

Pd(OH)₂/C (Pearlman's Catalyst): A Highly Active Catalyst for Fukuyama, Sonogashira, and Suzuki Coupling Reactions

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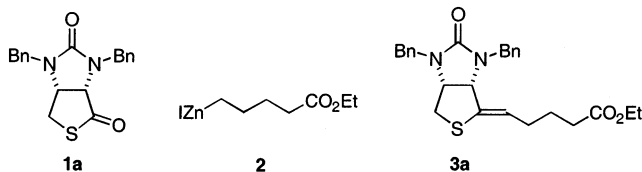
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Received October 5, 2002

Abstract: Treatment of thiol esters **1** with zinc reagent **2** in the presence of a small amount (<ca. 1 mol %) of nonpyrophoric Pd(OH)₂/C (Pearlman's catalyst) provided functionalized asymmetrical ketones **3** in high yields. The use of Pd(OH)₂/C was further applied to Sonogashira and Suzuki coupling reactions to afford the desired products in high yields.

The palladium-catalyzed coupling reactions have found wide application in the preparation of valuable compounds such as drugs and natural products.¹ One of the most attractive features of the method lies in the fact that it can be applied to the substrates carrying various functional groups. It eliminates the protection-deprotection sequence as well as the functional group transformation. From a practical point of view, reducing the amount of expensive Pd catalyst, its ready recovery,² and safe handling are crucial issues to be considered. We have recently reported a facile synthesis of an intermediate **3a** for (+)-biotin through the nonpyrophoric Pd(OH)₂/C (Pearlman's catalyst)-promoted coupling reaction of thio-lactone **1a** with 4-ethoxycarbonylbutylzinc iodide **2**.³ The synthesis is advantageous over the previously reported method⁴ using Pd/C in terms of quite low catalyst loading (ca. 1/8 amount of the catalyst compared to the method with Pd/C) and safe handling of the catalyst. We report herein Pd(OH)₂/C-promoted Fukuyama,⁵ Sonogashira, and Suzuki coupling reactions to demonstrate efficiency and versatility of the synthetic method with Pd(OH)₂/C.



Reaction rate of the coupling reaction in the presence of Pd(OH)₂/C or Pd/C was initially tested with thiol ester **1b** used as a typical substrate. Into zinc reagent **2** in THF prepared according to Knochel procedure⁶ were added **1b** in toluene, 0.15 mol % of the Pd catalyst, and DMF, and the mixture was stirred at 25 °C under N₂ atmosphere. As shown in Figure 1, both higher reaction rate and

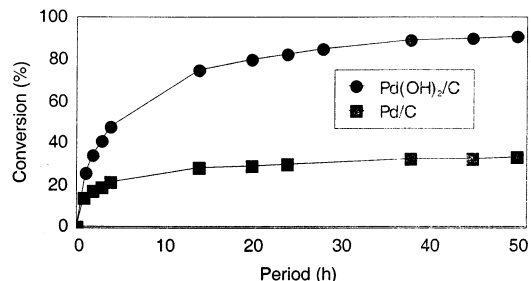


FIGURE 1. Comparison of the activity of Pd catalysts, Pd(OH)₂/C and Pd/C, in the coupling reaction between **1b** and **2**. The reaction was conducted in the presence of 0.15 mol % of the Pd catalyst. Conversion of the reaction was determined by HPLC (see, Experimental Section).

conversion were observed in the reaction with Pd(OH)₂/C than that with Pd/C. The isolated yields of ketone **3b** in 50 h with Pd(OH)₂/C and Pd/C were 84% and 30%, respectively.

The method was then applied to the reaction of various functionalized thiol esters **1c–i** with zinc reagent **2** (Table 1). In all cases, Pd(OH)₂/C is superior to Pd/C, providing the desired coupling products **3c–i** in much higher yields. The reaction between **2** and primary or secondary alkane thiol esters **1c–f** with or without an ester or a keto group afforded the corresponding ketones **3c–f** in good yields (Table 1, entries 2–5). Noteworthy is the reaction with aromatic thiol esters **1h,i**: while a chloro or a sulfide group in the thiol ester was detrimental when Pd/C was employed as the catalyst, Pd(OH)₂/C exerted higher activity as well for the reaction of **1h** and **1i** with **2** to provide ketones **3h** and **3i** in 73% and 61% yield, respectively (Table 1, entries 7 and 8).

