed by mild oxidation has thus been the most reliable and versatile method to prepare aldehydes. Fukuyama and co-workers have recently developed an elegant synthesis of the aldehydes through reduction of thiol esters with Et_3SiH in the presence of Pd/C catalyst.[2] The reaction takes place under mild reaction conditions, that is, at room temperature, for the substrates carrying various functional groups. It is, however, not entirely satisfactory for a practical use because of the need for relatively high catalyst loading (ca. 5 mol %) and purification of the products by silica-gel column chromatography. We describe herein a highly efficient Pd/C catalyst that allows the Fukuyama reduction with an extremely low catalyst loading (0.5–1.0 mol %), and a practical purification of the products by way of the bisulfite adducts. A possible reaction site and mechanism were discussed as well.

The Fukuyama reduction was optimized with thiol ester **1a**[3] used as a typical substrate (Eq. 1). In our initial study, the reaction was tested using Et_3SiH (2 equiv) and the Pd/C catalyst **D3**[4] (Pd: 10 wt %, 0.5 mol % relative to **1a**, H_2O: 1.8 wt %) in various solvents (Fig. 1). Although, in the reported procedure,[2] acetone or CH_2Cl_2 has been employed as the reaction solvent, a higher reaction rate and a conversion were observed in THF. While acetone may have an advantage of trapping

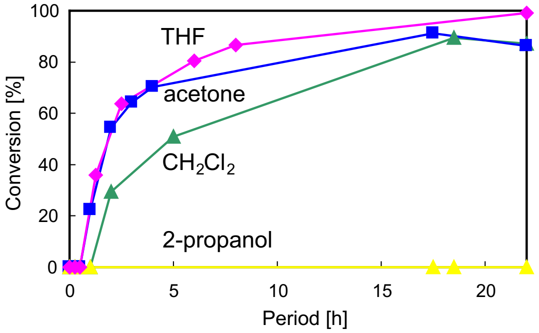

Figure 1. Influence of the solvent on the Fukuyama reduction of **1a** to **2a**. The reaction was conducted by the use of Et_3SiH (2.0 equiv) and Pd/C catalyst **D3** (0.5 mol %).

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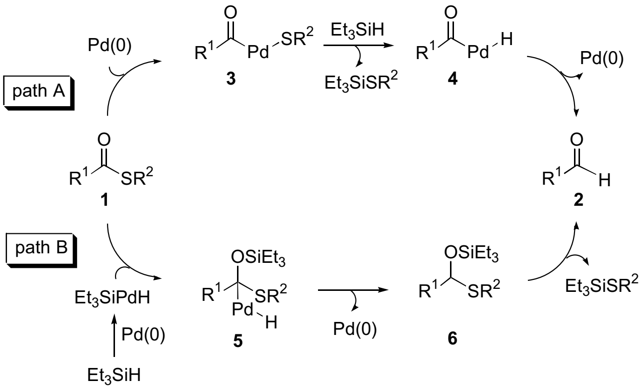
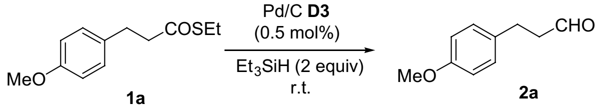


Scheme 1. Possible mechanisms for the Fukuyama reduction.

$Et_3SiSiEt$ generated in the reaction to prevent its further reaction with aldehydes, that is formation of *O*-triethylsilyl-*O*,*S*-acetals (Scheme 1, compound **6**), the use of THF appeared not to be accompanied by such side reactions.



(1)

Screen of the Pd/C catalysts **D1**, **D2**, **D4**, **D5**, **D6**, and **W2**[4] (Pd: 5 wt %, 0.5 mol % relative to **1a**) as well as the catalyst **D3**, having various chemical properties, in the reduction of **1a** was the next subject for our investigation.[5] The Pd distribution may have a significant impact on the catalytic efficiency. The Pd catalysts tested in this study have three types of Pd distribution: egg shell, thick shell, and uniform (Fig. 2). In the egg shell catalyst, Pd distributes close to the surface within 50–150 nm depth. In contrast, Pd disperses homogeneously in the uniform catalyst. The thick shell catalyst denotes the one whose Pd distributes until 200–500 nm from the surface.

