

Ruthenium-Catalyzed Heck-Type Olefination and Suzuki Coupling Reactions: Studies on the Nature of Catalytic Species

Youngim Na, Soyoung Park, Soo Bong Han, Hoon Han, Sangwon Ko, and Sukbok Chang*

Contribution from the Center for Molecular Design and Synthesis (CMDs), Department of Chemistry and School of Molecular Science (BK21), Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Korea

Received September 26, 2003; E-mail: sbchang@kaist.ac.kr

Abstract: Ruthenium-catalyzed Heck olefination and Suzuki cross coupling reactions have been developed. When starting with a ruthenium complex $[\text{RuCl}_2(p\text{-cymene})_2]$ as a homogeneous catalyst precursor, induction periods were observed and ruthenium colloids of zero oxidation state were generated under catalytic conditions. Isolated ruthenium colloids carried out the olefination, implying that active catalytic species are ruthenium nanoclusters. To support this hypothesis, ruthenium nanoparticles stabilized with dodecylamine were independently prepared via a hydride reduction procedure, and their catalytic activity was subsequently examined. Olefination of iodobenzene with ethyl acrylate was efficiently catalyzed by the ruthenium nanoparticles under the same conditions, which could be also reused for the next runs. In poisoning experiments, the conversion of the olefination was completely inhibited in the presence of mercury, thus supporting our assumption on the nature of catalytic species. No residual ruthenium was detected from the filtrate at the end of the reaction. On the basis of the postulation, a heterogeneous catalyst system of ruthenium supported on alumina was consequently developed for the Heck olefination and Suzuki cross coupling reactions for the first time. It turned out that substrate scope and selectivity were significantly improved with the *external ligand-free* catalyst even under milder reaction conditions when compared to results with the homogeneous precatalyst. It was also observed that the immobilized ruthenium catalyst was recovered and reused up to several runs with consistent efficiency. Especially in the Suzuki couplings, the reactions could be efficiently carried out with as low as 1 mol % of the supported catalyst over a wide range of substrates and were scaled up to a few grams without any practical problems, giving coupled products with high purity by a simple workup procedure.

Introduction

The Pd-catalyzed olefination of aryl halides (Heck–Mizoroki reaction)¹ and closely relevant cross couplings (e.g., Stille, Sonogashira, Suzuki–Miyaura reactions, etc.)² have been developed as one of the most useful tools for the carbon–carbon and carbon–heteroatom bond formation in organic synthesis. The catalytic procedures have been shown to be particularly attractive and versatile in numerous organic transformations because they usually offer high product yields, good regio- and stereoselectivity, and excellent compatibility with many functional groups. Efficiency of the reactions has been elegantly and widely demonstrated in the synthesis of natural products, organic building blocks, pharmaceuticals, and agricultural derivatives.³

Especially in recent years, optimization of suitable ligands has allowed the reactions to be carried out under mild conditions (e.g., room temperature) even with less reactive substrates, including aryl chlorides and alkyl halides.⁴ Whereas this field is largely dominated by palladium catalysts, the development of new catalytic protocols has also been actively investigated with the use of other transition-metal species such as nickel,⁵

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copper,⁶ iron,⁷ rhodium,⁸ and iridium.⁹ However, it is generally considered that the scope of the reactions with metal species other than palladium catalyst is narrower and that functional group tolerance is also limited with these catalysts. Despite the significant progresses in the Pd-catalyzed olefination and cross coupling reactions, efficiency and selectivity of those protocols are prone to be subtly sensitive to the use of ancillary ligands such as phosphanes. The employed ligands are presumed to control the steric and/or electronic property of coordinated metal species, thus making the catalysts sufficiently active for the desired transformations. Inhibiting precipitation of in situ reduced metals during the catalytic cycles is believed to be another important role of the added ligands. Some of these ligands, however, are expensive and/or sensitive to air and moisture, making them difficult to use under certain reaction conditions such as those of oxidation. This leads to extensive searches for *ligand-free* catalyst systems for the olefination and related cross coupling reactions by the use of nanoparticles, colloidal metal species,^{10,11} or polymer-entrapped metals.¹²