In a previously reported workup,^{3,4} the reaction mixture was directly filtered through Celite to recover the Pd catalyst. However, viscous zinc salts in the reaction mixture sometimes caused a prolonged period for filtration. As an improvement, prior to filtration, aqueous hydrochloric acid was added to the reaction mixture. It dissolved the zinc salts and permitted a facile filtration to leave the Pd catalyst as a filter cake. Any amount of

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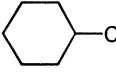
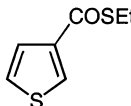
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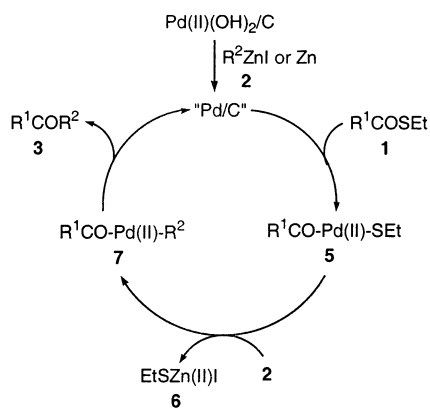
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TABLE 1. Fukuyama Coupling Reaction in the Presence of Pd(OH)₂/C

Entry	Thiol Ester (1)	Pd Catalyst (mol%)	t (h)	Ketone (3)	Yield (%) ^a	
					Pd(OH) ₂ /C	Pd/C
1	4-MeOPh(CH ₂) ₂ COSEt 1b	0.15	50	3b	84	30
2	CH ₃ (CH ₂) ₆ COSEt 1c	0.6	24	3c	93	52
3	 1d	0.6	72	3d	79	41
4	MeO ₂ C(CH ₂) ₄ COSEt 1e	0.9	17	3e	78	67
5	PhCO(CH ₂) ₂ COSEt 1f	0.9	23	3f	70	50
6	PhCOSEt 1g	0.9	71	3g	72	39
7	3-Cl-PhCOSEt 1h	0.6	25	3h	73	25
8	 1i	0.9	68	3i	61	19

^a Isolated yield.SCHEME 1. Possible Reaction Mechanism for the Pd(OH)₂/C-Promoted Fukuyama Coupling Reaction

Pd was not detected in the filtrate and recovery of Pd from the filter cake was quantitative.

Scheme 1 shows a possible reaction pathway involved in the catalytic cycle of the Fukuyama coupling reaction. Active "Pd/C" (designated as "Pd/C" to differentiate from commercially available prereduced Pd/C) should initially be in situ generated from Pd(OH)₂/C by reduction with zinc reagent **2** and/or zinc dust. The resultant "Pd/C" is likely to oxidatively add to thiol ester **1** due to high

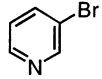
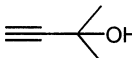

thiophilicity⁷ of the Pd metal. Transmetalation of Pd(II) complex **5** with zinc reagent **2** would then take place to afford the second Pd(II) complex **7**, which, on reductive elimination, might provide ketone **3** and regenerate "Pd/C". Much insight into the nature of heterogeneous catalysts in Heck, Suzuki, and Sonogashira coupling reactions has recently been addressed.^{21,2m,8} The coupling reactions were speculated to proceed in homogeneous phase rather than on heterogeneous solid support. There is, however, a contradicting question why such high recovery of Pd was achieved in the present reaction even after acidic workup. As oxidized Pd or Pd complex [Pd(II)X₂] adsorbed on charcoal matrix might more easily dissolve into the solution than reduced counterpart (Pd metal),⁹ the reactive intermediates **5** and **7** involving reactants (**1** and **2**) and products (**3** and **6**) should be located in the solution phase. This indicates the series of the reaction from **1** to **3** should take place in the solution phase. When the reaction is completed, most of the Pd might exist as the reduced form "Pd/C", which is

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TABLE 2. Sonogashira and Suzuki Coupling Reactions in the Presence of Pd(OH)₂/C

Entry	8	9 (equiv)	Pd(OH) ₂ /C (mol%)	Additive ^a (equiv)	t (h)	10	Yield (%) ^b	
							Pd(OH) ₂ /C	Pd/C
1			0.5	A	21	10a	84	11
2	8a		1.0	A	19	10b	71	61
3	4-NO ₂ PhBr	PhB(OH) ₂	1.1	B	43	10c	91	90
4	8b	4-MeOPhB(OH) ₂	1.1	B	43	10d	91	92