As shown in Figure 3, the reduced catalyst **D1**, **D2**, and **D3** exerted higher reaction rates than the oxidized counterparts **D4**, **D5**, and **D6**. The highest initial acceleration of the reaction was observed in the catalyst **D2** (egg shell) whose Pd is distributed closer to the surface than **D1** (thick shell). However, the reaction almost stopped in 1 h with a conversion of 75%. Although the increased surface area in the egg shell catalyst **D2** would enhance the reaction, it might lead to a facile precipitation of Pd on the solid support to retard the reaction.[6] The lower activity found in uniform catalyst **D3** may reflect that diffusion of **1a** to the Pd surface of the catalyst is a significant factor for the successful reaction. The catalyst **D1** is thus considered to be the most effective in the reduction of **1a** to provide aldehyde **2a** in 92% isolated yield with such a low catalyst loading as 0.5 mol % (Table 2, entry 1).

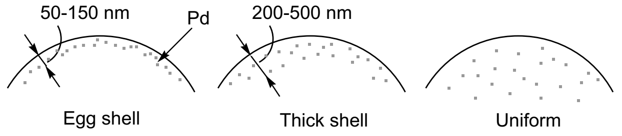


Figure 2. Distribution of Pd in the Pd/C catalysts.

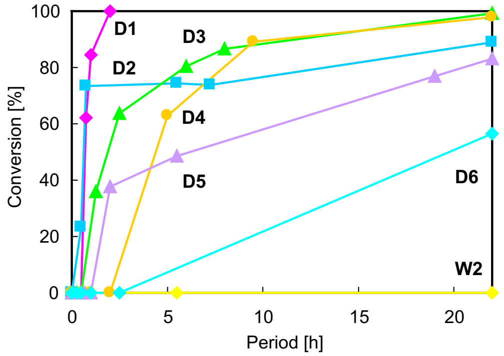


Figure 3. Variation of the Pd/C catalyst in the Fukuyama reduction of **1a** to **2a**. The reaction was conducted by the use of Et_3SiH (2 equiv) and Pd/C catalyst (0.5 mol %) in THF.

While the oxidized catalysts **D4**, **D5**, and **D6** required long periods for the onset of the reaction than **D1**, **D2**, and **D3**, they showed the similar order of the activities with respect to Pd impregnation depth: **D4** (thick shell) > **D5** (egg shell) > **D6** (uniform). Presence of water in the catalyst is detrimental for the reaction. The catalyst **W2** whose water content is 58% showed no catalytic activity. It is thus concluded that the most effective catalyst **D1** is characterized by thick shell type Pd distribution, a low oxidation state, a high Pd dispersion and a low water content (Table 1).

To investigate the reaction mechanism of the Fukuyama reduction, React IR analysis of the reaction mixture was conducted (Fig. 4).[7] By scanning the IR spectrum once for every 1 min from 650–4000 cm^{-1} during the reaction, three components that changed the concentration were

Table 1. Chemical properties of the Pd/C catalysts

Pd/C catalyst[a]	Pd distribution[b]	Impregnation depth (nm)[b]	Reduction degree (%)[c]	Pd dispersion (%)[d]	Water content (wt %)
D1	Thick shell	200–500	25–99	26	3.0
D2	Egg shell	50–150	25–99	27	4.2
W2	Egg shell	50–150	25–99	28	58
D3[e]	Uniform	—[f]	25–99	36	1.8
D4	Thick shell	200–500	0–25	35	1–1.5
D5	Egg shell	50–150	0–25	28	3.2
D6	Uniform	—[f]	0–25	36	1–1.5

[a] Purchased from Degussa Japan Co., Ltd, Catalysts Division except **D3**.

[b] Estimated by transmission electron microscopy (TEM).

