Advanced Synthesis & Catalysis

## Accepted Article

**Title:** A Palladium NNC-Pincer Complex as an Extremely Efficient Catalyst Precursor for the Mizoroki–Heck Reaction

**Authors:** Go Hamasaka, Shun Ichii, and Yasuhiro Uozumi



**To be cited as:** *Adv. Synth. Catal.* 10.1002/adsc.201800099

**Link to VoR:** http://dx.doi.org/10.1002/adsc.201800099

10.1002/adsc.201800099

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

# A Palladium NNC-Pincer Complex as an Efficient Catalyst Precursor for the Mizoroki–Heck Reaction

Go Hamasaka,[a,b] Shun Ichii,[a,b] and Yasuhiro Uozumi[a,b,c,d,*]

[a] Institute for Molecular Science (IMS), Myodaiji, Okazaki 444-8787, Japan
FAX: +81-564-59-5574; Phone: +81-564-59-5571; E-mail: uo@ims.ac.jp
[b] SOKENDAI (The Graduate University for Advanced Studies), Myodaiji, Okazaki 444-8787, Japan
[c] Green Nanocatalysis Research Team, RIKEN Center for Sustainable Resource Sciences, Hirosawa, Wako 351-0198, Japan
[d] JST-ACCEL, Myodaiji, Okazaki 444-8787, Japan

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

**Abstract.** The Mizoroki–Heck reaction of aryl halides (iodides, bromides, or chlorides) with activated alkenes in the presence of a palladium NNC-pincer complex at ppb to ppm loadings gave the corresponding internal alkenes in excellent yields. The total turnover number and turnover frequency reached up to $8.70 \times 10^8$ and $1.21 \times 10^7$ $h^{-1}$ ($3.36 \times 10^3$ $s^{-1}$), respectively. The catalyst was applied in a ten-gram-scale synthesis of the UV-B sunscreen agent octinoxate (2-ethylhexyl 4-methoxycinnamate). Reaction-rate analyses, transmission electron microscopic examination of the reaction mixture, and poisoning tests suggested that a monomeric palladium species is the catalytically active species in the catalytic cycle.

**Keywords:** Mizoroki-Heck reaction; palladium catalysis; pincer complex; aryl halides; alkenes

## Introduction

Palladium-catalyzed carbon–carbon bond-forming reactions are important and are widely used in syntheses of pharmaceuticals, agrochemicals, and organic materials on both laboratory and industrial scales.[1] In particular, Mizoroki–Heck,[2] Suzuki–Miyaura,[3] Negishi,[4] Migita–Kosugi–Stille,[5] Hiyama,[6] and Sonogashira[7] reactions are recognized as indispensable reactions in organic chemistry.[8] However, a percent (parts-per-hundred)-level loading of a palladium catalyst is usually required in these reactions to obtain the desired products in reasonable yields within acceptable reaction times. When these reactions are used in preparations of valuable products such as pharmaceuticals, agrochemicals, or organic materials, toxic palladium metal contaminants have to be removed from the final products; for example, the permissible level of Pd contaminants in oral drugs is 10 ppm or less.[9] Consequently, the removal of palladium contamination from commercial products involves considerable effort and cost. In addition, the depletion of palladium resources has been recognized as a problem awaiting a solution. Decreasing the loading of the palladium catalyst is one promising route toward a solution of these difficulties. In this context, the development of highly active catalysts that operate at ppm loadings is highly desirable.[10,11] Palladium pincer complexes are attracting considerable attention from organic chemists because such catalysts display the required high level of activity in a variety of catalytic reactions.[12] In particular, several palladium pincer complexes have been used in the Mizoroki–Heck reaction at ppb to ppm loadings.[13,14] However, the substrate scopes of these catalytic systems are generally too narrow.

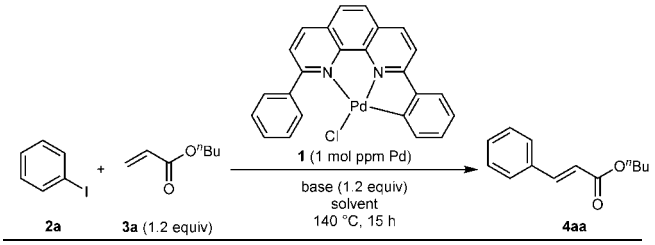
We recently reported that at loadings of 1 mol ppb to 1 mol ppm of the palladium NNC-pincer complex **1**[15] catalyzed the allylic arylation of allyl acetates with sodium tetraarylborates to give the corresponding products in high yields.[16] Inspired by these results, we conjectured that the palladium NNC-pincer complex **1** might also show a high catalytic activity in the Mizoroki–Heck reaction. Here we report successful Mizoriki–Heck reactions in the presence of ppb-to-ppm loadings of complex **1**. The reactions of a wide variety of aryl iodides or bromides with terminal alkenes proceeded smoothly with quite low loadings (1 mol ppb to 10 mol ppm) of complex **1**. The reaction of an activated aryl chloride also proceeded in the presence of complex **1** at a 100 mol ppm loading. To demonstrate the utility of this catalytic system, we conducted a ten-gram-scale synthesis of the UV-B sunscreen agent octinoxate (2-ethylhexyl 4-methoxycinnamate) in the presence of 1 mol ppm of complex **1**. Several experiments were

performed to identify the catalytically active species. Reaction-rate analyses, transmission electron microscopic analysis of the reaction mixture, and poisoning tests (mercury-amalgamation and Crabtree tests) showed that a ligandless monomeric palladium species is the catalytically active species in this reaction system.

## Results and Discussion

First, we screened the reaction conditions for the reaction of iodobenzene (**2a**) with butyl acrylate (**3a**) in the presence of a 1 mol ppm loading of complex **1** at 140 °C (Table 1). When we tested various bases in *N*-methylpyrrolidin-2-one (NMP), no reaction took place in the presence of potassium carbonate or sodium bicarbonate (Table 1, entries 1 and 2). When sodium acetate or potassium phosphate was used as the base, moderate yields of butyl cinnamate [**4aa**; butyl (2*E*)-3-phenylacrylate] were obtained (entries 3 and 4). The reaction in the presence of *N*,*N*-diisopropylethylamine gave cinnamate **4aa** in 23% yield (entry 5). A quantitative yield of **4aa** was obtained in the presence of tributylamine as the base (entry 6). We also screened various solvents [*N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), hexan-1-ol, *m*-xylene, benzonitrile, and diethylene glycol diethyl ether] (entries 7–12), and we found that NMP was the optimal solvent for this reaction.

