



# Palladium on charcoal-catalyzed Fukuyama coupling reaction

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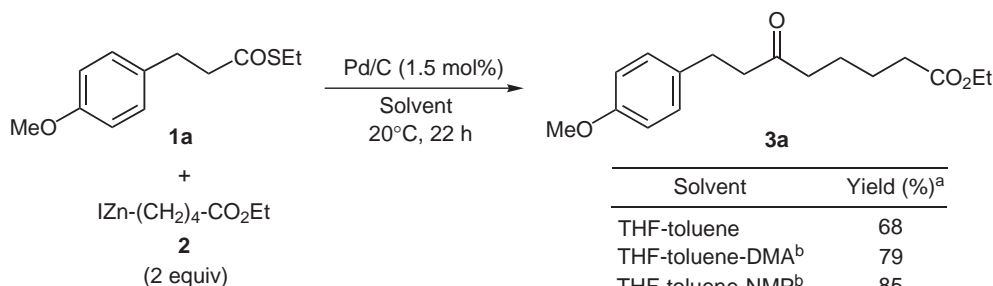
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**Abstract**—The Pd/C-catalyzed coupling reactions of thiol esters **1** with a zinc reagent **2** were accomplished in the presence of DMF leading to the polyfunctional ketones **3** in good yields under mild reaction conditions. The protocol was applied to the coupling reaction of a thiolactone **4c** with a zinc reagent **2** to provide, after dehydration, a dehydrobiotin derivative **5c** in 94% yield. © 2001 Elsevier Science Ltd. All rights reserved.

Palladium-catalyzed cross-coupling reactions have received considerable attention as versatile and reliable methods for synthesizing valuable compounds such as drugs and natural products.<sup>1</sup> The use of heterogeneous catalysts is much more important especially for a practical large scale preparation than the homogeneous counterparts because of low cost, stability, and ease of operation and recovery.<sup>2</sup> Recent papers in this context have shown that homogeneous palladium catalysts can be replaced by heterogeneous palladium on charcoal (Pd/C) in the Suzuki,<sup>3c,h</sup> Stille,<sup>3d,g</sup> Negishi,<sup>3e</sup> and Sonogashira couplings<sup>3a,f</sup> of aryl or alkenyl halides with aryl, alkenyl or alkynyl compounds of various metals (B, Sn, Zn, Cu). The use of the supported palladium catalysts

involving Pd/C was also found in the Heck arylation of a vinyl ether.<sup>3b</sup> However, any couplings of *sp*<sup>3</sup>-based organometallics in the presence of Pd/C have never been reported.

We have recently developed a novel synthesis of (+)-biotin via the Fukuyama coupling reaction<sup>4</sup> between a thiolactone **4c** and a zinc reagent **2** in the presence of a homogeneous catalyst, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>.<sup>5</sup> A pioneering work by Fukuyama and co-workers has shown that reduction of thiol esters to aldehydes (C–H bond forming reaction) with triethylsilane takes place in the presence of Pd/C.<sup>6</sup> These findings have led us to investigate Pd/C-catalyzed Fukuyama coupling reaction (C–C



Solvent	Yield (%) <sup>a</sup>
THF-toluene	68
THF-toluene-DMA <sup>b</sup>	79
THF-toluene-NMP <sup>b</sup>	85
THF-toluene-DMF <sup>b</sup>	87

a: Isolated yield, the compound **3a** was characterized by <sup>1</sup>H, <sup>13</sup>C NMR, IR and MS analysis; b: 4% (v/v) of DMA, NMP or DMF was added.

**Scheme 1.**

**Keywords:** palladium and compounds; sulfur compounds; zinc and compounds; vitamins.

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bond forming reaction) to ensure an economical access to (+)-biotin. Reported herein are the successful results to permit an efficient synthesis of (+)-biotin as well as other polyfunctional compounds by the use of the Pd/C-catalyzed Fukuyama coupling reaction.

