

A Practical Synthesis of Multifunctional Ketones through the Fukuyama Coupling Reaction

Yoshikazu Mori^a and Masahiko Seki^{a,*}

^a Tanabe Seiyaku Co., Ltd., 3-16-89, Kashima, Yodogawa-Ku, Osaka 532-8505, Japan

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Abstract: A highly efficient, robust and scalable protocol for the synthesis of multifunctional ketones through Fukuyama coupling, i.e., cross-coupling of thiol esters with zinc reagents, has been developed. Treatment of thiol esters with alkylzinc iodides or dialkyl zincs in the presence of palladium on activated carbon (Pd/C) or palladium acetate [Pd(OAc)₂] furnished the corresponding ketones in high yields. Evaluation of the properties-activities relationship of the Pd/C-catalyzed reaction has proven that oxidic Pd/C is much more potent than reduced Pd/C in the reaction of thiolactone **1a** with zinc reagent **2a**. Based on the dependence of the Pd/C-catalyzed reaction on the nature of Pd/C in combination with the extent of the Pd leaching from Pd/C to the solution, a dual reaction mechanism for the Pd/C-catalyzed

Fukuyama coupling reaction, which includes heterogeneous and homogeneous catalytic cycles, was proposed. The marked reduction of the zinc reagents and the use of Pd(OAc)₂ in much smaller amounts were achieved when zinc bromide was added. This supports a hypothesis where a shift of the Schlenk equilibrium from inactive dialkylzincs (R₂Zn) to active organozinc species, such as alkylzinc halides (RZnX) and three-coordinate species [(RZnX₂)⁻(ZnX)⁺], and generation of the stabilized monomeric Pd complexes during the reaction, may facilitate the reaction.

Keywords: cross-coupling; heterogeneous catalysis; ketones; palladium; sulfur; zinc

Introduction

Ketones, especially with functional groups and/or asymmetric centers, have been of great interest due to their significance in the synthesis of a wide variety of valuable compounds such as drugs and natural products.^[1] Among a number of approaches reported so far, synthesis using carboxylic acid derivatives as the starting material is a versatile and widely accepted approach in the synthetic community.

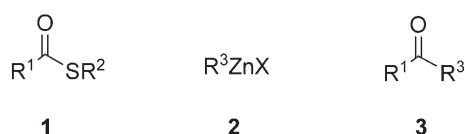
Fukuyama and co-workers have recently developed an efficient synthesis of multifunctional ketones **3** by the palladium-catalyzed coupling reaction of thiol esters **1** with zinc reagents **2**.^[2] The synthesis is a state-of-the-art technology, featured by high yield using less toxic reagents, i.e., zinc reagents, under mild conditions. The synthesis minimizes the use of steps that are required for protection-deprotections

and functional group oxidation state adjustments. It thus inherently meets the requirements for scale-up, especially when an industrial application is considered.^[3] We have thoroughly optimized the Fukuyama coupling to the extent that it is applied to the multi-kilogram scale synthesis of ketones and their derivatives.^[4] Among the key components essential to become a commercial process are robustness to assure both reproducibility and quality of the product as well as cost of the reagents needed to effect the reaction. The hitherto unknown reaction mechanism, especially focusing on the role of the heterogeneous Pd/C and the behavior of the zinc reagents, has been figured out to allow the rigorous improvement of the reaction process.

Result and Discussion

Synthesis of (+)-Biotin Intermediate **5** by means of the Pd/C-Catalyzed Fukuyama Coupling Reaction

(+)-Biotin, a water-soluble B series vitamin, has received a considerable attention, due to its significance



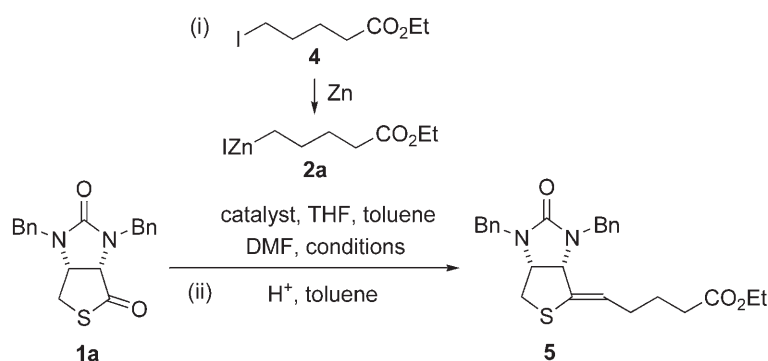
as a component of biological tools as well as human nutrition and animal health.^[5] Despite the enormous endeavors devoted toward the efficient access to (+)-biotin, an amount of around 100 tons per year of (+)-biotin has been produced by the total synthetic method, because of a lack of an efficient fermentation method. Among a number of synthetic approaches hitherto developed, the synthesis using thiolactone **1a** as the intermediate has been considered to be most reliable.^[6] However, the previous conversion of **1a** to (+)-biotin, i.e., installation of the 4-carboxybutyl chain, by means of the Grignard reaction, requires 6 steps using hazardous reagents. The optimum goal has not been attainable and development of an efficient alternative to effect the conversion in a more effective and safer manner has been of high demand to meet the enormous commercial opportunity.

To address these long outstanding bottlenecks, we envisioned a possible use of the Fukuyama coupling for the transformation. The intermediate with the required side chain would be formed in a single step through the Fukuyama coupling of **1a** with zinc reagent **2a** that carries an ester group.

While the Fukuyama coupling has originally been conducted using the expensive homogeneous palladium catalyst, PdCl₂(PPh₃)₂, it poses many challenges associated with scale-up, such as difficult recovery of expensive palladium and contamination of the toxic heavy metal to the product. We thus tested a heterogeneous variant using palladium on activated carbon (Pd/C) as the catalyst, which would also offer a significant cost advantage (Table 1).

Treatment of **1a** with **2a** in the presence of Pd/C did lead to the desired coupling product **5** albeit in a poor yield (50 %, Table 1, entry 1), possibly attributable to aggregation of the zinc reagents to inactive dimer or oligomers.^[7] Addition of *N,N*-dimethylformamide (DMF) was thus examined to allow their dissociation to active monomeric species. As expected, the yield dramatically surged up to 94 %, when DMF (4 % volume per total volume of solvent) was added to the reaction mixture (Table 1, entry 2). In addition, the use of the less flammable Pearlman's catalyst [Pd(OH)₂/C] gave **5** in high yield with a substantial lowering of the catalyst loading (Table 1, entry 3).

Table 1. Synthesis of biotin intermediate **5** through the Pd/C-catalyzed Fukuyama coupling reaction of thiolactone **1a** with zinc reagent **2a**.



Entry	DMF	Catalyst [mol % ^[b]]	4 [equivs. ^[b]]	Conditions	Yield [%] ^[c]	TON
1 ^[a]	none	Pd/C D4 ^[d] (5)	6.0	20 °C, 24 h	50	10
2 ^[a]	4 % (v/v)	Pd/C D4 ^[d] (5)	2.5	20 °C, 18 h	94 ^[e]	19
3 ^[a]	4 % (v/v)	Pd(OH) ₂ /C ^[f] (0.65)	2.5	25–30 °C, 2 h	92 ^[e]	142
4 ^[a]	4 % (v/v)	Pd/C D2 ^[g] (0.86)	2.5	25–30 °C, 18 h	95 ^[e]	110
5 ^[a]	4 % (v/v)	Pd/C D2 ^[g] (0.86)	1.4	25–30 °C, 18 h	59 ^[e]	49
6 ^[h]	4 % (v/v)	Pd/C D2 ^[g] (0.86)	1.4	28–40 °C, 5 h	94 ^[e]	78

^[a] Zinc dust was activated by the treatment with 1,2-dibromoethane (0.026 equivs. relative to Zn dust) followed by TMSCl (0.018 equivs.).^[8]

^[b] Mol %/equivalent relative to **1a**.