While ruthenium complexes have been widely used in numerous C–C bond formations,¹³ Ru-catalyzed Heck-type olefination and related cross coupling reactions have been disclosed only in a few limited examples.^{14,15} Our recent interests in ruthenium catalysis directed toward efficient and selective organic transformations¹⁶ as well as studies in the Pd-catalyzed cross coupling reactions¹⁷ led us to scrutinize a possibility whether ruthenium species can exhibit an equivalent catalytic role to palladium catalysts for the olefination and cross coupling reactions. Herein, we report our investigations on the ruthenium-catalyzed olefination and Suzuki-type cross coupling reactions.

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In addition, detailed studies on the nature of catalytic species in the catalysis led us to develop an *external ligand-free ruthenium system* as an efficient, selective, and practical catalyst for both olefination and Suzuki reactions.

Results and Discussion

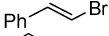
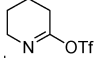
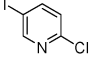
During the course of our studies on the ruthenium catalysis,¹⁶ we observed that an aryl halide bond of haloarenes was readily activated with a certain type of ruthenium species. For example, a treatment of [RuCl₂(benzene)]₂ with sodium acetate in DMF-d₇ at 135 °C for 2 h followed by the addition of iodobenzene resulted in a new set of ¹³C NMR signals in the aromatic region of iodobenzene at δ = 126.0, 128.9, 129.6, which are significantly different from those of original iodobenzene (δ = 94.7, 128.1, 130.9, 139.1).¹⁸ It was assumed that the newly generated species is an activated aryl ruthenium iodo moiety that may be resulted from the insertion of ruthenium into an aryl iodo bond.¹⁹ However, no detectable activation was observed at temperatures lower than 130 °C with the ruthenium complex.²⁰ When the activation experiment was carried out in the presence of an olefin (styrene, 3 equiv) and a base (KOAc, 2 equiv), it was observed that an olefinated adduct (*trans*-stilbene) was almost quantitatively obtained (98%) at 150 °C within 6 h.

This result led us to investigate a possible *catalytic* Heck-type olefination reaction with ruthenium complexes. A series of ruthenium species were first screened for the transformation, and among numerous complexes examined, [RuCl₂(*p*-cymene)]₂ (5 mol %) displayed the highest activity to afford *trans*-stilbene in 98% yield under the following conditions: DMF (1.0 M), 8 h, 150 °C, 3.0 equiv of styrene, and 2.0 equiv of KOAc. Other catalysts tested turned out to be less effective: RuCl₃ (23%), Ru(acac)₂ (14%), RuH₂(PPh₃)₄ (0%), Ru₃(CO)₁₂ (12%), RuH(CO)Cl(PPh₃)₃ (12%), [RuCl₂(CO)₃]₂ (62%), and RuCl₂(PPh₃)₃ (24%). Among various bases examined, 2 equiv of KOAc or NaOAc proved to be most suitable (>80%) in combination with [RuCl₂(*p*-cymene)]₂ (5 mol %), and use of others resulted in lower yields: Et₃N (30%), NaHCO₃ (8%), *t*-BuOK (60%), K₂CO₃ (8%), and KH₂PO₄ (15%). Solvents other than DMF were much less effective for the olefination reaction: dioxane (21%), DMSO (26%), toluene (11%), 2-propanol (16%), acetonitrile (65%), DME (3%), and THF (13%). Conversion became lower when the reactions were carried out at lower temperatures. For example, *trans*-stilbene was obtained only in 9% yield at 135 °C and <5% at 110 °C under otherwise identical conditions. However, reactions with substrates other than styrene could be carried out efficiently even at lower temperatures (vide infra).