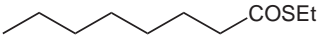
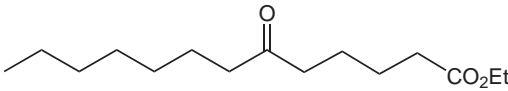
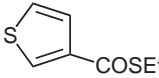
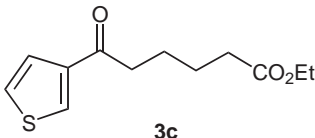
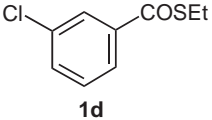
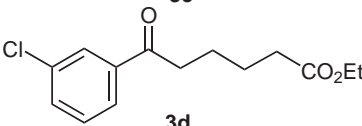
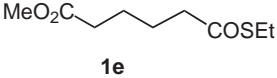
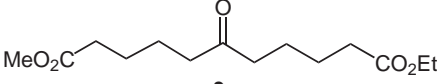
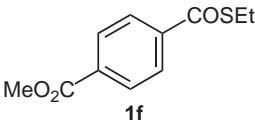
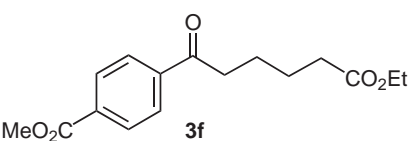
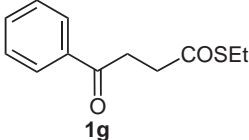
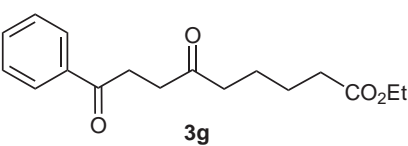
Our initial study was focused on the coupling reaction of a thiol ester **1a**<sup>7</sup> with the zinc reagent **2**<sup>5</sup> (Scheme 1). It was found that the coupling reaction in the presence of Pd/C (1.5 mol%) took place in 68% yield by the treatment of **1a** with **2** (2 equiv.) in a mixed solvent of THF and toluene. To the best of our knowledge, this represents the first example of the coupling of *sp*<sup>3</sup>-based organometallics in the presence of heterogeneous Pd/C. In order to improve the yield, addition of an aprotic polar solvent to the reaction mixture was tested because the zinc reagent might be activated by the solvent possibly by dissociation of the stabilized chelated structure.<sup>8</sup> As expected, when the reaction was conducted in the presence of DMA, NMP or DMF (4% volume of

DMA, NMP or DMF per total volume of the solvent (4% (v/v)), the coupling product **3a** was obtained in much improved yields (79, 85 and 87%,<sup>9</sup> respectively).

The protocol using Pd/C in the presence of DMF was successfully applied to the coupling reactions of other aliphatic or aromatic thiol esters **1b–g** with the zinc reagent **2** (Table 1). Remarkably the reaction can be extended to various functionalized thiol esters **1c–g** carrying a thiophene, a chlorophenyl, an ester or a ketone to give the corresponding coupling products **3c–g** in good yields without accompanying a problem of catalytic poison (Table 1, Entries 2–6).

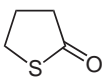
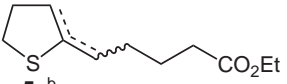
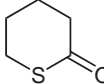
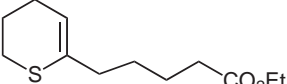
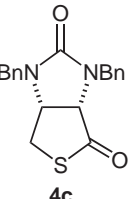
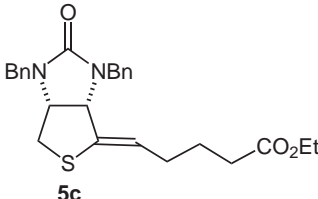
The coupling reaction with cyclic thiol esters (thiolactones) **4a–c** was the next subject for our investigation (Table 2). Treatment of a five-membered thiolactone **4a** with the zinc reagent **2** (2 equiv.) in the presence of 1.5 mol% of Pd/C provided, after dehydration, corresponding vinyl sulfide **5a** in 57% yield as a mixture of *endo*-

Table 1.

$\text{RCOSEt} \xrightarrow[\text{THF, toluene, DMF (4\% (v/v))}]{\text{IZn-(CH}_2\text{)}_4\text{-CO}_2\text{Et (2) (2 equiv) Pd/C (1.5 mol\%)}} \text{R-C(=O)-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{Et}$ <p style="text-align: center;"> <b>1b-i</b> <span style="margin-left: 150px;"></span> <b>3b-i</b> </p> <p style="text-align: center;">20°C, 22 h</p>			
Entry	Thiol ester (1)	Product (3)	Yield (%) <sup>a</sup>
1			91
2			67
3			90
4			76
5			70
6			74

a: Isolated yield, all compounds were characterized by <sup>1</sup>H, <sup>13</sup>C NMR, IR and MS analyses.

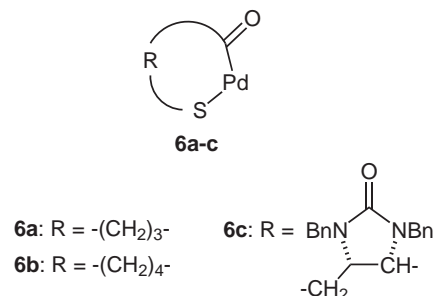
Table 2.