^[c] Isolated yield.

^[d] Purchased from Kawaken Fine Chemicals; Pd-distribution: uniform; reduction degree: 25–99 %; Pd dispersion: 36 %; water content: 1.8 %.

^[e] Recovery of Pd: > 95 % after subjection to a recovery process with combustion.

^[f] Purchased from Kawaken Fine Chemicals.

^[g] Purchased from Degussa Japan Co., Ltd; Pd-distribution: uniform; reduction degree: 0–25 %; Pd dispersion: 36 %; water content: 1–1.5 %.

^[h] Br₂ (0.26 equivs. relative to Zn dust) was used for activation of Zn dust (1.9 equivs. relative to **4**).

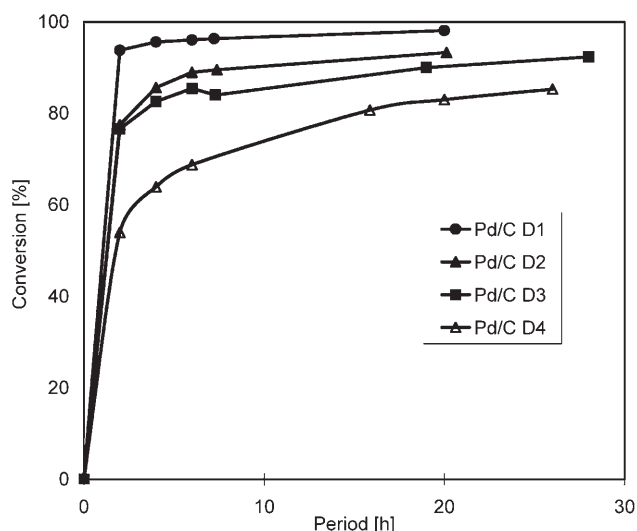


Figure 1. Screen of the Pd/C catalysts in the Fukuyama coupling of thiolactone **1a** with zinc reagents **2b**.

Efficiencies of the Pd/C-catalyzed coupling reactions respond strongly to the properties of Pd/C such as reduction degree and distribution of Pd.^[9–11] Screening of the Pd/C in the reaction of **1a** with **2a** has been conducted as shown in Figure 1. Among the Pd/C forms tested, oxidic Pd/C D1, D2 and D3, whose reduction degree [relative amount of Pd(0) species on the total amount of Pd] is from 0 to 25 %, are more active than the reduced counterpart Pd/C D4 whose reduction degree is from 25 to 99 %. Actually, active species of Pd/C is the reduced type Pd(0)/C. The reduced type Pd(0)/C, which are generated *in situ* under mild reaction conditions, are likely to have higher activities than those with pre-reduced Pd(0)/C.

As for the distribution of Pd, three types of Pd/C, i.e., eggshell, thickshell and uniform Pd/C, are important for the liquid phase reactions (see Experimental Section, Table 7).^[9–11] In eggshell Pd/C, Pd distributes in close proximity within 50 to 150 nm from the surface. In uniform Pd/C, in contrast, Pd distributes uniformly in the catalyst. In thickshell Pd/C, Pd distributes intermediately within 200 to 500 nm depth. As shown in Figure 1, thickshell or uniform catalysts, D1 and D2, respectively, whose Pd distributes more uniformly in the charcoal matrix, are more potent than eggshell catalyst D3. When Pd distributes widely in the charcoal matrix, it can avoid inactivation by aggregation to Pd black. However, diffusion of the substrates to the Pd particles, existing deep in the solid support, has to be overridden. There thus may be a trade-off between the catalyst performance and impregnation depth of Pd (distribution of Pd).^[10]

In our initial study, zinc dust (Zn) has been activated using Knochel's procedure,^[8] i.e., addition of carbi-

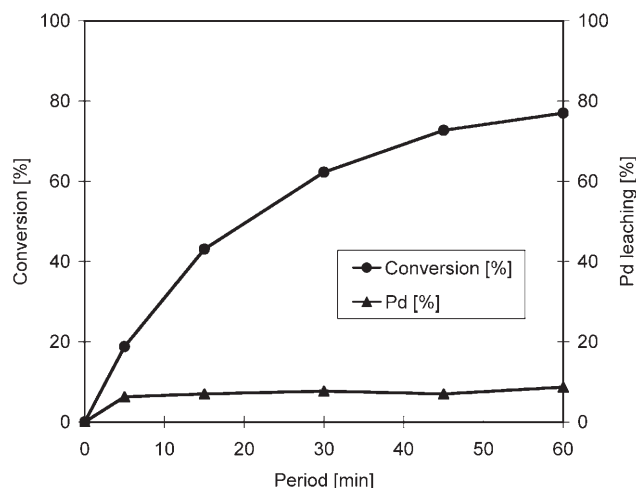
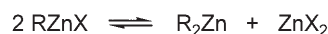


Figure 2. Behavior of Pd in the Fukuyama coupling of thiolactone **1a** with Et₂Zn **2b** [**1a** (4.46 mmol), **2b** (4.46 mmol), Zn (8.93 mmol), Br₂ (4.46 mmol), Pd/C D1 (0.223 mmol), THF (8.0 mL), toluene (11.2 mL), DMF (1.7 mL), 35–40 °C].

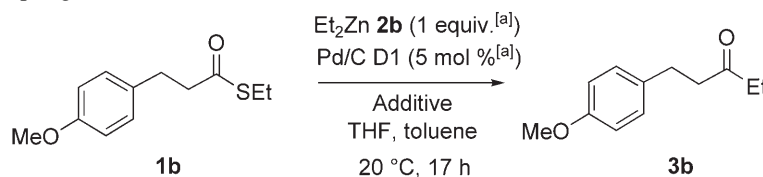
nogenic 1,2-dibromoethane followed by chlorotrimethylsilane (TMSCl) to Zn. However, a serious issue raised is the requirement of as much as 2.5 equivalents of expensive iodide **4** to complete the reaction (Table 1, entries 4 and 5). In addition, formation of the zinc reagent **2a** was sometimes not complete, being unable to assure enough reproducibility compatible for scale-up.

Alkylzinc halides (RZnX) are known to form a Schlenk equilibrium^[12] with dialkylzincs (R₂Zn) as shown in Scheme 1. The Fukuyama coupling is report-



Scheme 1. The Schlenk equilibrium of zinc reagents.

ed to be active for RZnX, while inactive for R₂Zn. To reduce the amount of iodide **2a**, we envisioned addition of zinc halide to the reaction mixture to shift the equilibrium from inactive R₂Zn to active RZnX. The reaction was thus conducted by initial addition of bromine to the suspension of Zn to generate zinc bromide (ZnBr₂) and to simultaneously activate Zn. As expected, through the pre-treatment, the process was significantly improved: the most consistent and reproducible formation of the zinc reagent **2a** was achieved with the amount of the iodide **4** being reduced from 2.5 equivs. to 1.4 equivs. to give **5** in high yield as well (Table 1, entry 6). The protocol has been successfully advanced to a large-scale production as far as a 500-kg scale and has contributed tremendously in reducing the cost for producing (+)-biotin.