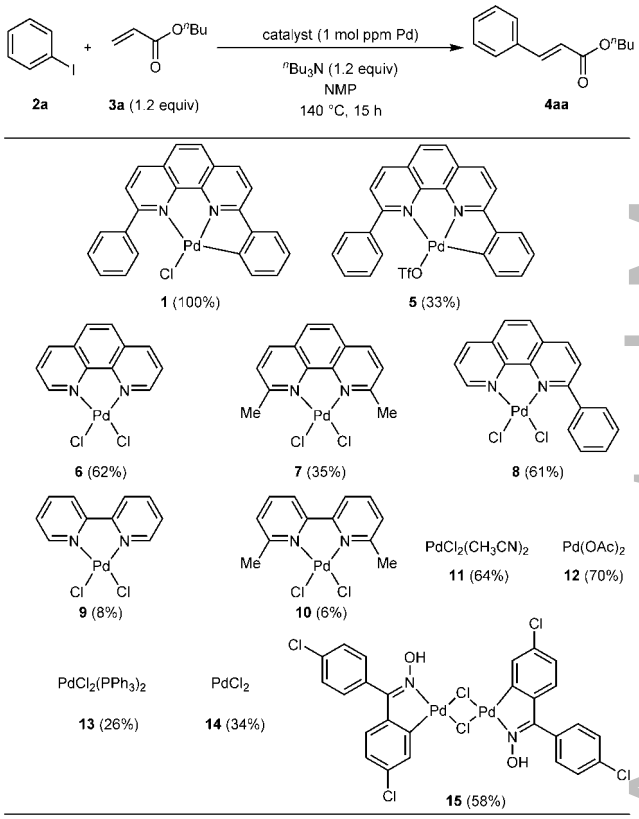
**Table 1.** Screening of Bases and Solvents in the Mizoroki–Heck Reaction of Iodobenzene (**2a**) with Butyl Acrylate (**3a**) in the Presence of 1 mol ppm Complex **1**[a]




| Entry | Base | Solvent | Yield, %[b] |
|---|---|---|---|
| 1 | $K_2CO_3$ | NMP | 0 |
| 2 | $NaHCO_3$ | NMP | 0 |
| 3 | NaOAc | NMP | 45 |
| 4 | $K_3PO_4$ | NMP | 52 |
| 5 | $^{i}Pr_2NEt$ | NMP | 23 |
| 6 | $^{n}Bu_3N$ | NMP | 100 (99)[c] |
| 7 | $^{n}Bu_3N$ | DMF | 24 |
| 8 | $^{n}Bu_3N$ | DMA | 28 |
| 9 | $^{n}Bu_3N$ | Hexan-1-ol | 24 |
| 10 | $^{n}Bu_3N$ | *m*-xylene | 4 |
| 11 | $^{n}Bu_3N$ | PhCN | 58 |
| 12 | $^{n}Bu_3N$ | $EtO[(CH_2)_2O]_2Et$ | 16 |

[a] *Reaction conditions*: **1** (1 mol ppm, $1.0 \times 10^{-6}$ mmol), **2a** (1.0 mmol), **3a** (1.2 mmol), base (1.2 mmol), solvent (1.0 mL), 140 °C, 15 h. [b] Determined by GC analysis with an internal standard (mesitylene). [c] Isolated yield.

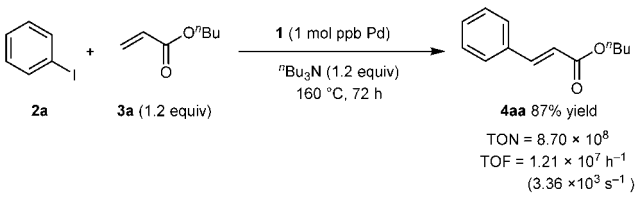
We also examined the catalytic activity of various other palladium catalysts in this reaction (Scheme 1). The cationic palladium NNC-pincer complex **5** showed a lower catalytic activity than complex **1**. Nonsubstituted, dimethyl, or monophenyl 1,10-phenanthroline palladium complexes **6**–**8** gave cinnamate **4aa** in 35–62% yield. A low yield (<10%) of **4aa** was obtained when the bipyridine-based complexes **9** and **10** were used as catalysts. The 1,10-phenanthroline framework is therefore effective in this reaction. The reaction with bis(acetonitrile)palladium dichloride (**11**) or palladium(II) acetate (**12**) afforded **4aa** in 64 and 70% yield, respectively. The catalytic activities of bis(triphenylphosphine)palladium(II) chloride (**13**) and palladium(II) chloride (**14**) were lower than those of **11** and **12**. Phosphine ligand did not enhance the catalytic activity. We also examined the reaction with Nájera's catalyst **15**,[17] which is known to be an effective catalyst for the Mizoroki–Heck reaction, and we obtained **4aa** in 58% yield. During the screening of the catalysts, complex **1** therefore showed the highest catalytic activity.




**Scheme 1.** Screening of Palladium Catalysts in the Mizoroki–Heck Reaction of Iodobenzene (**2a**) with Butyl Acrylate (**3a**). *Reaction conditions*: catalyst (1 mol ppm, $1.0 \times 10^{-6}$ mmol), **2a** (1.0 mmol), **3a** (1.2 mmol), $^{n}Bu_3N$ (1.2 mmol), NMP (1.0 mL), 140 °C, 15 h. The yield was determined by GC analysis with mesitylene as an internal standard.

10.1002/adsc.201800099

To demonstrate that our catalytic system works at a ppb loading, we examined the Mizoroki–Heck reaction of iodobenzene (**2a**) with butyl acrylate (**3a**) in the presence of a 1 mol ppb loading of complex **1** (Scheme 2) under solvent-free conditions at 160 °C for 72 h, and we obtained cinnamate **4aa** in 87% yield. In this case, the total turnover number was 8.70 × $10^8$ and the turnover frequency was 1.21 × $10^7$ $h^{-1}$ (3.36 × $10^3$ $s^{-1}$).