As shown in Table 1, under the optimized conditions, the Heck-type olefination reactions of aryl and alkenyl (pseudo)-halides were readily achieved with a variety of olefinic counterparts. Iodobenzene was reacted to give the corresponding olefinated products in good to excellent yields with ethyl acrylate (entry 1), *N,N*-dimethyl acryl amide (entry 2), and phenyl vinyl sulfone (entry 3) within 12 h at 135 °C using sodium acetate as

- (18) See the Supporting Information for a copy of the ¹³C NMR spectrum of the iodobenzene activation experiments.
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Table 1. Olefination of Aryl and Alkenyl (Pseudo)Halides with the Use of $[\text{RuCl}_2(p\text{-cymene})]_2$ Catalyst^a

entry	R ₁ -X	R ₂	T (°C) / h	yield (%) ^b
1	C ₆ H ₅ I	CO ₂ Et	135 (12)	95
2	C ₆ H ₅ I	CONMe ₂	135 (12)	74
3	C ₆ H ₅ I	SO ₂ Ph	135 (12)	84
4 ^c	C ₆ H ₅ I	C ₆ H ₅	150 (8)	99
5	C ₆ H ₅ I	CN	135 (12)	54 ^d
6	4-AcC ₆ H ₄ I	CO ₂ Et	135 (12)	83
7	4-AcC ₆ H ₄ I	CONMe ₂	135 (12)	94
8 ^c	4-AcC ₆ H ₄ I	C ₆ H ₅	150 (8)	94
9	4-MeC ₆ H ₄ I	CO ₂ Et	135 (12)	83
10 ^c	4-MeC ₆ H ₄ I	C ₆ H ₅	150 (8)	64
11 ^e	C ₆ H ₅ OTf	CO ₂ Et	135 (12)	60
12		CO ₂ Et	135 (12)	64
13 ^c		CO ₂ Et	115 (7)	42
14		CO ₂ Et	135 (12)	87

^a Iodobenzene (0.5 mmol), olefin (1.5 mmol), ruthenium catalyst (5 mol %), NaOAc (1.0 mmol), and solvent (0.5 mL). ^b Isolated yield. ^c KOAc was used as a base. ^d *E/Z* = 1:1. ^e K₂CO₃ was used as a base.

a base. The geometry of the generated double bonds was exclusively in (*E*)-form, and no isomeric adducts were detected. However, when acrylonitrile was allowed to react, cinnamionitrile was obtained with a poor selectivity (*E/Z*, 1:1, entry 5).²¹ Electronic variation on aryl iodide derivatives has little effects on both efficiency and selectivity of the vinylation reactions. For example, 4'-iodoacetophenone was readily olefinated with ethyl acrylate, acryl amide, and phenyl vinyl sulfone to furnish the corresponding conjugated (*E*)-olefinic adducts in high yields (entries 6–8). In addition, 4-iodotoluene showed a comparable reactivity and selectivity as iodobenzene and iodoacetophenone (entries 9 and 10). Aryl triflate was also reacted with ethyl acrylate to afford ethyl *trans*-cinnamate under the same reaction conditions except base (K₂CO₃), albeit with a rather moderate yield (entry 11). Alkenyl halide, exemplified by β -bromostyrene, underwent the olefination with ethyl acrylate to afford (*E,E*)-ethyl 5-phenyl-2,4-pentadiene ester in acceptable yield (entry 12). Imidoyl triflate was also olefinated to give conjugated dienyl product with (*E*)-geometry (entry 13). A complete chemoselectivity as well as a functional group tolerance was observed when 2-chloro-5-iodopyridine was allowed to react (entry 14).

Initial studies on the mechanistic aspects in the present catalyst system were next performed on the basis of NMR spectroscopy (Figure 1). The proton NMR spectrum shows that the coordinated *p*-cymene ligand in a dimeric ruthenium species, $[\text{RuCl}_2(p\text{-cymene})]_2$, starts to dissociate into free *p*-cymene upon

(21) This is not an unprecedented result even in the case of palladium catalysis, in which the ratio of *E/Z* is varied depending on the ligands employed. See ref 1.