Table 2. The Fukuyama coupling reaction of thiol ester **1b** with Et₂Zn **2b**.

Entry	Additive [equivs. ^[b]]	Yield [%] ^[c]	TON
1	none	36	7
2	ZnBr ₂ [Zn (2.0), Br ₂ (1.0)]	84	17
3	ZnBr ₂ [Zn (2.0), Br ₂ (1.0)], DMF (4.9)	95	19

^[a] Equivalents relative to thiol ester **1b**.

^[b] Equivalents relative to Et₂Zn **2b**.

^[c] Isolated yield.

Synthesis of Multifunctional Ketones **3** by means of the Pd/C-Catalyzed Fukuyama Coupling Reaction of Et₂Zn

If the hypothesis to facilitate the Fukuyama coupling through the shift of the Schlenk equilibrium is true, the Fukuyama coupling reaction employing inactive R₂Zn would take place in the presence of ZnBr₂. The Fukuyama coupling of R₂Zn with thiol esters was aimed at in the presence of ZnBr₂.

In our initial study, the reaction of Et₂Zn **2b** with thiol ester **1b** was tested. Treatment of **1b** with **2b** in the presence of Pd/C D1 in a mixed solvent of THF and toluene provided the desired ketone **3b** only in a poor yield (36%, Table 1, entry 1). To improve the yield, addition of ZnBr₂ to the reaction mixture was examined. As expected, when ZnBr₂ (1.0 equiv.), freshly prepared from Zn (2.0 equivs.) and bromine (1.0 equiv.), was added, the desired ketone **3b** was obtained in a much higher yield (84%) (Table 2, entry 2). Addition of DMF was again effective for the coupling reaction to afford **3b** in an excellent yield (95%) (Table 2, entry 3, cf. Table 1). As mentioned above, we attribute the effect to DMF dissociating less-active dimer and/or oligomers of the zinc reagents.

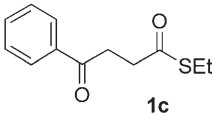
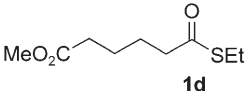
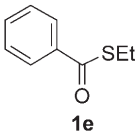
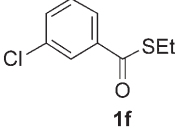
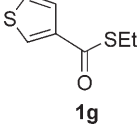
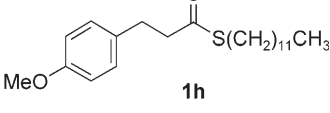
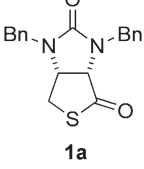
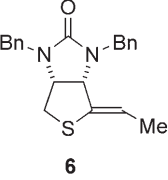
The present method was applied to the coupling reaction of various substrates (Table 3). It turned out that thiol esters **1c**, **1d** and **1f** carrying a ketone, an ester and a chloro group, were applicable to the coupling reaction to afford the corresponding ketones **3c**, **3d** and **3f** in high yields (Table 3, entries 1, 2 and 4). Although aromatic thiol esters **1e**, **1f** and **1g** were less reactive than aliphatic counterparts **1c**, **1d** and **1h**, moderate to high yields were obtained in longer reaction periods (compare Table 2, entry 3 and Table 3, entries 1 and 2 with Table 3, entries 3–5). The use of a practically attractive and odorless thiol ester **1h**, prepared from dodecanethiol, worked equally well to give the desired ketone **3b** in good yield as well (Table 3, entry 6). Thiolactone **1a** was also applicable

to the reaction with **2b** to afford **6** in high yield (Table 2, entry 7).

Reaction Mechanism of the Pd/C-Catalyzed Fukuyama Coupling Reaction

Although the understanding of a precise mechanism of the Pd/C-catalyzed coupling reactions has sparked a great deal of discussion, it still remains elusive.^[9] The issue of controversy is whether the reaction takes place heterogeneously on the surface of the Pd attached to the charcoal matrix or homogeneously in the solution. The behavior of Pd in the Fukuyama coupling reaction was investigated using the reaction of thiolactone **1a** with Et₂Zn **2b** as the typical example. The extent of Pd leaching was estimated by periodical filtration of the reaction mixture and subjecting the resulting filtrates to X-ray fluorescence analysis. As shown in Figure 2, about 5 min after starting the reaction, the concentration of Pd in the solution reached to ca. 8% of the initially added Pd and remained almost unchanged until the end of the reaction. In the presence of such an amount of Pd, i.e., 0.4 mol% to **1a**, the reaction should take place, because, as described later, the reaction did proceed with 0.1 mol% of Pd(OAc)₂ (Table 5, entry 4). However, the reaction is considered not to proceed completely in a homogeneous fashion, because the Pd level in the solution phase remained constant. If the re-deposition of Pd would not occur, Pd in the charcoal matrix may leach into the solution and, eventually, all the Pd should dissolve into the solution phase. To further support the hypothesis, the reaction stopped at around 60% conversion after removal of the solid Pd/C by filtration at the point when the reaction reached 50% conversion. The considerable dependence of the efficiency of the reaction on the nature of Pd/C such as Pd distribution in the charcoal matrix (Figure 1) may account for the heterogeneous nature of the re-

Table 3. Synthesis of multifunctional ketones **3c–h** through the Pd/C-catalyzed Fukuyama coupling reaction of thiol esters **1c–h** with Et₂Zn **2b**.

$ \begin{array}{c} \text{Et}_2\text{Zn } \mathbf{2b} \text{ (1 equiv.}^{[b]}) \\ \text{Zn (2.0 equivs.}^{[a]}) \text{, Br}_2 \text{ (1.0 equiv.}^{[a]}) \\ \text{Pd/C D1 (5 mol \%}^{[b]}) \\ \xrightarrow{\text{THF, toluene, DMF (4.9 equivs.}^{[b]})} \\ \begin{array}{ccc} \text{R}^1-\text{C}(=\text{O})-\text{SR}^2 & & \text{R}^1-\text{C}(=\text{O})-\text{Et} \\ \mathbf{1c-h} & & \mathbf{3c-h} \end{array} \end{array} $					
Entry	Thiol ester 1c–h	Period [h]	Product 3c–h	Yield ^[b] [%]	TON
1		17	3c	95	19
2		17	3d	quant.	20
3		48	3e	85	17
4		48	3f	83	17
5		48	3g	57	11
6		48	3b	72	14
7		26		75	15

[a] Equivalents relative to Et₂Zn **2b**.[b] Equivalents/mol % relative to thiol ester **1**.

[c] Isolated yield.

action as well. The eggshell Pd/C D3, which is intuitively advantageous for dissolution of Pd, is actually inferior to thickshell and uniform Pd/C, D1 and D2.

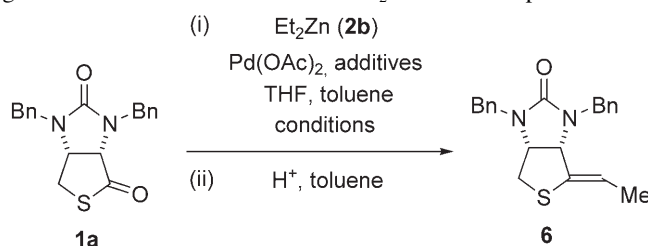
The Pd/C-catalyzed reaction may thus take place heterogeneously (Scheme 2) and/or homogeneously (*vide infra*, Scheme 3) through exchange of the ligands existed on the charcoal matrix and in the solution.