$  \begin{array}{c}  \text{R} \\  \diagup \\  \text{S} \text{---} \text{C(=O)} \\  \text{4a-c}  \end{array}  \xrightarrow[\text{ii) p-TsOH, toluene, 20}^\circ\text{C, 18 h}]{\text{i) IZn-(CH}_2\text{)}_4\text{-CO}_2\text{Et (2), Catalyst, THF, toluene, DMF (4\% (v/v)), 25}^\circ\text{C, 18 h}}  \begin{array}{c}  \text{R} \\  \diagup \\  \text{S} \text{---} \text{C(=CH-CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{Et)} \\  \text{5a-c}  \end{array}  $					
Entry	Thiolactone (4)	Catalyst (mol%)	2 (equiv)	Product (5)	Yield (%) <sup>a</sup>
1		Pd/C (1.5)	2.0		57
2	<b>4a</b>	Pd/C (5)	2.5	<b>5a<sup>b</sup></b>	49
3		Pd/C (1.5)	2.0		38
4 <sup>5</sup>		PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (10)	3.0		86
5 <sup>c</sup>		PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (10)	6.0		80
6		PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (10)	2.5		34
7		Pd/C (5)	2.5		94
	<b>4c</b>			<b>5c</b>	

a: Isolated yield, all compounds were characterized by <sup>1</sup>H, <sup>13</sup>C NMR, IR and MS analyses; b: the product was obtained as a mixture of *endo*- and *exo*-isomers (contained *E*- and *Z*-isomers); c: the reaction was conducted without DMF.

and *exo*-isomers (contained *E*- and *Z*-isomers) (Table 2, Entry 1). When a six-membered thiolactone **4b** was allowed to the coupling reaction, the coupling product **5b** was obtained in poor yield (38%) as an *endo*-isomer (Table 2, Entry 3). These results might reflect the order of the reactivity of Pd(0) toward **4a** and **4b** to form the possible palladacyclic intermediates **6a** and **6b**, respectively. The six-membered palladacycle **6a** should be generated more easily than the seven-membered derivative **6b** to result in the better yield of **5a** than **5b**. The coupling reaction was then applied to the synthesis of (+)-biotin. The C-2 side-chain of (+)-biotin was efficiently introduced to the bicyclic five-membered thiolactone **4c** by the use of 5 mol% of Pd/C and 2.5 equiv. of the zinc reagent **2** to provide the dehydrobiotin derivative **5c** in 94% yield (Table 2, Entry 7). This result is superior to those obtained under homogeneous catalytic conditions (Table 2, Entry 7 versus Entries 4<sup>5</sup>–6). The excellent yield of the coupling reaction with **4c** (Table 2, Entry 7 versus Entry 2) should arise from the stabilization of the six-membered palladacycle **6c** by means of the favorable conformational effect of the *N*-benzyl-2-imidazolidinone ring.<sup>12</sup>

To make sure the possibility of the recovery of the catalyst, we measured the palladium in the reaction of **4c** with **2** by employing atomic absorption spectroscopy (initially added Pd/C: 5 mol% relative to **4c**).<sup>13</sup> Thus, after the reaction was completed, the mixture was



filtered through Celite, and the filtrate was evaporated and digested with aqua regia to provide a sample for the measurement. Only a small amount of the palladium (5.8% relative to the initially added Pd/C or 0.29 mol% relative to the initially added **4c**) was found in the filtrate and thus most of the palladium remained in the filter cake. The coupling reaction did not proceed to any appreciable extent in the presence of such a small amount of palladium catalyst (0.29 mol% of Pd/C or PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>). The observations suggest that the coupling reaction should take place on the surface of the Pd/C and, after the reaction, most of the catalyst might be recovered by the simple filtration. Further investigation on the re-use of the recovered catalyst is under current investigation.

In conclusion, Pd/C-catalyzed Fukuyama coupling reaction was accomplished. The Pd/C-catalyzed reaction was successfully applied to the synthesis of various

functionalized ketones involving chiral compound. The C-2 side chain of (+)-biotin was efficiently installed into the thiolactone derivative by the use of the protocol using inexpensive Pd/C. The good yields, simple operations, mild reaction conditions and ease of the recovery of the catalyst would permit a ready access to the synthetically useful ketones for a practical large scale preparation.

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13. The atomic absorption spectrum was measured using Hitachi 180-60 Polarized Zeeman Atomic Absorption Spectrophotometer.