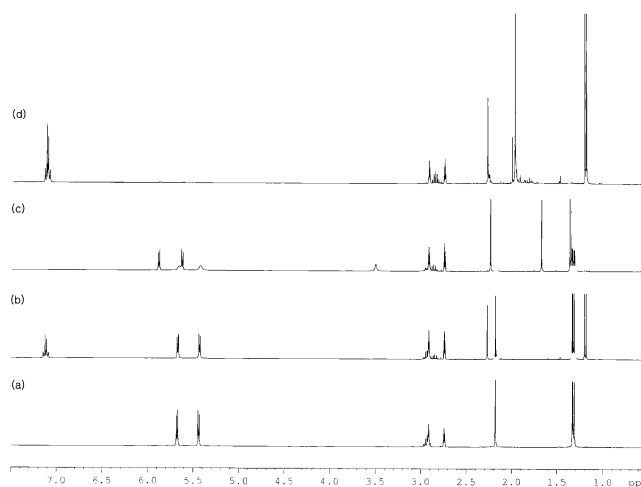


Figure 1. (a) ¹H NMR (400 MHz) spectra of $[\text{RuCl}_2(p\text{-cymene})]_2$ in DMF-*d*₇. (b) After heating a solution of $[\text{RuCl}_2(p\text{-cymene})]_2$ in DMF-*d*₇ for 12 h at 135 °C. (c) After 15 min at 135 °C upon addition of NaOAc (5 equiv) to a solution of $[\text{RuCl}_2(p\text{-cymene})]_2$ in DMF-*d*₇. (d) Spectrum of the solution (c) after 2 h at 135 °C.

heating (135 °C) in DMF-*d*₇. The dissociation, however, did not proceed into completion even after a prolonged time, and the ratio of coordinated dimeric ligand and free *p*-cymene remained almost 1:1 after 12 h at the same temperature. In contrast, as shown in Figure 1c, when a certain base such as sodium acetate (5 equiv) was added into a solution of $[\text{RuCl}_2(p\text{-cymene})]_2$ in deuterated DMF, ¹H NMR spectroscopy revealed that the dimeric ruthenium species immediately dissociated into a monomeric ruthenium adduct that is assumed to be coordinated by the added base with 1:1 ratio, $\text{RuCl}(p\text{-cymene})(\text{OAc})$. Chemical shifts of the presumed ruthenium acetato species are consistent with those of a previously reported case.²² A sharp singlet peak at δ 1.67 ppm in Figure 1c is ascribed to a coordinated acetato methyl group, which is then completely shifted downfield to 1.96 ppm (free acetate) after 2 h (d). Although we could not isolate the base-coordinated monomeric ruthenium moiety from this research, a similar pattern of chemical shift change of *p*-cymene peaks was previously observed in our early study upon addition of amine bases into a solution of the dimeric ruthenium precursor, which was also attributed to the formation of a monomeric ruthenium adduct bound with the added base.^{16d} As shown in Figure 1d, the coordinated *p*-cymene peaks of the presumed monomeric species disappeared completely after 2 h at 135 °C, and only free *p*-cymene peaks and a free acetate peak (1.96 ppm) were detected from the ¹H NMR spectrum. In addition, formation of insoluble colloids was observed from the reaction mixture. The initial pale brown solution of $[\text{RuCl}_2(p\text{-cymene})]_2$ in DMF turned to black upon heating after addition of sodium acetate.²³ These observations led us to hypothesize that ruthenium colloids are generated upon addition of sodium acetate to a solution of the homogeneous precursor under the heating conditions.

Indeed, our assumption was confirmed by the isolation of the in situ generated ruthenium colloids from the mixture of

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(23) This color change has been regarded as one of the strong signs for in situ formation of ruthenium nanoparticles starting from homogeneous precursors. See: Widegren, J. A.; Bennett, M. A.; Finke, R. G. *J. Am. Chem. Soc.* **2003**, 125, 10301.