A possible heterogeneous mechanism for the Pd/C-catalyzed Fukuyama coupling reaction is described in

Scheme 2. Pd, in the Pd/C catalyst is believed to be bound to the solid support through coordination with oxygen-containing functional groups, like complex **7**.^[10c] Amatore and Jutand have recently reported a reaction mechanism of homogeneous Pd-catalyzed cross coupling reactions, where three-coordinate Pd(0) species are intervening as the intermediate.^[13] On the basis of their mechanism, the Pd(II) complex **7** would first give three-coordinate Pd(0) complex **8**

Table 4. Synthesis of biotin intermediate **5** through the Pd(OAc)₂-catalyzed Fukuyama coupling of thiolactone **1a** with zinc reagent **2a**.

Entry	Catalyst [mol %] ^[a]	Additives [equivs.] ^[b]	Iodide 4 [equivs.] ^[b]	Conditions	Assay Yield ^[c] [%]	TON
1	Pd(OAc) ₂ (1.2)	Zn (2.7), Br ₂ (0.7), DMF (1.1)	1.4	30–35 °C, 20 h	98	82
2	PdCl ₂ (1.2)	Zn (2.7), Br ₂ (0.7), DMF (1.1)	1.4	30–35 °C, 20 h	11	9
3 ^[d]	Pd(OAc) ₂ (1.2)	Zn (2.7), Br ₂ (0.7), DMF (1.1)	1.4	30–35 °C, 20 h	9	8
4	PdCl ₂ (PPh ₃) ₂ (1.2)	Zn (2.7), Br ₂ (0.7), DMF (1.1)	1.4	30–35 °C, 20 h	36	30
5	Pd(OAc) ₂ (0.1)	Zn (2.7), Br ₂ (0.7), DMF (1.1)	1.4	30–35 °C, 20 h	90	900
6	Pd(OAc) ₂ (0.01)	Zn (2.7), Br ₂ (0.7), DMF (1.1)	1.4	30–35 °C, 20 h	68	6800

^[a] Mol % relative to thiolactone **1a**.^[b] Equivalents relative to **1a**.^[c] Determined by HPLC.^[d] Triphenylphosphine (4.8 mol % relative to **1a**) was added.**Table 5.** The Fukuyama coupling reaction of thiolactone **1a** with Et₂Zn **2b** in the presence of Pd(OAc)₂ and additives.

Entry	Catalyst [mol %] ^[a]	Additives [equivs.] ^[b]	Et ₂ Zn (2b) [equivs.]	Conditions	Yield [%]	TON
1	Pd(OAc) ₂ (1.2)	Zn (2.0), Br ₂ (1.0), DMF (1.1)	0.6	30–35 °C, 22 h	52	43
2	Pd(OAc) ₂ (1.2)	ZnBr ₂ ^[c] (0.6), DMF (1.1)	0.6	35 °C, 18 h	53	44
3	Pd(OAc) ₂ (1.2)	DMF (1.1)	0.6	35 °C, 18 h	19	16
4	Pd(OAc) ₂ (0.1)	Zn (2.0), Br ₂ (1.0), DMF (1.1)	1.0	45 °C, 2 h	76	760
5	Pd(OAc) ₂ (0.1)	Zn (2.0), Br ₂ (1.0), DMA (0.9)	1.0	45 °C, 2.5 h	66	660

^[a] Mol % relative to thiolactone **1a**.^[b] Equivalents relative to thiolactone **1a**.^[c] Purchased from Nacalai Tesque Ltd. and used as received.

through reduction with Zn along with ZnBr₂. The Pd(0) complex **8**, thus obtained, is activated through coordination of the carbonyl oxygen with Zn⁺Br cation to form active Pd(0) species. This complex **8** is active because, due to ion pairing, it resembles the coordinatively unsaturated two-coordinate Pd(0) complex. While in Amatore's system, this type of intermediate has been generated by reduction at electrode, the present reaction, that employs Zn as the reductant, is practically much easier to conduct on a large-scale preparation.

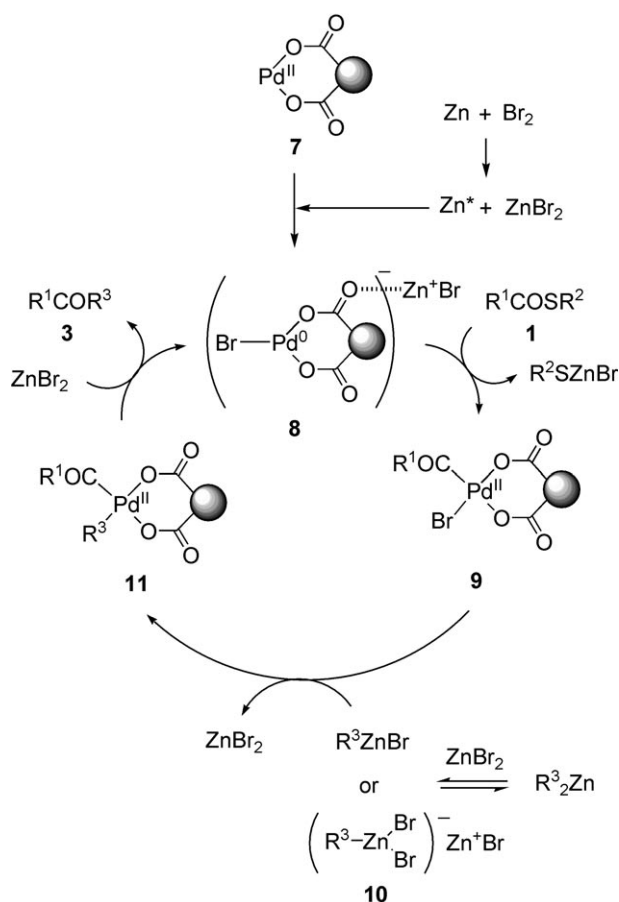
Oxidative addition of thiol ester **1** to **8** subsequently proceeds by liberating R²SZnBr to form a *cis*-tetra-substituted Pd(II) complex **9**.