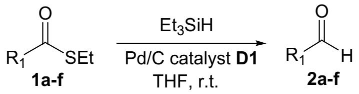
[c] Detected by temperature programmed reduction (TPR) measurement.

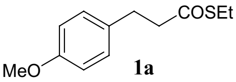
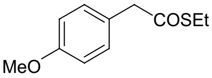
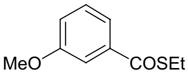
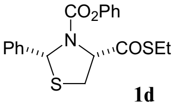
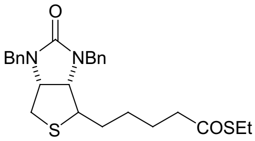
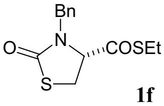
[d] Pd dispersion is calculated with CO chemisorption.

[e] Purchased from Kawaken Fine Chemicals.

[f] Not determined.

Table 2. The Fukuyama reduction of thiol esters **1a**–**f**



Entry	Thiol ester **1**	Catalyst **D1** (mol%)	Et_3SiH (equiv)	*t* (h)	Aldehyde **2**	Yield (%)[a]
1	 **1a**	0.5	2	2	**2a**	92
2	 **1b**	0.5	2	2	**2b**	93
3	 **1c**	0.5	2	5	**2c**	90
4	 **1d**	1.0	3	17	**2d**[b]	92
5	 **1e**	1.0	3	17	**2e**	97
6	 **1f**	1.0	3	17	**2f**[b]	90

[a] Isolated yield after purification with silica-gel column chromatography.

[b] Optical purity of **2d** and **2f** was confirmed to be >99% ee.

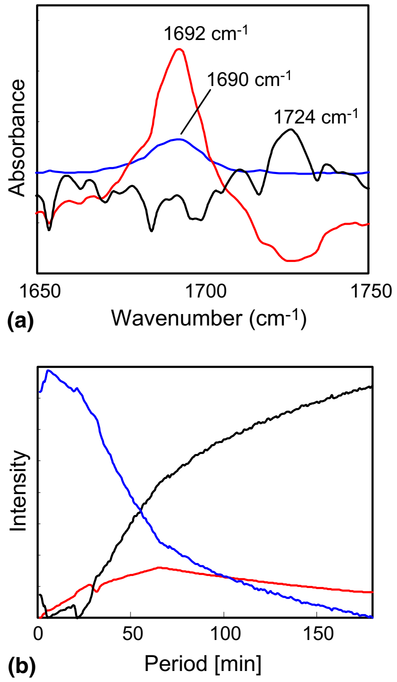


Figure 4. React IR analysis of the Fukuyama reduction of **1a** to **2a**: (a) component spectrum, (b) component profile. Curves are shown for **1a** (——), **2a** (——), and an intermediate (——). The reaction was conducted by the use of Et_3SiH (2 equiv) and Pd/C catalyst **D1** (0.5 mol%) in THF.

detected. Comparing with the IR spectra of the authentic samples, the blue and black lines are assigned as thiol ester **1a** and aldehyde **2a**, respectively. Another species, shown in the red line, is of particular interest. It showed an absorbance at 1692 cm^{-1} and initially grew, but then slowly disappeared as the reaction progressed. This absorbance can be attributed to transient formation of an intermediate carrying a carbonyl group attached to Pd (Scheme 1, compound **3** or **4**).[8]

In the carbon–carbon bond forming reactions between thiol esters and boronic acids, oxidative addition of thiol esters to Pd(0) has been suggested as a possible reaction mechanism because of the high thiophilicity of Pd.[9] In the present reaction, path A involving the oxidative addition of thiol ester **1** to Pd and subsequent transmetallation with triethylsilane may be operative as well (Scheme 1). Although an alternative reaction mechanism, path B, which takes place through direct hydrosilylation of the carbonyl group of **1** may be possible,[10] it should be ruled out since compound **3** or **4** does exist (vide supra) and any *O*-triethylsilyl-*O*,*S*-acetals **6** were not detected at all in the reaction mixture.