**Scheme 2.** The Mizoroki–Heck Reaction of Iodobenzene (**2a**) with Butyl Acrylate (**3a**) in the Presence of 1 mol ppb of Complex **1**.

We performed several experiments to identify the catalytically active species in our reaction. Initially, we checked the time course of the yield of cinnamate **4aa** in the reaction of iodobenzene (**2a**) with butyl acrylate (**3a**) in the presence of 1 mol ppm of complex **1** [Figure 1 (black line) and Scheme 3(a)]. An induction period was observed in the initial stages of this reaction (up to 1 h), suggesting that the catalytic active species is generated in situ. We next performed a transmission electron microscopy (TEM) analysis of the reaction mixture after the reaction. Palladium nanoparticles were observed in the reaction mixture (Figure 2). The average size of these nanoparticles was estimated to be 2.2 ± 0.7 nm. These experimental results showed that complex **1** is a precursor of the actual catalytically active species in this reaction. To obtain more information on the catalytic active species, we performed a mercury-amalgamation test.[18] Under the standard reaction conditions (Table 1 entry 6), the addition of one drop of mercury to the reaction mixture at two hours, when the GC yield of **4aa** was 15%, significantly retarded the reaction, which finally gave **4aa** in 19% GC yield after an additional eight hours [Figure 1 (blue line) and Scheme 3(b)]. If a ligandless palladium metal species (i.e., a ligandless monomeric palladium species and/or palladium cluster) is generated in situ, the reaction should be inhibited by the amalgamation of this species with Hg. This experimental result indicates that a ligandless palladium species is indeed the catalytically active species in this reaction. Although the TEM observations and the mercury-amalgamation test suggested that the complex **1** is a precursor of the catalytically active species, it was unclear at this stage whether the catalytically active species consists of palladium clusters or monomeric palladium species. We therefore performed a Crabtree test [the addition of dibenzo[*a*,*e*]cyclooctene (DCT)].[19] After starting the reaction under the standard conditions (Table 1 entry 6) for 2 h, when the yield of **4aa** was 13%, we added DCT to the reaction mixture. A suppression of the reaction was then observed (Figure 1, red line), and the desired product **4aa** was obtained in 37% GC yield after an additional 8 h [Scheme 3(c)]. It has been reported that DCT coordinates to monomeric palladium species[20] to give a stable and catalytically inactive DCT–Pd complex [Figure 3(a)], whereas DCT cannot coordinate to palladium clusters because of its structural rigidity [Figure 3(b)]. Consequently, the result of the Crabtree test suggests that a monomeric palladium species is involved in this catalytic cycle. If palladium clusters were essential to promote the catalytic process, the Mizoroki–Heck reaction should proceed efficiently in the presence of DCT. Although palladium nanoparticles were observed by the TEM analysis, the Crabtree test suggested that monomeric palladium species are generated under the reaction conditions. From these experimental results, the catalytic cycle shown in Scheme 4 is proposed. Palladium complex **1** is reduced under the thermal conditions to form the monomeric palladium(0) species **A** and/or palladium(0) clusters **E**. An equilibrium between **A** and **E** should exist under the reaction conditions. The monomeric Pd(0) species **A** promotes the Mizoroki–Heck reaction, and a monomeric palladium(II) species **B** is generated through the reaction of **A** with the haloarene. The usual Mizoroki–Heck process then takes place, giving desired product along with regeneration of **A**. Therefore, complex **1** acts as a good precursor for the catalytically highly active palladium(0) species **A**.

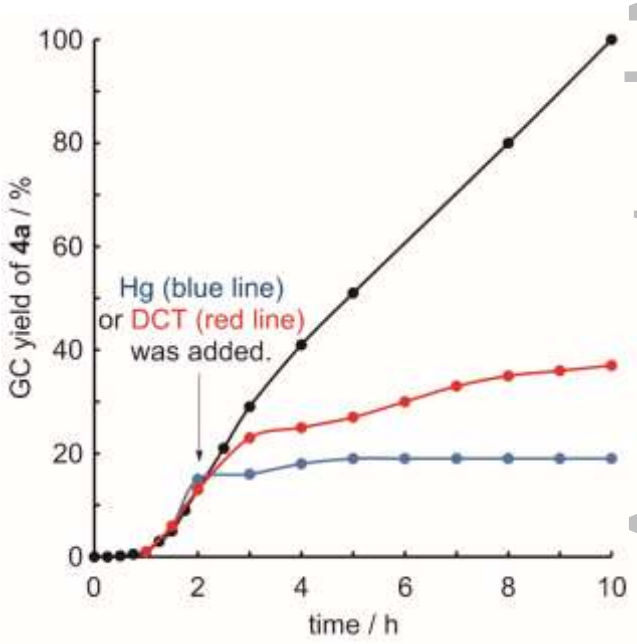
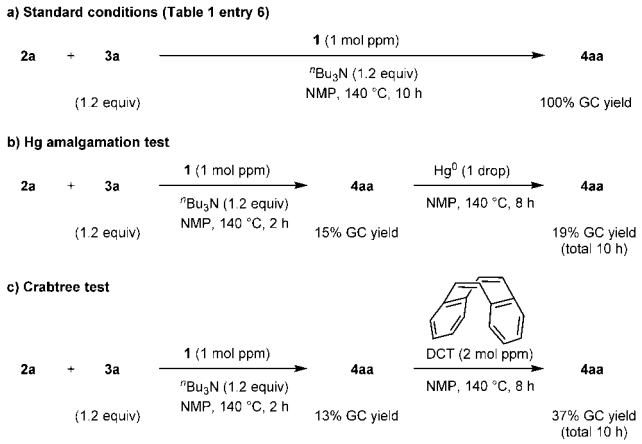



**Figure 1.** Time Course of the Yield of the Reaction of Iodobenzene (**2a**) with Butyl Acrylate (**3a**) in the Presence of 1 mol ppm Complex **1**. Standard Conditions (black line); Mercury-Amalgamation Test (blue line); Crabtree Test (red line).