The zinc reagent is activated by the addition of ZnBr₂, which was identified by the following NMR studies. Diethylzinc (Et₂Zn) **2b** was treated with ZnBr₂ (1 equiv.) in a mixture of toluene-*d*₈, THF-*d*₈ and DMF-*d*₇. The signals, assigned to Et₂Zn, com-

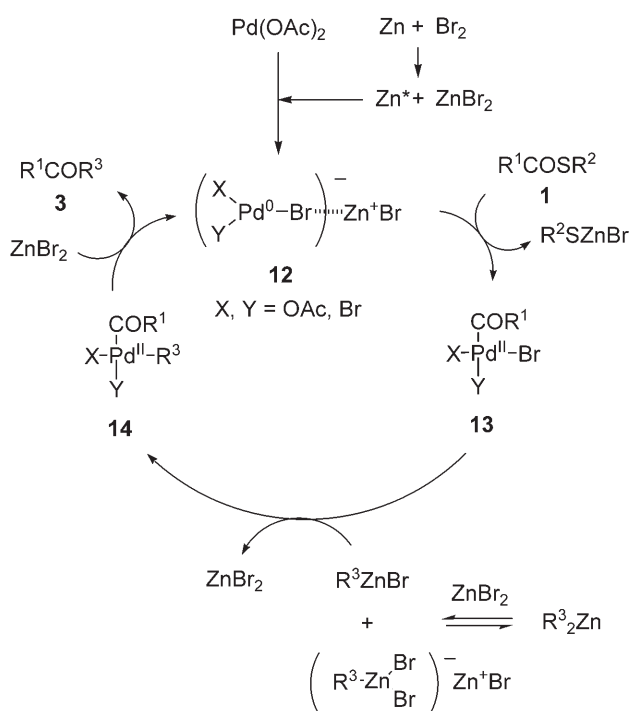
pletely disappeared, and a mixture of reactive species, EtZnBr and hypervalent (EtZnBr₂)[−]·Zn⁺Br **10** (EtZnBr/**10** = 2:1), was formed in nearly quantitative yield, as determined by ¹H NMR analysis.^[14] Facile transmetalation of **9** with EtZnBr or **10** with liberation of ZnBr₂ of good leaving group ability should afford **11**. Once the *cis*-complex **11** is formed, upon reductive elimination, it would provide **3** and regenerate trisubstituted Pd(0) complex **8** to complete the catalytic cycle.

Synthesis of (+)-Biotin Intermediate **5** by means of the Pd(OAc)₂-Catalyzed Fukuyama Coupling Reaction

One of the significant advantages to employ *heterogeneous* Pd/C as the catalyst is to help Pd highly disperse on the solid support to allow the formation of



Scheme 2. A possible mechanism for the Pd/C-catalyzed Fukuyama coupling.



Scheme 3. A possible mechanism for the Pd(OAc)₂-catalyzed Fukuyama coupling.

active monomeric Pd species like **8** in Scheme 2 without aggregating to inactive Pd black. A similar efficient reaction may thus be attained as well in the *homogeneous* system, given a catalytic system which allows the formation of the active monomeric Pd species to be achieved. We envisioned that addition of Zn and ZnBr₂ to the reaction mixture under diluted conditions, i.e., with low catalyst loading, would ensure the formation of the monomeric Pd species.

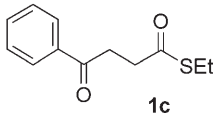
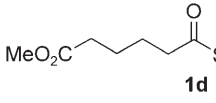
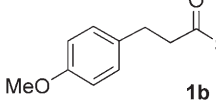
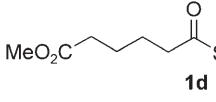
Zn (2.7 equivs.) was thus first treated with Br₂ (0.7 equivs.) followed by addition of iodide **4** provided a suspension involving zinc reagent **2a**, activated Zn and ZnBr₂. Pd(OAc)₂ (1.2 mol %), thiolactone **1a** and DMF were then successively added, and the mixture was stirred at 30–35 °C for 20 h. As expected, the reaction smoothly proceeded to afford, after treatment with aqueous HCl, the desired coupling product **5** in 98 % yield (TON = 82, Table 4, entry 1). The use of palladium(II) chloride (PdCl₂) in place of Pd(OAc)₂ resulted in a poor yield (11 % yield, Table 4, entry 2). Either addition of triphenylphosphine (PPh₃) (4.8 mol %) or employment of the phosphine-containing Pd catalyst, dichlorobis(triphenylphosphine)palladium(II) [PdCl₂(PPh₃)₂], was detrimental to the reaction, providing **5** in 9 % and 36 % yield, respectively (Table 4, entries 3 and 4). The trend is very different from other types of coupling reactions in terms of requirement for the phosphine ligands.^[15] Reduction of the catalyst loading from 1.2 mol % to 0.1 mol % and 0.01 mol % provided **5** in 90 % and 68 % yield, respectively, with turnover numbers (TON) of 900 and 6800 (Table 4, entries 5 and 6).

Synthesis of Multifunctional Ketones and Related Compounds by means of the Pd(OAc)₂-Catalyzed Fukuyama Coupling Reaction

The Pd(OAc)₂-catalyzed reaction was applied to the synthesis using Et₂Zn. In the reaction of thiolactone **1a** with Et₂Zn, the desired coupling product **6** was obtained in a moderate yield (52 %, Table 5, entry 1). A similar outcome was obtained by the use of pre-formed and commercially available ZnBr₂ (Table 5, entry 2). The yield dramatically dropped down in the absence of Zn and ZnBr₂ (Table 5, entry 3). Lowering the catalyst loading at elevated temperature resulted in improvement of the yield as well as reduction of the reaction period (Table 5, entry 4). Use of *N,N*-dimethylacetamide (DMA) in place of DMF gave somewhat an inferior yield (Table 5, entry 5).

The reaction was further applied to the synthesis using various thiol esters as shown in Table 6. The use of substrates **1** with a ketone and an ester functionality is compatible with the reaction to provide the corresponding ketones **3** in good yields.

Table 6. Synthesis of multifunctional ketones **3** through the Pd(OAc)₂-catalyzed Fukuyama coupling reaction of thiol esters **1** with zinc reagents **2** using Pd(OAc)₂ as the catalyst.

$\text{R}^1\text{C}(=\text{O})\text{SR}^2$ 1b – d zinc reagent 2a, b (2 equivs.) $\text{Pd}(\text{OAc})_2, \text{Zn}, \text{Br}_2$ THF, toluene, DMF $\xrightarrow{\hspace{1cm}}$ $\text{R}^1\text{C}(=\text{O})\text{R}^3$ 3b, d, i, j							
Entry	Thiol ester 1b–d	Zinc reagent (equivs.)	$\text{Pd}(\text{OAc})_2$ [mol %] ^[a]	Conditions	Ketone 3b, 3d, 3i, 3j	Yield ^[b] [%]	TON
1 ^[c]	 1c	2a (2.0)	0.2	25 °C, 24 h	3i	71	355
2 ^[c]	 1d	2a (2.0)	0.2	25 °C, 20 h	3j	77	385
3 ^[d]	 1b	2b (1.0)	0.1	40 °C, 66 h	3b	85	850
4 ^[c]	 1d	2b (1.0)	0.1	30 °C, 22 h	3d	72	720

^[a] Mol % relative to thiol ester **1**.^[b] Isolated yield.^[c] DMF (6 equivs. relative to thiol ester **1**) was added.^[d] DMF (1.1 equivs. relative to thiol ester **1**) was added.**Table 7.** Properties of the Pd/C catalysts.

Catalyst ^[a]	Pd distribution	Impregnation depth [nm]	Reduction degree [%] ^[b]	Dispersion of Pd [%] ^[c]	Water content [wt. %] ^[c]
Pd/C D1	thickshell	200–500	0–25	35	1–1.5
Pd/C D2	uniform	– ^[d]	0–25	36	1–1.5
Pd/C D3	eggshell	50–150	0–25	28	3.2
Pd/C D4 ^[e]	uniform	– ^[d]	25–99	36	1.8

^[a] Purchased from Degussa Japan Co., Ltd. Catalysts Division except Pd/C D4.^[8]^[b] Detected by temperature programmed reduction (TPR) measurement.^[c] Pd dispersion is calculated with CO chemisorption.^[d] Not determined.^[e] Purchased from Kawaken Fine Chemicals.