^a A:^{2f} K₂CO₃ (2.5), CuI (0.04), PPh₃ (0.08). B:^{2c} Na₂CO₃ (3.8), PPh₃ (0.18). ^b Isolated yield.

tightly bound to solid support possibly as “large particles”.^{2l,m,8} It can avoid bleed of Pd to the solution phase and permits high recovery of Pd after simple filtration. Nonetheless, the reason Pd(OH)₂/C is so effective compared to Pd/C has not been cleared up. More information on the structure of the solid support and Pd distribution of the catalyst are needed in order to fully understand the high activity of Pd(OH)₂/C as well as the precise mechanism of the Pd(OH)₂/C-promoted coupling reaction.

The present procedure was further applied to Sonogashira and Suzuki coupling reactions (Table 2). When Pd(OH)₂/C was employed for the Sonogashira coupling reaction,^{2f} it expectedly gave higher yields than Pd/C (Table 2, entries 1 and 2). While, in the case of Suzuki coupling reaction,^{2c} the use of Pd(OH)₂/C was proven to result in similar yields to that of Pd/C (Table 2, entries 3 and 4), the former has such advantage as removing some hazard in adding the catalyst to flammable organic solvents.

In conclusion, a practical synthetic method of functionalized ketones, arylalkynes, and biaryls with non-pyrophoric Pd(OH)₂/C was accomplished. The present method is efficient in terms of high activity, safe handling, and high recovery of the Pd catalyst, permitting a practical access to these synthetically useful compounds not only for laboratory use but also for practical large-scale production.

Experimental Section

General Method. Melting points are uncorrected. ¹H and ¹³C NMR spectra were recorded with tetramethylsilane used as an internal standard. Thiol esters **1b–i** were prepared from the corresponding carboxylic acids according to our previously reported procedure.¹⁰ All reactions were conducted under N₂ atmosphere. All solvents and reagents were used as received.

A Typical Procedure for the Fukuyama Coupling Reaction (Preparation of Ethyl 8-(4-Methoxyphenyl)-6-oxooctanoate **3b).** To a suspension of zinc powder (2.95 g, 45.1 mmol) in THF (6.8 mL) was added 1,2-dibromoethane (100 μL, 1.2 mmol) and the mixture was heated to reflux for 3 min. After the mixture was cooled to 25 °C, chlorotrimethylsilane (100 μL, 0.8 mmol) was added, and the slurry was stirred for 15 min. The mixture was warmed to 55 °C, and ethyl 5-iodopentanoate (5.70 g, 22.3 mmol) was added at 55–60 °C for 30 min. After the mixture was stirred at the same temperature for 30 min, it was cooled to 25 °C. To the mixture were added **1b** (2.5 g, 11.1 mmol), toluene (12.5 mL), 10% Pd(OH)₂/C (18 mg, 0.017 mmol), and DMF (0.85 mL), and the mixture was stirred at 25 °C for 50 h. To the mixture was added 3 N HCl (20 mL) and the solution was filtered. The filtrate was partitioned by adding AcOEt (20 mL), and the organic layer was washed with water, dried over anhydrous MgSO₄, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt 10:1) to give **3b** (2.74 g, 84%) as a colorless oil. IR (KBr) ν = 1730, 1711 cm⁻¹; ¹H NMR (CDCl₃) δ 7.09 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.85–2.81 (m, 2H), 2.71–2.67 (m, 2H), 2.41–2.38 (m, 2H), 2.30–2.27 (m, 2H), 1.60–1.57 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H); HRMS *m/z* (M + H)⁺ calcd for C₁₇H₂₅O₄ 293.1753, found 293.1775. For the preparation of **3c–i**, the amount of Pd(OH)₂/C and the reaction period were varied according to those described in Table 1.

Determination of the Conversion from **1b to **3b**.** The reaction mixture (ca. 20 μL) was added to 2 N HCl (200 μL) and the products were extracted with AcOEt (100 μL). The organic layer was analyzed by HPLC (L-Column, MeCN/THF/H₂O 50:10:40; 40 °C; 1 mL/min; **1b**, 6.8 min; **3b**, 4.9 min).