10.1002/adsc.201800099




**Scheme 3.** (a) Standard Reaction Conditions; (b) Mercury-Amalgamation Test; (c) Crabtree Test.

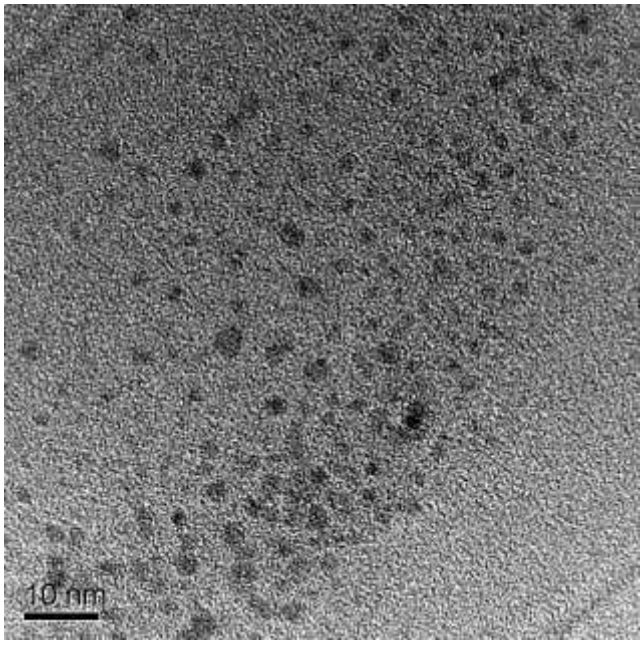



**Figure 2.** TEM Image of the Reaction Mixture (Table 1, entry 6). Average diameter of nanoparticles: 2.2 ± 0.7 nm.

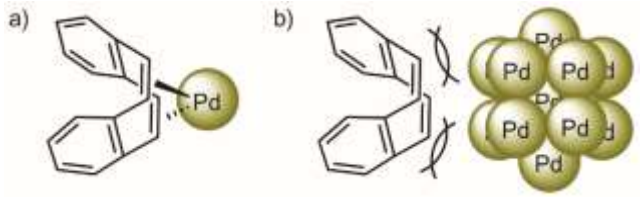
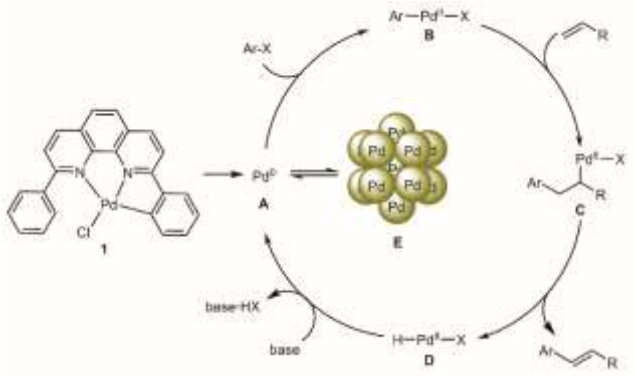



**Figure 3.** Schematic Structures of DCT (a) with Monomeric Pd Species, (b) with Pd Clusters.

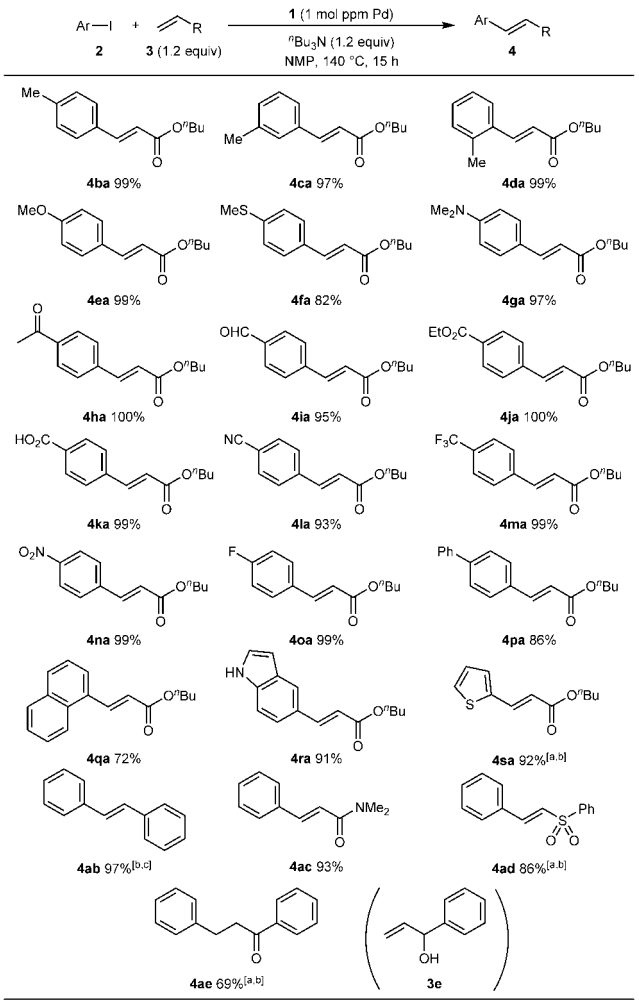



**Scheme 4.** Proposed Catalytic Cycle.

Complex **1** was used in the Mizoroki–Heck reactions of a variety of aryl iodides with alkenes (Scheme 5). The reaction of *p*-, *m*-, and *o*-iodotoluenes (**2b**–**d**) with butyl acrylate (**3a**) in the presence of a 1 mol ppm loading of complex **1** gave the corresponding tolylacrylates **4ba**, **4ca**, and **4da** in high yields. The position of the methyl group on the aromatic ring did not affect the efficiency of the reaction. A variety of iodobenzenes substituted with electron-donating groups (**2e**–**g**) or electron-withdrawing groups (**2h**–**n**) gave the corresponding internal alkenes **4ea**–**na** in high yields. This reaction system tolerated catalyst-poisoning functionalities such as methylsulfanyl (**4fa**) or dimethylamino (**4ga**) groups. The reactions of 1-fluoro-4-iodobenzene (**2o**), 4-iodobiphenyl (**2p**), and 1-iodonaphthalene (**2q**) with acrylate **3a** gave the corresponding alkenes **4oa**, **4pa**, and **4qa** in 99, 86, and 72% yield, respectively. In this catalytic system, iodohetarenes also underwent the reaction. Complex **1** catalyzed the reaction of 5-iodoindole (**2r**) with **3a** to give **4ra** in 91% yield. The reaction of 2-iodothiophene (**2s**), carried out in the presence of 10 mol ppm of complex **1** and NaOAc instead of $Bu_3N$, gave the desired alkene **4sa** in 92% yield.