Reaction Mechanism of the Pd(OAc)₂-Catalyzed Fukuyama Coupling Reaction

A possible reaction pathway of the present reaction is outlined in Scheme 3. Similar to the mechanism using Pd/C as the catalyst (Scheme 2), trisubstituted Pd(0) complex **12** might be formed on reaction of Pd(OAc)₂ with Zn and ZnBr₂. Retardation of the reaction by the addition of PPh₃ was observed (Table 4, entries 3

and 4). Rapid ligand exchange of acetoxo group of Pd(OAc)₂ with PPh₃ results in the formation of Pd(II) species, Pd(OAc)_x(PPh₃)_y, which are less susceptible to reduction with Zn. The unexpected rate acceleration by lowering the catalyst loading (Table 5, entries 1 and 4) might be due to the facile formation of the monomeric active Pd species like **12**, **13** and **14** without aggregating to inactive Pd black.

Conclusions

As described above, we have managed to come up with an efficient synthetic method to effectively and inexpensively produce multifunctional ketones through the Fukuyama coupling reaction.

The use of heterogeneous Pd/C not only eases the recovery of Pd but also eliminates the metal contamination to the product. It decisively underscores the value of Pd/C. Although, from the experiments on Pd leaching from Pd/C, the Pd/C-catalyzed Fukuyama coupling reactions were deduced to take place heterogeneously and/or homogeneously, the critical role of the activated carbon in Pd/C is, in part, to help highly disperse Pd on the solid support to form the active Pd complex without aggregating to inactive Pd black. A diffusion issue, i.e., access of the substrate to the Pd surface located in the charcoal matrix will arise, depending on the size of the substrate.^[9,10] When a molecule of relatively larger size is employed as the substrate, Pd/C whose Pd locates closer to the surface should perform better: eggshell > thickshell > uniform. The selection of the Pd/C thus partly depends on the nature of the substrate. In the case of the Fukuyama coupling of thiolactone **1a** with zinc reagent **2a**, thick-shell or uniform Pd/C, D1 or D2, are specifically preferred to eggshell Pd/C D3. The substrates are likely to be small enough to permit their ready access to Pd surfaces located deep in the catalyst.

To account for the exquisite dependency of the reaction on the properties of Pd/C in combination with the extent of the Pd leaching from Pd/C to the solution, the Pd/C-catalyzed Fukuyama coupling reaction may take place in a dual manner, i.e., both heterogeneously and homogeneously, although some extent of Pd leaching was observed during the reaction.

The homogeneous catalytic system using Pd(OAc)₂ as the catalyst, when combined with the addition of Zn and ZnBr₂, offers an efficient alternative to the heterogeneous system. Due to the nature of the reaction that enables more direct interaction with substrates, the catalyst loading that the homogeneous reaction requires is generally much smaller than those for Pd/C. Zn and ZnBr₂ working alone or together for generating the properly activated/inactivated Pd species which eliminates aggregation to inactive Pd black.

Because the reaction of **1a** with **2a** is located at the late stage of the synthesis of (+)-biotin, avoidance of metal contamination is a big challenge for obtaining the final compound of sufficient quality. As the cost of expensive Pd should be reduced to enable a more efficient and thus a more profitable production of (+)-biotin, a complete recovery of Pd is significant as well. The heterogeneous Pd/C process meets these requirements and has thus undoubtedly confirmed that

it can be a practical large-scale production method for (+)-biotin.

The practical approach to multifunctional ketones through the Fukuyama coupling reaction using either Pd/C or Pd(OAc)₂ as the catalyst would ease access to the important class of compounds from readily available thiol esters. The consideration of the reaction mechanism in combined with the optimization of the reaction conditions have made us aware of the significance of designing a proper catalytic system that allows robust formation of Pd species of good catalytic performance. The present example using Pd/C or Pd(OAc)₂ as the catalyst would offer one general solution to address these challenges.

Experimental Section

General

Melting points are uncorrected. ¹H and ¹³C NMR spectra (400 and 100 MHz, respectively) were recorded with tetramethylsilane used as an internal standard. Silica gel column chromatography was performed using Kieselgel 60 (E. Merck). Thin layer chromatography (TLC) was carried out on E. Merck 0.25 mm pre-coated glass-backed plates (60 F₂₅₄). Development was accomplished using 5% phosphomolybdic acid in ethanol/heat or visualized by UV light where feasible. All solvents and reagents were used as received. Zinc dust was purchased from Merck (GR for analysis, particle size <45 μm, Merck 108789). Pd/C D1, D2 and D3 were purchased from Degussa Japan Co., Ltd., while Pd/C D4 was from Kawaken Fine Chemicals. They have the chemical properties listed in Table 7.

Ethyl (3*aS*,4*Z*,6*aR*)-5-[1,3-Dibenzyl-2,3,3*a*,4,6,6*a*-hexahydro-2-oxo-1*H*-thienol[3,4-*d*]imidazol-5-ylidene]-pentanoate (**5**); Use of Pd/C D2 (Table 1, entry 6)

To a suspension of zinc dust (9.3 g, 0.14 mol) in THF (18 mL) and toluene (12 mL) was added bromine (5.8 g, 36 mmol) at 10–40 °C for 15 min and the mixture was heated up to 50 °C. To the mixture was then added dropwise ethyl 5-iodopentanoate **4** (18.6 g, 72.8 mmol) at 50–60 °C over 1 h. After stirring the mixture for 1 h, the mixture was cooled down to 30 °C. To the resulting mixture were added **1a** (17.6 g, 52 mmol), toluene (36 mL), DMF (4.4 mL) and 10% Pd/C D2 (0.5 g, 0.45 mmol) and the mixture was stirred at 28–40 °C for 5 h. The mixture was treated with 18% HCl (34 mL) at 10–30 °C. After stirring the mixture at 20 °C for 1 h, the mixture was filtered. The organic phase of the filtrate was washed successively with water, sat. aq. sodium sulfite and water, dried over MgSO₄ and evaporated to give **5** as a viscous oil; yield: 22 g (94%); [α]_D²⁵: +190.9 (*c* 0.95 in MeOH); ¹H NMR (400 MHz, CDCl₃): δ = 7.08–6.95 (m, 10H), 5.13 (dd, *J* = 8.0 Hz, 1H), 4.59 (m, 2H), 3.99–3.72 (m, 6H), 2.71–2.62 (m, 2H), 1.99–1.95 (m, 2H), 1.88–1.72 (m, 2H), 1.45–1.35 (m, 2H), 0.96 (dd, *J* = 8.0 Hz, 3H); ¹³C NMR (400 MHz, CDCl₃): δ = 173.3, 159.0, 137.9, 137.1 (4s), 129.0–127.3, 125.7, 64.6, 59.0 (13d), 60.3, 46.5, 44.9, 37.1, 33.6, 31.1, 24.2 (7t), 14.3 (1q); IR (KBr): ν_{max} = 2932, 1691 cm^{−1}; HR-

MS m/z $[M-H]^-$: calcd. for $C_{26}H_{30}N_2O_3S$: 450.1977, found: 450.1966.