Ethyl 6-oxotridecanoate (3c**):** yield 93%; IR (KBr) ν = 1734, 1716 cm⁻¹; ¹H NMR (CDCl₃) δ 4.12 (q, *J* = 7.1 Hz, 2H), 2.45–2.38 (m, 4H), 2.31 (t, *J* = 7.1 Hz, 2H), 1.66–1.52 (m, 6H), 1.35–1.23 (m, 8H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.89–0.86 (m, 3H); HRMS *m/z* (M + H)⁺ calcd for C₁₅H₂₉O₃ 257.2117, found, 257.2127.

Ethyl 6-cyclohexyl-6-oxohexanoate (3d**):** yield 79%; IR (KBr) ν = 1733, 1706 cm⁻¹; ¹H NMR (CDCl₃) δ 4.12 (q, *J* = 7.1 Hz, 2H), 2.45 (t, *J* = 6.9 Hz, 2H), 2.35–2.29 (m, 1H), 2.30 (t, *J* = 7.1 Hz, 2H), 1.86–1.73 (m, 4H), 1.69–1.55 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.37–1.14 (m, 5H); HRMS *m/z* (M + H)⁺ calcd for C₁₄H₂₅O₃ 241.1804, found 241.1785.

Ethyl 10-methoxycarbonyl-6-oxodecanoate (3e**):** yield 78%; IR (KBr) ν = 1731, 1713 cm⁻¹; ¹H NMR (CDCl₃) δ 4.12 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 3H), 2.44–2.40 (m, 4H), 2.34–2.29 (m,

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4H), 1.66–1.54 (m, 8H), 1.25 (t, $J = 7.1$ Hz, 3H); HRMS m/z ($M + H$)⁺ calcd for C₁₄H₂₅O₅ 273.1702, found 273.1717.

Ethyl 6,9-dioxo-9-phenylnonanoate (3f): yield 70%; IR (KBr) $\nu = 1729, 1717, 1684$ cm⁻¹; ¹H NMR (CDCl₃) δ 7.99–7.97 (m, 2H), 7.59–7.54 (m, 1H), 7.48–7.44 (m, 2H), 4.13 (q, $J = 7.1$ Hz, 2H), 3.30–3.27 (m, 2H), 2.87–2.84 (m, 2H), 2.59–2.55 (m, 2H), 2.34–2.30 (m, 2H), 1.69–1.63 (m, 4H), 1.25 (t, $J = 7.1$ Hz, 3H); HRMS m/z ($M + H$)⁺ calcd for C₁₇H₂₃O₄ 291.1596, found 291.1603.

Ethyl 6-oxo-6-phenylhexanoate (3g): yield 72%; IR (KBr) $\nu = 1730, 1684$ cm⁻¹; ¹H NMR (CDCl₃) δ 7.97–7.94 (m, 2H), 7.58–7.54 (m, 1H), 7.48–7.44 (m, 2H), 4.13 (q, $J = 7.1$ Hz, 2H), 3.02–2.98 (m, 2H), 2.38–2.34 (m, 2H), 1.83–1.68 (m, 4H), 1.25 (t, $J = 7.1$ Hz, 3H); HRMS m/z ($M + H$)⁺ calcd for C₁₄H₁₉O₃ 235.1334, found 235.1345.

Ethyl 6-(3-chlorophenyl)-6-oxohexanoate (3h): yield 73%; IR (KBr) $\nu = 1729, 1688$ cm⁻¹; ¹H NMR (CDCl₃) δ 7.92 (t, $J = 1.8$ Hz, 1H), 7.84–7.81 (m, 1H), 7.54–7.52 (m, 1H), 7.43–7.39 (m, 1H), 4.13 (q, $J = 7.1$ Hz, 2H), 2.99–2.96 (m, 2H), 2.38–2.34 (m, 2H), 1.82–1.68 (m, 4H), 1.26 (t, $J = 7.1$ Hz, 3H); HRMS m/z ($M + H$)⁺ calcd for C₁₄H₁₈O₃Cl 269.0944, found, 269.1116; SIMS m/z 268 (M^+).

Ethyl 6-oxo-6-(3-thienyl)hexanoate (3i): yield 61%; IR (KBr) $\nu = 1726, 1666$ cm⁻¹; ¹H NMR (CDCl₃) δ 8.04 (dd, $J = 2.9, 1.3$ Hz, 1H), 7.54 (dd, $J = 5.1, 1.3$ Hz, 1H), 7.32 (dd, $J = 5.1, 2.9$ Hz, 1H), 4.13 (q, $J = 7.1$ Hz, 2H), 2.92–2.89 (m, 2H), 2.37–2.34 (m, 2H), 1.81–1.67 (m, 4H), 1.25 (t, $J = 7.1$ Hz, 3H); HRMS m/z ($M + H$)⁺ calcd for C₁₂H₁₇O₃S 241.0898, found 241.0879.