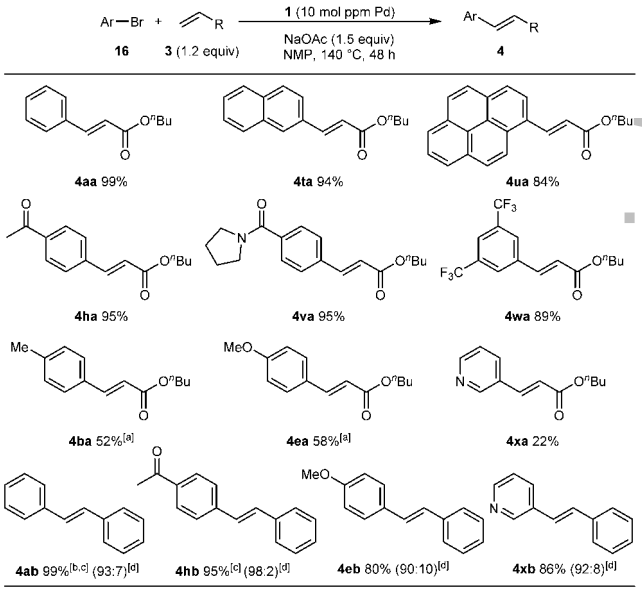
Next, we examined the reaction with other terminal alkenes **3b**–**e**. Styrene (**3b**) and *N*,*N*-dimethylacrylamide (**3c**) gave the desired products **4ab** and **4ac**, respectively, in good yields. The reaction of iodobenzene (**2a**) with phenyl vinyl sulfone (**3d**) or 1-phenylprop-2-en-1-ol (**3e**) also proceeded in the presence of 10 mol ppm of complex **1** to afford **4ad** and **4ae** in 86 and 69% yield, respectively.

10.1002/adsc.201800099



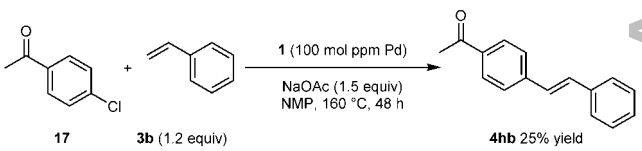

**Scheme 5.** Substrate Scope of the Mizoriki–Heck Reaction of Aryl Iodides **2** with Alkenes **3** in the Presence of Complex **1**. *Reaction conditions*: **1** (1 mol ppm, $1.0 \times 10^{-6}$ mmol), **2** (1.0 mmol), **3** (1.2 mmol), $^{n}Bu_3N$ (1.2 mmol), NMP (1.0 mL), 140 °C, 15 h. The yields refer to isolated products. [a] **1** (10 mol ppm, $1.0 \times 10^{-5}$ mmol). [b] NaOAc (1.5 mmol) was used instead of $^{n}Bu_3N$. [c] Containing 9% of the α-arylated product.

A ppm loading of complex **1** also catalyzed the Mizoroki–Heck reaction of aryl bromides (Scheme 6). The reaction of bromobenzene (**16a**) with butyl acrylate (**3a**) in the presence of a 10 mol ppm loading of complex **1** in NMP at 140 °C for 48 hours gave alkene **4aa** in 99% isolated yield.[21,22] 2-Bromonaphthalene (**16b**) and 1-bromopyrene (**16c**) also underwent the reaction to afford the corresponding alkenes **4ta** and **4ua** in 94 and 84% yield, respectively. The reaction of bromobenzenes **16h**, **16v**, and **16w**, containing electron-withdrawing groups, proceeded smoothly to give the corresponding acrylates **4ha**, **4va**, and **4wa** in good yields. On the other hand, bromobenzenes **16b** and **16e**, containing electron-donating substituents, gave moderate yields of the corresponding products **4ba** and **4ea**. The reaction of 3-bromopyridine (**16x**) with **3a** also failed to proceed efficiently. When styrene (**2b**) was used as the coupling partner, the reaction efficiency increased dramatically. A lower catalyst loading (1 mol ppm) and a shorter reaction time (24 h) could be achieved in the reactions of bromobenzene (**16a**) and 4-bromoacetophenone (**16h**) with styrene (**2b**), giving the stilbenes **4ab** and **4hb** in 99 and 95% yield, respectively. Whereas the reactions of **16e** and **16x** with **3a** did not proceed efficiently, these compounds reacted efficiently with styrene (**2b**) to give **4eb** and **4xb**, respectively, in good yields.




**Scheme 6.** Substrate Scope of the Mizoriki–Heck Reaction of Aryl Bromides **16** with Alkenes **3** in the Presence of Complex **1**. *Reaction conditions*: **1** (10 mol ppm, $1.0 \times 10^{-5}$ mmol), **16** (1.0 mmol), **3** (1.2 mmol), NaOAc (1.5 mmol), NMP (1.0 mL), 140 °C, 48 h. The yields refer to isolated products. [a] 160 °C. [b] **1** (1 mol ppm, $1.0 \times 10^{-6}$ mmol). [c] 24 h. [d] The ratio of regioisomers (β arylation/α arylation) was determined by $^{1}H$ NMR.