Use of $Pd(OAc)_2$ (Table 4, entry 5)

To a suspension of zinc dust (3.57 g, 54.6 mmol) in a mixed solvent of THF (7.0 mL) and toluene (4.7 mL) was added bromine (0.72 mL, 14.0 mmol) below 40 °C for 5 min. After the mixture was stirred at 25 °C for 30 min, it was warmed up to 50 °C, and ethyl 5-iodopentanoate **4** (7.16 g, 28.0 mmol) was added at 50–55 °C for 30 min. The mixture was stirred at the same temperature for 1 h and cooled down to 30 °C. To the mixture were added thiolactone **1a** (6.77 g, 20.0 mmol), toluene (9.3 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and DMF (1.7 mL, 22.0 mmol), and the mixture was stirred at 30–35 °C for 20 h. The mixture was cooled down to 5 °C, and 3N HCl (21 mL) was added to the mixture below 20 °C. The mixture was stirred at 25 °C for 30 min and was filtered. To the filtrate was added AcOEt (30 mL), and the organic layer was warmed up to 45 °C and evaporated. A part of the residue was analyzed by HPLC (L-Column, MeCN/THF/0.03 M phosphate buffer ($K_2HPO_4/KH_2PO_4=1:1$)=40:8:52, 40 °C, 1 mL min⁻¹, 254 nm). The assay yield of **5** was determined to be 90 %. The residue was purified by silica gel column chromatography (toluene/AcOEt=15:1) to give **5** as a slightly yellow oil; yield: 7.87 g (87 %). The spectroscopic data of the product were in complete accordance with those described above.

Typical Procedure for the Synthesis of Ketones **3b–g** by the Reaction of Thiol Esters **1b–h** with Et_2Zn in the Presence of Pd/C

1-(4-Methoxyphenyl)-3-oxopentane (3b): Into a suspension of zinc dust (584 mg, 8.93 mmol) in THF (2.5 mL) and toluene (2.5 mL) was added dropwise bromine (0.23 mL, 4.46 mmol) at <30 °C. Thiol ester **1b** (1.00 g, 4.46 mmol) in toluene (1 mL) was then added to the mixture at 20 °C followed by Pd/C D1 (20 wt.%, 123 mg, 0.23 mmol). Into the mixture was added dropwise Et_2Zn (1.1 M toluene solution, Aldrich, 4.05 mL, 4.46 mmol) at under 25 °C followed by DMF (1.7 mL). The mixture was stirred at 20 °C for 17 h. Into the suspension was carefully added 18 % aqueous HCl (10 mL) at <30 °C to dissolve excess zinc dust. The mixture was filtered and the filtrate was separated. The resulting organic phase was washed three times with water, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (hexane to hexane/AcOEt=30/1) to afford ethyl ketone **3b** as a yellow oil; yield: 814 mg (95 %). IR (ATR): $\nu_{max}=1712\text{ cm}^{-1}$; 1H NMR ($CDCl_3$): $\delta=7.10$ (d, $J=8.7$ Hz, 2H), 6.82 (d, $J=8.7$ Hz, 2H), 3.78 (s, 3H), 2.87–2.82 (m, 2H), 2.72–2.67 (m, 2H), 2.39 (q, $J=7.3$ Hz, 2H), 1.04 (t, $J=7.3$ Hz, 3H); EI-MS: $m/z=192$ (M^+); APCI $m/z=193$ ($M+1$).

1,4-Dioxo-1-phenylhexane (3c):^[16] Yield: 95 %; IR (ATR): $\nu_{max}=1713, 1683\text{ cm}^{-1}$; 1H NMR ($CDCl_3$): $\delta=8.00$ –7.97 (m, 2H), 7.59–7.54 (m, 1H), 7.49–7.43 (m, 2H), 3.32–3.27 (m, 2H), 2.89–2.84 (m, 2H), 2.57 (q, $J=7.3$ Hz, 2H), 1.10 (t, $J=7.3$ Hz, 3H); APCI: $m/z=191$ ($M+1$).

Methyl 6-oxooctanoate (3d):^[17] Yield: quantitative; IR (ATR): $\nu_{max}=1735, 1713\text{ cm}^{-1}$; 1H NMR ($CDCl_3$): $\delta=3.67$

(s, 3H), 2.46–2.40 (m, 2H), 2.43 (q, $J=7.3$ Hz, 2H), 2.35–2.31 (m, 2H), 1.66–1.55 (m, 4H), 1.05 (t, $J=7.3$ Hz, 3H).

Propiophenone (3e):^[18] Yield: 85 %; IR (ATR): $\nu_{max}=1685\text{ cm}^{-1}$; 1H NMR ($CDCl_3$): $\delta=7.99$ –7.95 (m, 2H), 7.58–7.52 (m, 1H), 7.49–7.43 (m, 2H), 3.01 (q, $J=7.2$ Hz, 2H), 1.23 (t, $J=7.2$ Hz, 3H).

1-Oxo-1-(3-chlorophenyl)propane (3f):^[19] Yield: 83 %; IR (ATR): $\nu_{max}=1682\text{ cm}^{-1}$; 1H NMR ($CDCl_3$): $\delta=7.95$ –7.92 (m, 1H), 7.86–7.82 (m, 1H), 7.55–7.50 (m, 1H), 7.40 (t, $J=8.0$ Hz, 1H), 2.98 (q, $J=7.2$ Hz, 2H), 1.23 (t, $J=7.2$ Hz, 3H).

1-Oxo-1-(3-thienyl)propane (3g):^[20] Yield: 57 %; IR (ATR): $\nu_{max}=1670\text{ cm}^{-1}$; 1H NMR ($CDCl_3$): $\delta=8.04$ (dd, $J=2.9, 1.3$ Hz, 1H), 7.55 (dd, $J=5.1, 1.3$ Hz, 1H), 7.31 (dd, $J=5.1, 2.9$ Hz, 1H), 2.92 (q, $J=7.3$ Hz, 2H), 1.21 (t, $J=7.3$ Hz, 3H).

(3aS,4Z,6aR)-2-[1,3-Dibenzyl-2,3,3a,4,6,6a-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-ylidene]-ethane (6): Mp 89–91 °C; $[\alpha]_D^{25}+255.1$ (c, 0.5, MeOH); IR (ATR): $\nu_{max}=1687, 1650\text{ cm}^{-1}$; 1H NMR ($CDCl_3$): $\delta=7.38$ –7.24 (m, 10H), 5.52 (q, $J=6.7$ Hz, 1H), 4.97 (d, $J=16$ Hz, 1H), 4.82 (d, $J=15$ Hz, 1H), 4.27 (d, $J=7.7$ Hz, 1H), 4.21 (d, $J=15$ Hz, 1H), 4.11–4.06 (m, 1H), 4.03 (d, $J=16$ Hz, 1H), 3.02–2.92 (m, 2H), 1.71 (d, $J=6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta=158.9, 137.7, 137.2, 137.1$ (4 s), 128.6, 128.5, 128.0, 127.9, 127.5, 127.2, 121.3, 64.4, 59.1 (9d), 46.4, 44.7, 36.9 (3t), 16.8 (q); SIMS: $m/z=351$ ($M+1$); anal. calcd for $C_{21}H_{22}N_2OS$: C 71.97, H 6.33, N 7.99; found: C 71.87, H 6.35, N 8.03.