To elucidate the reaction site as well as the loss of Pd from the solid support, the concentration of Pd in the solution during the reaction was measured by XRF (X-ray fluorescence) analysis of the reaction mixture periodically obtained and filtered through Celite. Only a small amount of Pd was found to bleed from the solid support during the reaction though a maximum concentration of Pd (4.5% relative to the initially added catalyst **D1** or 0.023 mol% relative to the initially added **1a**) was found in 0.5 h. The reduction did not proceed to any appreciable extent in the presence of such a small amount of Pd catalyst [0.023 mol% of the catalyst **D3** or $Pd(PPh_3)_4$]. The pore size distribution plays a significant role for the activity of the Pd/C catalyst as well.[11] The Pd/C **D1** possesses pore volumes of 0.9–1.3 mL/g and ca. 50% of the pores consists of mesopores (diameters: 2–50 nm) where most of the organic molecules involving thiol esters **1**, aldehydes **2**, and the Pd intermediates **3** and **4** can penetrate through the pores.[11]

These results together with the chemical properties of the optimized Pd/C catalyst **D1** may suggest that the reaction takes place predominantly on the Pd surface of the Pd/C catalyst not in the solution phase outside the pores.[12] The reactant **1** should adsorb on the Pd surface in the charcoal matrix of the Pd/C catalyst while the product **2** being continuously pushed out from there (Fig. 5). This is in remarkable contrast with Heck reactions[6] that have been supposed to be catalyzed by Pd dissolved in solution. After the reaction, virtually complete recovery of Pd (>95%) was accomplished by simple filtration and subsequent treatment involving combustion of the solids obtained.

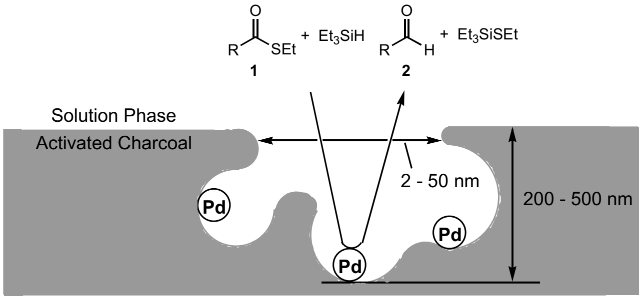
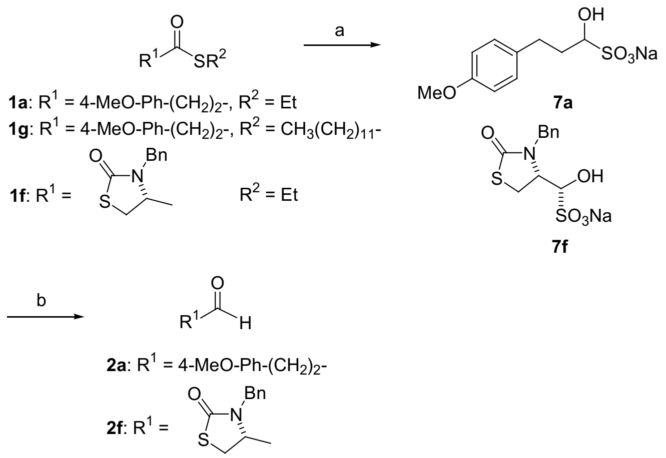


Figure 5. A possible reaction site for the Fukuyama reduction.

The Fukuyama reduction of thiol esters **1b–f** carrying various functional groups was tested using the present protocol to provide the corresponding aldehydes **2b–f** in high yields in the presence of 0.5–1.0 mol% of the catalyst **D1** (Table 2). Although the compound **2f**, an intermediate for (+)-biotin,[13] is quite labile for racemization, the present reaction took place with the stereogenic center retained as such, which was confirmed by chiral HPLC analysis of the alcohol obtained by reduction of **2f** with $NaBH_4$.