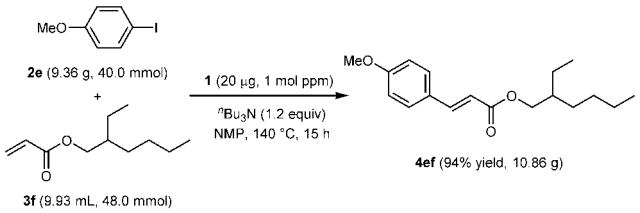
We also applied our catalytic system to the reaction of a less-reactive aryl chloride. Thus, the reaction of 4-chloroacetophenone (**17**) with styrene (**3b**) proceeded in the presence of 100 ppm loading of **1** in NMP at 160 °C for 48 hours to give alkene 4hb in 25% yield (Scheme 7).




**Scheme 7.** The Mizoroki–Heck Reaction of 4-Chloroacetophenone (**17**) with Styrene (**3b**).

To demonstrate the utility of our catalytic system, we used complex **1** in a ten-gram-scale synthesis of the UV-B sunscreen agent octinoxate (**4ef**; 2-

ethylhexyl 4-methoxycinnamate)[23] (Scheme 8). The reaction of 1-iodo-4-methoxybenzene (**2e**; 9.36 g, 40.0 mmol) with acrylate **3f** (9.93 mL, 48.0 mmol) in the presence of 1 mol ppm complex **1** (20 μg) and tributylamine in NMP at 140 °C for 15 h gave 10.86 g (94%) of octinoxate (**4ef**). The resulting product **4ef** was tested for metal contamination by ICP-AES analysis to detect palladium. This result indicated that the content of palladium in the product was below 1 weight ppm (<1 μg Pd/g **4ef**).




**Scheme 8.** Ten-Gram-Scale Synthesis of the UV-B Sunscreen Agent Octinoxate (**4ef**) in the Presence of 1 mol ppm Complex **1**.

## Conclusion

In summary, we have found that complex **1** is a good catalyst precursor for the Mizoroki–Heck reaction. The reaction of aryl halides with activated terminal alkenes in the presence of quite low loadings of complex **1** gave the desired coupling products in excellent yields. In the reaction of iodobenzene with butyl acrylate, the total turnover number and turnover frequency reached $8.70 \times 10^8$ and $1.21 \times 10^7$ $h^{-1}$ ($3.36 \times 10^3$ $s^{-1}$), respectively. Reaction-rate analysis, poisoning tests (mercury-amalgamation and Crabtree tests), and TEM analyses of the reaction mixture suggested that a monomeric Pd(0) species is involved in the catalytic cycle. The catalyst was successfully applied to a ten-gram-scale synthesis of the UV-B sunscreen agent octinoxate. Further catalytic applications of complex **1** are now under investigation in our laboratory.

## Experimental Section

**Typical Procedure for the Mizoroki–Heck Reaction of Aryl Halides with Alkenes (Table 1, entry 6):** A Schlenk tube and a stirrer bar were treated with aqua regia (1:3 concd aq HCl– concd aq $HNO_3$) for 30 min, washed sequentially with pure water and acetone, and dried with heating. The palladium complex **1** (0.47 mg, 0.001 mmol) was dissolved in NMP (10 mL), and the catalyst solution (10 μL, $1 \times 10^{-6}$ mmol) was added to a mixture of PhI (**2a**; 203 mg, 1.0 mmol), butyl acrylate (**3a**; 0.17 mL, 1.2 mmol), and $Bu_3N$ (0.28 mL, 1.2 mmol) in NMP (1.0 mL). The resulting solution was degassed by means of three freeze–pump–thaw cycles, and then stirred vigorously at 140 °C for 15 h under $N_2$. The mixture was then cooled to 25 °C, diluted with *t*-BuOMe (15 mL), transferred to a separatory funnel, and washed with 0.5 M aq HCl (20 mL). The aqueous layer was extracted with *t*-BuOMe (3 × 10 mL), and the extracts were combined, washed with brine (20 mL), and dried over $Na_2SO_4$. The resulting solution was concentrated under reduced pressure to give a crude product that was purified by chromatography [silica gel, hexane–EtOAc (20:1)] to give butyl (2*E*)-3-phenylacrylate (**4aa**) as a colorless oil; yield: 201 mg (0.99 mmol, 99%).

**Butyl (2*E*)-3-Phenylacrylate (4aa)** [CAS: 52392-64-0]: Colorless oil. $^1$H NMR (396 MHz, $CDCl_3$, δ): 7.69 (d, *J* = 16.0 Hz, 1H), 7.55–7.51 (m, 2H), 7.40–7.37 (m, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 4.21 (t, *J* = 6.8 Hz, 2H), 1.73–1.66 (m, 2H), 1.49–1.40 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 167.20, 144.63, 134.52, 130.28, 128.93, 128.12, 118.33, 64.51, 30.83, 19.28, 13.84. EI-MS: *m/z* 204 ($M^+$).

**The Mizoroki–Heck Reaction of Iodobenzene (2a) with Butyl Acrylate (3a) in the Presence of a 1 mol ppb Loading of the Complex 1 (Scheme 2):** A Schlenk tube and a stirrer bar were treated with piranha solution (3:1 concd $H_2SO_4$–30% aq $H_2O_2$) for 30 min, then rinsed with pure water and treated with aqua regia (1:3 concd aq HCl–concd. aq $HNO_3$) for 30 min. The treated Schlenk tube and stirrer bar were rinsed vigorously with pure water to remove acid components then dried with heating. This reaction vessel was charged with dry $Et_2O$ (5 mL), $Et_3N$ (1 mL), and TMSCl (0.5 mL) under $N_2$ to cap any surface silanols on the glassware. After stirring at room temperature for 30 min, the mixture was removed by decantation and the vessel was washed with acetone and pure water, then dried with heating.

The palladium complex **1** (0.47 mg, 0.001 mmol) was dissolved in NMP (10 mL). The catalyst solution (10 μL; $1.0 \times 10^{-6}$ mmol) was further diluted with NMP (10 mL). The resulting solution (10 μL, $1.0 \times 10^{-9}$ mmol) was added to a mixture of PhI (**2a**; 203 mg, 1.0 mmol), butyl acrylate (**3a**; 0.17 mL, 1.2 mmol), and $Bu_3N$ (0.28 mL, 1.2 mmol), and the resulting mixture was degassed by three freeze–pump–thaw cycles. The mixture was then stirred vigorously at 160 °C for 72 h under $N_2$. The mixture was cooled to 25 °C, and purified by direct chromatography [silica gel, hexane–EtOAc (20:1)] to give butyl (2*E*)-3-phenylacrylate (**4aa**); yield: 177 mg (0.87 mmol, 87%).