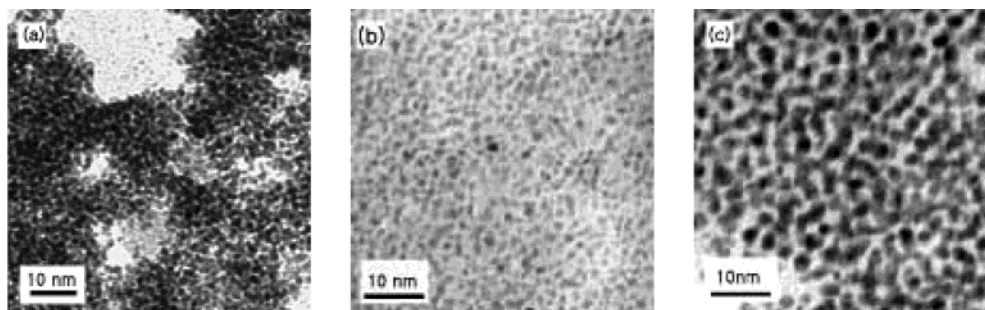


Figure 2. TEM images of isolated ruthenium colloids (a) from the reaction of $[\text{RuCl}_2(p\text{-cymene})]_2$ with NaOAc, (b) from the reaction of $[\text{RuCl}_2(p\text{-cymene})]_2$ with NaOAc in the presence of iodobenzene and ethyl acrylate, and (c) of independently prepared Ru nanoparticles that are stabilized with dodecylamine.

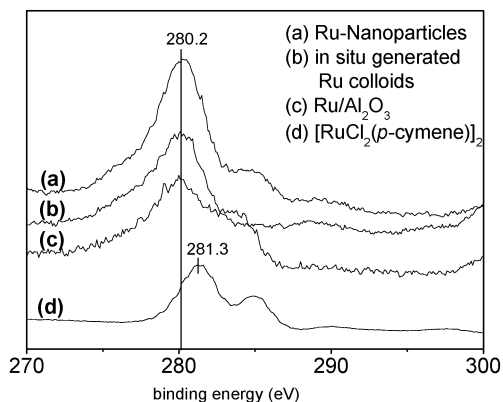


Figure 3. XPS of (a) ruthenium nanoparticles stabilized by dodecylamine, (b) isolated ruthenium colloids from the reaction of $[\text{RuCl}_2(p\text{-cymene})]_2$ with NaOAc, (c) $\text{Ru}/\text{Al}_2\text{O}_3$, and (d) $[\text{RuCl}_2(p\text{-cymene})]_2$.

$[\text{RuCl}_2(p\text{-cymene})]_2$ (30 mg) and NaOAc (40 equiv) in DMF at 135 °C (2 h). Upon centrifugation of the reaction mixture, we could isolate ruthenium nanoparticles (7 mg).²⁴ The size of the obtained nanoparticles was in a range of 1 to 2 nm, as determined by transmission electron microscopy (TEM, Figure 2a), and they are presumed to be coordinated by acetate ion or solvent (DMF) as illustrated in previous reports.²⁵ Likewise, ruthenium colloids could also be isolated from the reaction mixture under the olefination conditions containing all reagents (iodobenzene, ethyl acrylate, and sodium acetate). They also have a similar size distribution of 2 to 3 nm (Figure 2b). Oxidation state of the isolated ruthenium particles was determined to be zero by X-ray photoelectron spectroscopy (XPS, Figure 3b), which was compared to those of commercially available species, $\text{Ru}/\text{Al}_2\text{O}_3$ (Figure 3c) and $[\text{RuCl}_2(p\text{-cymene})]_2$ (Figure 3d). For energy calibration, we used an alumina 1s photoelectron line and 1s binding energy, which was taken to be 74.0 eV. The narrow scans of Ru 3d shown in Figure 3 revealed that a peak of $3d_{5/2}$ of Ru(0) was distinctly detected at 280.0 eV.²⁶ The samples of (a) ruthenium nanoparticles capped with dodecylamine, (b) in situ generated Ru colloids, and (c) commercially available $\text{Ru}/\text{Al}_2\text{O}_3$ equally showed a peak at