Assessment of Behavior of Pd in the Fukuyama Coupling of Thiolactone **1a** with Et_2Zn **2b** (Figure 2)

Into a suspension of zinc dust (584 mg, 8.93 mmol) in THF (8.0 mL) and toluene (8.0 mL) was added dropwise bromine (0.229 mL, 4.46 mmol) at <32 °C. Thiolactone **1a** (1.51 g, 4.46 mmol) was then added to the mixture at 20 °C followed by Pd/C D1 (5 wt.%, 475 mg, 0.223 mmol) and toluene (3.2 mL). Into the mixture was added dropwise Et_2Zn **2b** (1.0 M hexane solution, 4.46 mL, 4.46 mmol) at <32 °C followed by DMF (1.7 mL). The mixture was warmed up to 35–40 °C. A sample (4 mL) was periodically taken from the reaction mixture by syringe with a thick needle under stirring. A part of the sample was transferred to the flask. To the flask was added 3N HCl and the mixture was stirred at 55 °C until the alcohol formed was completely dehydrated into the corresponding olefin. To the flask was added ethyl acetate and the organic layer was analyzed by HPLC to determine the conversion (L-Column, MeCN/THF/0.03 M phosphate buffer ($K_2HPO_4/KH_2PO_4=1:1$)=40:8:52, 40 °C, 1 mL min⁻¹, 254 nm). The remaining sample was transferred to a test tube. Allowing the tarry material to settle down to the bottom of the test tube, supernatant was taken by syringe and filtered by PTFE membrane filter (0.45 μ m). Amount of Pd in the filtrate was estimated by X-ray fluorescent analysis.

Characterization of Zinc Species using 1H NMR

Et_2Zn (1.1 M toluene solution, Aldrich) was added to a mixture of toluene- d_8 , THF- d_8 and DMF- d_7 (1.4:1:0.7) (v/v/v) and 1H NMR of the mixture was measured ($\delta=0.33$ ppm, $EtZnCH_2CH_3$). To a suspension of Zn dust in a mixture of toluene- d_8 , THF- d_8 and DMF- d_7 (1.4:1:0.7) (v/v/v) was added Br_2 followed by Et_2Zn (1.1 M toluene solution, Al-

drich) and the mixture was filtered and ^1H NMR of the filtrate was measured. The signals assigned to Et_2Zn disappeared and new sets of signals corresponding to $\text{CH}_3\text{CH}_2\text{ZnBr}$ ($\delta=0.51$ ppm) and $(\text{CH}_3\text{CH}_2\text{ZnBr}_2)\cdot\text{Zn}^+\text{Br}$ ($\delta=0.41$ ppm) appeared with a strength of $\text{EtZnBr}/(\text{EtZnBr}_2)\cdot\text{Zn}^+\text{Br}=2:1$. For assignment of ^1H NMR of the zinc reagents, see ref.^[14]

Typical Procedure for the Synthesis of Ketones **3i, j** by the Reaction of Thiol Esters **1c, d** with Zinc Reagent **2a** in the Presence of $\text{Pd}(\text{OAc})_2$

Ethyl 6,9-dioxo-9-phenylnonanoate (3i): To a suspension of zinc dust (2.35 g, 36.0 mmol) in THF (3.9 mL) and toluene (2.6 mL) was added bromine (0.77 mL, 15.0 mmol) below 43°C for 6 min. After the mixture was stirred at 25°C for 30 min, it was warmed up to 50°C , and ethyl 5-iodopentanoate (5.12 g, 20.0 mmol) was added at 50 – 55°C for 30 min. After the mixture was stirred at the same temperature for 30 min, it was cooled down to 30°C . To the mixture were added thiol ester **1c** (2.22 g, 10.0 mmol), toluene (5.3 mL), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 0.02 mmol), DMF (4.6 mL, 60.0 mmol), and the mixture was stirred at 25°C for 24 h. The mixture was cooled down to 10°C , and 3N HCl (5 mL) was added to the mixture below 20°C . The mixture was stirred at 25°C for 30 min and it was filtered. The filtrate was partitioned by adding AcOEt (30 mL) and the aqueous layer was separated. The aqueous layer was extracted with AcOEt (10 mL). The organic layers were combined, washed with water, dried over anhydrous MgSO_4 and evaporated. The residue was purified by silica gel chromatography (hexane/AcOEt = 5:1) to give **3i** as a yellow oil; yield: 2.06 g (71 %). IR (KBr) $\nu_{\text{max}} = 1729, 1717, 1684\text{ cm}^{-1}$; ^1H NMR (CDCl_3): $\delta = 7.99$ – 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); HR-MS: m/z ($\text{M} + \text{H}^+$): calcd. for $\text{C}_{17}\text{H}_{23}\text{O}_4$, 291.1596; found: 291.1603.

Ethyl 10-methoxycarbonyl-6-oxodecanoate (3j): Yield 77 %; IR (KBr): $\nu_{\text{max}} = 1731, 1713\text{ cm}^{-1}$; ^1H NMR (CDCl_3): $\delta = 4.12$ (q, $J = 7.1$ Hz, 2H), 3.67 (s, 3H), 2.44–2.40 (m, 4H), 2.34–2.29 (m, 4H), 1.66–1.54 (m, 8H), 1.25 (t, $J = 7.1$ Hz, 3H); HR-MS: m/z ($\text{M} + \text{H}^+$): calcd. for $\text{C}_{14}\text{H}_{25}\text{O}_5$, 273.1702; found: 273.1717.

Typical Procedure for the Synthesis of Ketones **3b, d** by the Reaction of Thiol Esters **1b, d** with Et_2Zn **2b** in the Presence of $\text{Pd}(\text{OAc})_2$

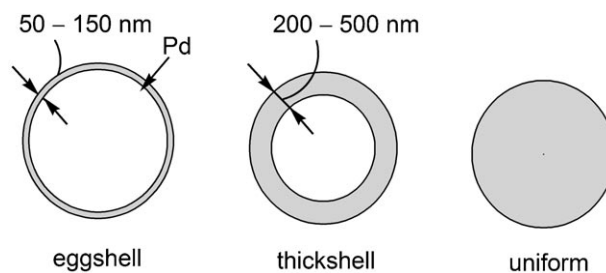
1-(4-Methoxyphenyl)-3-oxopentane (3b): To a suspension of zinc dust (0.65 g, 10 mmol) in THF (1.8 mL) and toluene (1.2 mL) was added bromine (0.26 mL, 5.0 mmol) below 42°C for 3 min. After the mixture had been stirred at 25°C for 15 min, 1.0M Et_2Zn (toluene solution, 5.0 mL, 5.0 mmol) was added to the mixture below 35°C . The mixture was stirred for 5 min, and to the mixture were added thiol ester **1b** (1.12 g, 5.0 mmol), toluene (2.4 mL), $\text{Pd}(\text{OAc})_2$ (1.1 mg, 0.005 mmol), DMF (0.4 mL, 5.4 mmol). The mixture was warmed up to 40°C and stirred at the same temperature for 66 h. The mixture was cooled down to 10°C , and 3N HCl (5 mL) was added to the mixture below 20°C . The mixture was stirred at 25°C for 30 min and filtered. The filtrate was

partitioned by adding AcOEt (20 mL). The organic layer was washed with water, dried over anhydrous MgSO_4 and evaporated. The residue was purified by silica gel chromatography (hexane/AcOEt = 4:1) to give **3b** as a yellow oil; yield: 1.63 g (85 %).

Methyl 6-oxooctanoate (3d): Yield 72 %; IR, NMR and MS data are completely identical with those obtained by the method described above.

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