**Ten-Gram-Scale Synthesis of the UV-B Sunscreen Agent Octinoxate (4ef) (Scheme 8).** A Schlenk tube and a stirrer bar were cleaned with aqua regia (1:3 concd aq HCl–concd aq $HNO_3$) for 30 min, washed with sequentially with pure water and acetone, and dried with heating. The palladium complex **1** (0.47 mg, 0.001 mmol) was dissolved in NMP (10 mL). The catalyst solution (400 μL, 20 μg, $4.0 \times 10^{-5}$ mmol) was added to a mixture of 4-iodoanisole (**2e**; 9.36 g, 40.0 mmol), 2-ethylhexyl acrylate (**3f;** 9.93 mL, 48.0 mmol), and $Bu_3N$ (11.2 mL, 48.0 mmol) in NMP (40 mL). The resulting solution was degassed by three freeze–pump–thaw cycles, and then stirred vigorously at 140 °C for 15 h under $N_2$. The mixture was then cooled to 25 °C, diluted with *t*-BuOMe (40 mL), and washed with 0.5 M aq HCl (60 mL). The aqueous layer was extracted with *t*-BuOMe (3 × 20 mL) and the extracts were combined, washed with brine (50 mL), and dried over $Na_2SO_4$. The resulting solution was concentrated under reduced pressure to give a crude product was that was purified by chromatography [silica gel, hexane–EtOAc (20:1)] to give 2-ethylhexyl (2*E*)-3-(4-methoxyphenyl)acrylate (**4ef**) as a colorless oil; yield: 10.86 g (37.6 mmol, 94%).

**2-Ethylhexyl (2*E*)-3-(4-Methoxyphenyl)acrylate (4ef)** [CAS: 83834-59-7]: Colorless oil. $^1$H NMR (396 MHz, $CDCl_3$, δ): 7.63 (d, *J* = 16.0 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 9.2 Hz, 2H), 6.32 (d, *J* = 16.0 Hz, 1H), 4.12–4.10 (m, 2H), 3.84 (s, 1H), 1.68–1.62 (m, 1H), 1.46–1.24 (m, 9H), 0.94–0.89 (m, 7H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 167.65, 161.37, 144.22, 129.77, 127.28, 115.88, 114.35, 66.88, 55.43, 38.95, 30.54, 29.04, 23.91, 23.08, 14.16, 11.11. EI-MS: *m/z* 290 ($M^+$).

**TEM Analysis:** A sample for TEM analysis was prepared as follows. After the Heck reaction of iodobenzene (**2a**)

with butyl acrylate (**3a**), the reaction mixture was dropped onto a copper grid covered with a carbon membrane. The sample was rinsed with water and ethanol then dried under air. The resulting sample was then examined by TEM.

**Poisoning Tests:** The palladium complex **1** (0.47 mg, 0.001 mmol) was dissolved in NMP (10 mL). The resulting catalyst solution (10 µL, 1 mol ppm Pd) was added to a mixture of PhI (**2a**) (203 mg, 1.0 mmol), butyl acrylate (**3a**) (0.17 mL, 1.2 mmol), and $Bu_3N$ (0.28 mL, 1.2 mmol) in NMP (1.0 mL). The resulting solution was degassed by three freeze–pump–thaw cycles, and then stirred vigorously at 140 °C for 2 h under $N_2$. Then one drop of Hg(0) or a 2 mol ppm solution of DCT in NMP was added under flowing $N_2$. The mixture was further stirred at 140 °C. Yields were determined by GC, with mesitylene as an internal standard.

## Acknowledgements

*This research project was supported by JST-ACCEL program (JPMJAC1401). We appreciate funding from the JSPS (Grant-in-Aid for Young Scientists (B) No. 17K14524 and Grant-in-Aid for JSPS Research Fellow No. 17J05446).*

## References

[1] a) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027–3043; b) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177–2250; c) A. F. P. Biajoli, C. S. Schwalm, J. Limberger, T. S. Claudino, A. L. Monteiro, *J. Braz. Chem. Soc.* **2014**, *25*, 2186–2214; d) S. Xu, E. H. Kim, A. Wei, E.-i. Negishi, *Sci. Technol. Adv. Mater.* **2014**, *15*, 044201 (23 pp).

[2] a) T. Mizoroki, K. Mori, A. Ozaki *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; b) R. F. Heck, J. P. Nolley, Jr., *J. Org. Chem.* **1972**, *37*, 2320–2322; c) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.

[3] a) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437–3440; b) N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513–519; c) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483

[4] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821–1823; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340–348; c) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117–2188.

[5] a) M. Kosugi, K. Sasazawa, Y. Shimizu, T. Migita, *Chem. Lett.* **1977**, *6*, 301–302; b) D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638; c) J. K. Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524; *Angew. Chem.* **1986**, *98*, 504–519.

[6] a) Y. Hatanaka, T. Hiyama, *J. Org. Chem.* **1988**, *53*, 918–920; b) S. E. Denmark, J. H.-C. Liu, *Angew. Chem. Int. Ed.* **2010**, *49*, 2978–2986; *Angew. Chem.* **2010**, *122*, 3040–3049; c) Y. Nakao, T. Hiyama, *Chem. Soc. Rev.* **2011**, *40*, 4893–4901; d) T. Komiyama, Y. Minami, T. Hiyama, *ACS Catal.* **2017**, *7*, 631–651.

[7] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470; b) K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46–49.

[8] C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; *Angew. Chem.* **2012**, *124*, 5150–5174.

[9] In the preparation of oral drugs, the permitted level of contamination of the products by palladium is than 10 ppm. The ICH Q3D guidelines can be downloaded here: http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html (accessed Jan 5, 2018).