280.2 eV, while $[\text{RuCl}_2(p\text{-cymene})]_2$ showed a peak at 281.3 eV. Such a difference in the binding energy (1.1 eV) between the Ru(II) species and the prepared ruthenium nanoparticles as well as the in situ generated ruthenium colloids is regarded as strong evidence for the difference in the oxidation state on the basis of the known literature data.²⁷ Thus, we were convinced that generated ruthenium colloids were in zero oxidation state under the above catalytic conditions with the use of $[\text{RuCl}_2(p\text{-cymene})]_2$ as a homogeneous precursor. When the filtered ruthenium colloids were used as a catalyst (about 20 mol %) for the olefination of iodobenzene with styrene, it was observed that they indeed did carry out the transformation albeit with lower activity (18 h, 24%) compared to the homogeneous precursor, $[\text{RuCl}_2(p\text{-cymene})]_2$. Decreased reactivity of the isolated ruthenium colloids may be attributed to the surface contamination of the metal such as with water, salts, organic residues, or an oxide shell resulting from the reaction conditions in analogy with the reported cases.²⁸

The observation that ruthenium colloids are generated under the Heck-type reaction conditions with the use of a homogeneous ruthenium precursor and that the isolated particles display a measurable catalytic activity for the olefination led us to surmise that the reaction is catalyzed by ruthenium nanoparticles of zero oxidation state regardless of the ruthenium precursors employed. To verify our assumption on the nature of the catalytic species, we decided to prepare ruthenium nanoparticles with stabilizing molecules. With a modification of the known procedure,²⁹ ruthenium nanoparticles capped with dodecylamine were readily prepared from a Ru(III) precursor using a hydride reduction protocol. The size of the prepared nanoparticles was with a mean size near 2 to 3 nm (Figure 2c), and XPS of the particles (Figure 3a) revealed that they are in zero oxidation state, which is in good correlation with the isolated ruthenium colloids generated from the reaction mixture of $[\text{RuCl}_2(p\text{-cymene})]_2$ and sodium acetate (Figure 3b). As expected, the ruthenium nanoparticles stabilized with dodecylamine displayed almost the same catalytic activity and selectivity for the olefination compared to the homogeneous precursor, $[\text{RuCl}_2(p\text{-cymene})]_2$. For example, when the prepared ruthenium nanoparticles were used as a catalyst (10 mol %) in the reaction

(24) The isolated particles were moisture-sensitive, but they did not burn in the open air.

(25) For example, see: (a) Franke, R.; Rothe, J.; Pollmann, J.; Hormes, J.; Bönemann, H.; Brijoux, W.; Hindenburg, Th. *J. Am. Chem. Soc.* **1996**, *118*, 12090. (b) Vidoni, O.; Philippot, K.; Amiens, C.; Chaudret, B.; Balmes, O.; Malm, J.-O.; Bovin, J.-O.; Senocq, F.; Casanove, M.-J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3736.

(26) This value comes from a reference. See: Wagner, C. D.; Riggs, W. M.; Davis, L. E.; Moulder, J. F. In *Handbook of X-ray Photoelectron Spectroscopy*; Muilenberg, G. E., Ed.; Perkin-Elmer Corporation Physical Electronics Division, Eden Prairie, MN, 1979.

(27) For a previous example of using XPS for determining different Pt oxidation states, see: Muijsers, J. C.; Niemantsverdriet, J. W.; Wehman-Ooyevaar, I. C. M.; Grove, D. M.; van Koten, G. *Inorg. Chem.* **1992**, *31*, 2655.

(28) (a) Bönemann, H.; Braun, G.; Brijoux, W.; Brinkmann, R.; Schulze-Tilling, A.; Seevogel, K.; Siepen, K. *J. Organomet. Chem.* **1996**, *520*, 143. (b) Peng, X.; Schlamp, M. C.; Kadavanich, A. V.; Alivisatos, A. P. *J. Am. Chem. Soc.* **1997**, *119*, 7019.

(29) Pan, C.; Pelzer, K.; Philippot, K.; Chaudret, B.; Dassenoy, F.; Lecante, P.; Casanove, M.-J. *J. Am. Chem. Soc.* **2001**, *123*, 7584.