A Typical Procedure for the Sonogashira Coupling Reaction (Preparation of 2-Methy-4-(3-pyridyl)-3-butyn-2-ol 10a¹). To a mixture of 3-bromopyridine **8a** (474 mg, 3 mmol), K₂CO₃ (1.04 g, 7.5 mmol), CuI (23 mg, 0.12 mmol), and PPh₃ (63 mg, 0.24 mmol) in 1,2-dimethoxyethane (5 mL) and H₂O (5 mL) was added 10% Pd(OH)₂/C (52.8% wet, 33.8 mg, 0.015 mmol) and the suspension was stirred at 25 °C for 30 min. 3-Methyl-1-butyn-3-ol **9a** (630 mg, 7.5 mmol) was then added and the suspension was stirred at 80 °C for 21 h. The mixture

was cooled to 25 °C and filtered. To the filtrate was added AcOEt, and the organic layer was washed with H₂O, dried over anhydrous MgSO₄, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt 2:1) to give **10a** (406 mg, 84%) as yellow crystals. Mp 59–60 °C; IR (KBr) $\nu = 3184, 2232$ cm⁻¹; ¹H NMR (CDCl₃) δ 8.74 (d, $J = 1.5$ Hz, 1H), 8.52–8.49 (m, 1H), 7.73–7.69 (m, 1H), 7.27–7.23 (m, 1H), 3.67 (br s, 1H), 1.63 (s, 6H); SIMS m/z 162 ($M^+ + 1$). For the preparation of **10b**, the amount of Pd(OH)₂/C was increased from 0.5 mol % to 1.0 mol % relative to **8a**.

3-(2-Phenylethynyl)pyridine (10b):¹² mp 50–51 °C; IR (KBr) $\nu = 2193$ cm⁻¹; ¹H NMR (CDCl₃) δ 8.77 (dd, $J = 2.0, 0.8$ Hz, 1H), 8.56–8.54 (m, 1H), 7.82–7.79 (m, 1H), 7.58–7.52 (m, 2H), 7.41–7.35 (m, 3H), 7.30–7.26 (m, 1H); SIMS m/z 180 ($M^+ + 1$).

A Typical Procedure for the Suzuki Coupling Reaction (Preparation of 4-Nitrobiphenyl 10c²³). To a mixture of phenyl boronic acid **9c** (391 mg, 3.21 mmol), 1-bromo-4-nitrobenzene **8b** (537 mg, 2.66 mmol), and PPh₃ (122 mg, 0.47 mmol) in 1,2-dimethoxyethane (10 mL) was added 10% Pd(OH)₂/C (52.8% wet, 68 mg, 0.03 mmol) and the mixture was stirred at 25 °C for 20 min. To the mixture was added aq Na₂CO₃ [Na₂CO₃ (1.06 g) + H₂O (5 mL)] and the solution was stirred at 80 °C for 43 h. The mixture was cooled to 25 °C and filtered. To the filtrate was added AcOEt and the organic layer was washed with H₂O, dried over anhydrous MgSO₄, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt 200:1) to give **10c** (482 mg, 91%) as slightly yellow crystals. Mp 111–112 °C; IR (KBr) $\nu = 1511, 1339$ cm⁻¹; ¹H NMR (CDCl₃) δ 8.32–8.28 (m, 2H), 7.76–7.72 (m, 2H), 7.64–7.61 (m, 2H), 7.53–7.42 (m, 3H); SIMS m/z 199 (M^+).

4-Methoxy-4'-nitrobiphenyl (10d):²³ mp 100–101 °C; IR (KBr) $\nu = 1506, 1341$ cm⁻¹; ¹H NMR (CDCl₃) δ 8.27 (d, $J = 9.1$ Hz, 2H), 7.69 (d, $J = 9.1$ Hz, 2H), 7.58 (d, $J = 8.8$ Hz, 2H), 7.02 (d, $J = 8.8$ Hz, 2H), 3.87 (s, 3H); SIMS m/z 229 (M^+).

JO0265277