[10] a) V. Farina, *Adv. Synth. Catal.* **2004**, *346*, 1553–1582; b) C. Deraedt, D. Astruc, *Acc. Chem. Res.* **2014**, *47*, 494–503; c) D. Roy. Y. Uozumi, *Adv. Synth. Catal.* **2018**, *360*, 602–625.

[11] For recent examples on the C-C bond forming reaction with palladium catalysts at ppm loadings, see: a) T. Baran, N. Baran, A. Mentes, *Appl. Organomet. Chem.* **2018**, *32*, e4076; b) T. Baran, I. Sargin, M. Kaya, P. Mulercikas, S. Kazlauskaite, A. Mentes, *Chem. Eng. J.* **2018**, *331*, 102–113; c) P. A. Mane, S. Dey, K. V. Vivekananda, *Tetrahedron Lett.* **2017**, *58*, 25–29; d) F. Puls, N. Richter, O. Kataeva, H. J. Knolker, *Chem. Eur. J.* **2017**, *23*, 17576–17583; e) V. Ramakrishna, N. D. Reddy, *Dalton Trans.* **2017**, *46*, 8598–8610; f) S. J. Sabounchei, M. Hosseinzadeh, M. Zarepour-jevinani, B. Ghanbari, *New J. Chem.* **2017**, *41*, 9701–9709.

[12] a) M. Albrecht, G. van Koten, *Angew. Chem. Int. Ed.* **2001**, *40*, 3750–3781; *Angew. Chem.* **2001**, *113*, 3886–3898; b) M. E. van der Boom, D. Milstein, *Chem. Rev.* **2003**, *103*, 1759–1792; c) J. T. Singleton, *Tetrahedron*, **2003**, *59*, 1837–1857; d) K. J. Szabó, *Synlett*, **2006**, 811–824; e) D. Benito-Garagorri, K. Kirchner, *Acc. Chem. Res.* **2008**, *41*, 201–213; f) N. Selander, K. J. Szabó, *Dalton Trans.* **2009**, 6267–6279; g) N. Selander, K. J. Szabó, *Chem. Rev.* **2011**, *111*, 2048–2076; h) *Organometallic Pincer Chemistry*, *Topics in Organometallic Chemistry; Vol. 40*; Springer, (Eds.: G. van Koten, D. Milstein), Heidelberg, **2013**.

[13] For reports on the Mizoroki–Heck reaction with palladium pincer complexes at ppm loadings, see: a) M. Ohff, A Ohff, M. E. van der Boom, D. Milstein, *J. Am. Chem. Soc.* **1997**, *119*, 11687–11688; b) F. Miyazaki, K. Yamaguchi, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 7379–7383; c) D. Morales-Morales, C. Grause, K. Kasaoka, R. Redón, R. E. Cramer, C. M. Jensen, *Inorg. Chim. Acta*, **2000**, *300–302*, 958–963; d) S. Sjövall, O. F. Wendt, C. Andersson, *J. Chem. Soc., Dalton Trans.* **2002**, 1396–1400; e) I. G. Jung, S. U. Son, K. H. Park, K.-C. Chung, J. W. Lee, Y. K. Chung, *Organometallics* **2003**, *22*, 4715–4720; f) M.-H. Huang, L.-C. Liang, *Organometallics* **2004**, *23*, 2813–2816; g) C. S. Consorti, G. Ebeling, F. R. Flores, F. Rominger, J. Dupont, *Adv. Synth. Catal.* **2004**, *346*, 617–624; h) K. Takenaka, M. Minakawa, Y. Uozumi, *J. Am. Chem. Soc.* **2005**, *127*, 12273–12281; i) J. L. Bolliger, O. Blacque, C. M. Frech, *Chem. Eur. J.* **2008**, *14*, 7969–7977; j) Q.-L. Luo, J.-P. Tan, Z.-F. Li, Y. Qin, L. Ma, D.-R. Xiao *Dalton Trans.* **2011**, *40*, 3601–3609.

[14] For reports on the Mizoroki–Heck reaction with palladium pincer-complexes at ppb loadings, see: a) K.

Takenaka, Y. Uozumi, *Adv. Synth. Catal.* **2004**, *346*, 1693–1696; b) M. S. Yoo, D. Ryu, J. Kim, K. H. Ahn, *Organometallics* **2006**, *25*, 2409–2411.

[15] M. Kuritani, S. Tashiro, M. Shionoya, *Chem. Asian J.* **2013**, *8*, 1368–1371.

[16] G. Hamasaka, F. Sakurai, Y. Uozumi, *Chem. Commun.* **2015**, *51*, 3886–3888.

[17] D. A. Alonso, C. Nájera, C. Pacheco, *Adv. Synth. Catal.* **2002**, *344*, 172–183.

[18] G. M. Whitesides, M. Hackett, R. L. Brainard, J.-P. P. M. Lavalleye, A. F. Sowinski, A. M. Izumi, S. S. Moore, D. W. Brown, E. M. Staudt, *Organometallics* **1985**, *4*, 1819–1830.

[19] a) D. R. Anton, R. H. Crabtree, *Organometallics* **1983**, *2*, 855–859; b) C. S. Consorti, F. R. Flores, J. Dupont, *J. Am. Chem. Soc.* **2005**, *127*, 12054–12065.

[20] In ref. 19, it was reported that DCT coordinates to homogeneous platinum metal to form stable and catalytically inactive complexes. To discuss the mechanism of our catalytic system briefly, we consider homogeneous palladium as a monomeric palladium species.

[21] No reaction of **16a** with **3a** took place in the presence of $Bu_3N$.

[22] When $Pd(OAc)_2$ was used as the catalyst, the reaction of **16a** with **3a** proceeded to give **4aa** in 51% yield. The catalytic activity of complex **1** was superior to that of $Pd(OAc)_2$ in this reaction.

[23] For information on octinoxate, see: http://www.smartskincare.com/skinprotection/sunblocks/sunblock_octinoxate.html (accessed Jan 5, 2018)

10.1002/adsc.201800099

**FULL PAPER**

A Palladium NNC-Pincer Complex as an Extremely Efficient Catalyst Precursor for the Mizoroki–Heck Reaction

*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

Go Hamasaka, Shun Ichii, Yasuhiro Uozumi*