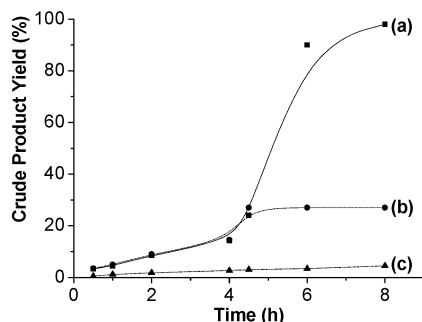


Figure 4. Plot of crude proton NMR yield of *trans*-stilbene vs time from the reaction of iodobenzene with styrene (a) under the standard conditions, (b) after addition of mercury (3 equiv to Ru) at 4.5 h, and (c) in the presence of mercury (3 equiv to Ru) from the beginning.

of iodobenzene with ethyl acrylate, ethyl *trans*-cinnamate was isolated in 92% yield under otherwise identical conditions (compare this to entry 1 in Table 1).³⁰ Furthermore, the ruthenium nanoparticles were easily recovered from the reaction mixture by a simple centrifugation, and they could be reused for the second olefination with a similar efficiency (94%). However, catalytic activity was sharply decreased after the second cycle, and only low yield (34%) was obtained from the third cycle. This is presumably due to a significant aggregation of the nanoparticles over recycles under the reaction conditions,³¹ which was verified from a TEM analysis of the recovered ruthenium nanoparticles, showing that the size increases up to 150 nm after the second cycle.³²

These results further solidify our assumption that the olefination is catalyzed by ruthenium colloidal particles of zero oxidation state that form in situ under the reaction conditions starting with a homogeneous ruthenium precursor, $[\text{RuCl}_2(p\text{-cymene})]_2$. Indeed, we observed that there are some induction periods in the olefination reaction with $[\text{RuCl}_2(p\text{-cymene})]_2$ catalyst. It proceeds relatively slower during the initial stages and gets faster after about 4 h (Figure 4a). This is presumably due to an induction period, which is the prerequisite step for reduction of ruthenium(II) species to ruthenium(0) particles under the olefination reaction conditions. A similar observation of induction periods was previously reported when starting with homogeneous precatalysts, and it was claimed that nucleation of free metals to form metal clusters was responsible for the phenomenon and that, therefore, true catalytic species are metal nanoclusters.³³

Although extensive studies have been carried out to elucidate the true catalytic species in the heterogeneous Pd-catalyzed Heck reaction, it is still unclear in many cases whether the reaction takes place on the surfaces of the solid Pd catalyst³⁴ or whether the active catalyst is dissolved Pd species that are leached from the support, simply acting as a Pd reservoir.³⁵ Among the several

approaches to answer the question, “is it homogeneous or heterogeneous catalysis?”,³⁶ mercury poisoning experiments have been widely practiced as one of the most decisive tests for distinguishing it, although careful precaution has to be used for the interpretation of experimental results.³⁷ This is based on the ability of the added mercury to poison metal(0) heterogeneous catalysts by either formation of amalgam or adsorption on the metal surface. Therefore, suppression of a catalysis by the presence of Hg(0) is generally regarded as strong evidence for any heterogeneous metal(0) catalysts examined. Whereas the olefination of iodobenzene with styrene reaches a complete conversion within 8 h under the standard conditions using $[\text{RuCl}_2(p\text{-cymene})]_2$ catalyst (Figure 4a), it was observed that the reaction was totally shut down in the presence of mercury (3 equiv to $[\text{RuCl}_2(p\text{-cymene})]_2$) under otherwise identical conditions (Figure 4c). A control experiment revealed that mercury itself does not react with the homogeneous ruthenium species employed.³⁸ When mercury (3 equiv to Ru) was added to the reaction mixture after achieving some conversion (4.5 h in this case), no further conversion was observed after the addition point (Figure 4b). Likewise, catalytic activities of other ruthenium sources including ruthenium nanoparticles and Ru/alumina (vide infra) were also completely suppressed by the action of mercury.