Although the Fukuyama reduction generally affords aldehydes in excellent yields, it is often difficult to separate the product from unreacted Et_3SiH, Et_3S:SEt and/or $Et_3SiSiEt_3$.[14] The problem becomes much more serious when thiol ester **1g** obtained from an odorless high boiling point dodecane thiol[15] is employed as the substrate. We envisioned a possible use of a water-soluble bisulfite adduct **7** for the purification of the product (Scheme 2). After the reduction of **1a**, **1f**, and **1g**, the reaction mixture was filtered. Into the filtrate was added an aqueous solution of sodium bisulfite and the mixture was vigorously stirred. In the case of **1a** and **1g**, the bisulfite adduct **7a** was obtained in 86% and 90% yield, respectively, as water-soluble crystalline solids by simple filtration. While the bisulfite adduct **7f** did not crystallize without concentration, it was obtained quantitatively as an aqueous solution by simple separation of the aqueous phase. Treatment of the adduct **7a** and **7f** (aqueous solution) with aq K_2CO_3 in ether quantitatively provided pure aldehyde **2a** and **2f**, respectively.[16]

In conclusion, a practical synthesis of multifunctional aldehydes through Fukuyama reduction was worked out by combining the use of readily accessible Pd/C catalyst **D1** and the simple purification via bisulfite adducts. The reduction may take place on the surface of the Pd/C catalyst not in the solution phase outside the pores. The considerable low catalyst loading as well as the simple work-up of the present protocol would permit a facile access to the multifunctional aldehydes, compounds of glowing significance.



Scheme 2. Isolation of aldehydes **2** through bisulfite adducts **7**. (a) (i) Pd/C, Et_3SiH, THF, rt, 2 h, 90%, (ii) $NaHSO_3$, AcOEt, H_2O, 86% (from **1a**), quant. (from **1f**), 90% (from **1g**); (b) K_2CO_3, H_2O, Et_2O, quant.

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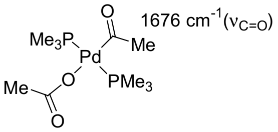

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16. A typical procedure for the Fukuyama reduction (preparation of **2a**). To a solution of **1a** (10 g, 45 mmol) in THF (45 mL) was added Pd/C catalyst **D1**[4] (5 wt%, 3 wt% water, 474 mg, 0.22 mmol) under N_2 atmosphere. To the suspension was added dropwise Et_3SiH (14 mL, 89 mmol) over 1 h. After stirring the mixture at 20 °C for 1 h, the mixture was filtered. The filtrate was evaporated and to the residue were added AcOEt (30 mL), H_2O (30 mL) and $NaHSO_3$ (5.4 g, 52 mmol) and the mixture was vigorously stirred at 20 °C for 17 h. The solids formed were collected, washed with AcOEt and dried to give compound **7a** (10 g, 86%) as colorless crystals. Mp 165.6–166.5 °C; IR (ATR) $\nu = 1611$, 1515, 1033, 635 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.09 (d, $J = 8.0$ Hz, 2H), 6.83 (d, $J = 8.0$ Hz, 2H), 5.36 (d, $J = 4.0$ Hz, 1H) 3.34–3.81 (m, 4H), 2.50 (s, 3H); SIMS m/z 245 (M^++1); Anal. Calcd for $C_{10}H_{13}O_5SNa$: C, 44.77; H, 4.88. Found: C, 44.37; H, 4.76. To the solution of K_2CO_3 (25 g, 0.18 mol) in water (175 mL) was added the compound **7a** (10 g, 37 mmol) and Et_2O (75 mL). After stirring the mixture at 20 °C for 2 h, the organic phase was separated, washed twice with water and dried over anhydrous $MgSO_4$ and evaporated to afford **2a** (6.1 g, quant) as colorless oil. IR (ATR) $\nu = 1720$, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.77 (s, 1H), 7.09 (d, $J = 8$ Hz, 2H), 6.82 (d, $J = 8$ Hz, 2H), 3.78 (s, 3H), 2.70–2.90 (m, 4H); SIMS m/z 164 (M^++1).