On the basis of our assumption that ruthenium(0) colloids catalyze the Heck-type olefination without the need for any ancillary ligands, the same transformation was next examined with the use of commercially available Ru/Al₂O₃ as a catalyst on the basis of a practical point of view.³⁹ We were pleased to observe that the supported zerovalent ruthenium catalyst indeed performs the olefination with high efficiency and selectivity (Table 2).

Surprisingly, the immobilized species displayed wider substrate scope and higher selectivity even under milder reaction conditions when compared to the homogeneous precursor, $[\text{RuCl}_2(p\text{-cymene})]_2$. For example, whereas $[\text{RuCl}_2(p\text{-cymene})]_2$ carried out the reaction of iodobenzene with ethyl acrylate with low yield (<30%) at temperatures below 130 °C, the same conversion was completed even at 115 °C with the use of the same mole percent of Ru/Al₂O₃ catalyst (Table 2, entry 1). A

(30) For selected recent examples of using stabilized Pd colloids for Heck reactions, see: (a) Beller, M.; Fischer, H.; Kühlein, K.; Reisinger, C. P.; Herrmann, W. A. *J. Organomet. Chem.* **1996**, *520*, 257. (b) Zhao, F.; Bhanage, B. M.; Shirai, M.; Arai, M. *Chem.-Eur. J.* **2000**, *6*, 843. (c) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127. (31) For a similar phenomenon of decrease in catalytic activity over recycles using palladium nanoparticles, see: Narayanan, R.; El-Sayed, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 8340. (32) See the Supporting Information for a copy of a TEM image of the aggregated ruthenium particles after the second cycle. (33) (a) Lewis, L. N.; Lewis, N. *J. Am. Chem. Soc.* **1986**, *108*, 7228. (b) Rocaboy, C.; Gladysz, J. A. *New. J. Chem.* **2003**, *27*, 39. (c) Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165. (d) Reference 23.

(34) For some selected examples of heterogeneous Heck reaction, see: (a) Djakovitch, L.; Koehler, K. *J. Am. Chem. Soc.* **2001**, *123*, 5990. (b) Mori, K.; Yamaguchi, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2002**, *124*, 11572. (c) Sasson, Y.; Mukhopadhyay, S.; Rothenberg, G.; Joshi, A.; Baidossi, M. *Adv. Synth. Catal.* **2002**, *344*, 348. (d) Köhler, K.; Heidreich, R. G.; Krauter, J. G. E.; Pitsch, J. *Chem.-Eur. J.* **2002**, *8*, 622. (35) For some examples showing that heterogeneous catalysts serve as catalytic precursors for homogeneous catalysis, see: (a) Zhao, F.; Murakami, K.; Shirai, M.; Arai, M. *J. Catal.* **2000**, *194*, 479. (b) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139. (c) Novák, Z.; Szabó, A.; Répási, J.; Kotschy, A. *J. Org. Chem.* **2003**, *68*, 3327. (36) For discussions on the nature of true catalytic species to distinguish homogeneous and heterogeneous catalysis, see: (a) Collman, J. P.; Kosydar, K. M.; Bressan, M.; Lamanna, W.; Garrett, T. *J. Am. Chem. Soc.* **1984**, *106*, 2569. (b) Weddle, K. S.; Aiken, J. D., III; Finke, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 5653. (c) Stein, J.; Lewis, L. N.; Gao, Y.; Scott, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 3693. (d) Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A: Chem.* **2003**, *198*, 317. (37) For examples of inhibition studies with the use of added ligands, see: (a) Anton, D. R.; Crabtree, R. H. *Organometallics* **1983**, *2*, 855. (b) Lin, Y.; Finke, R. G. *Inorg. Chem.* **1994**, *33*, 4891. (c) Chauhan, B. P. S.; Rathore, J. S.; Chauhan, M.; Krawicz, A. *J. Am. Chem. Soc.* **2003**, *125*, 2876. (38) For detailed control experiments and spectroscopic data, see the Supporting Information. (39) For recent examples on the use of Ru/Al₂O₃ as a catalyst for organic transformations, see: (a) Bond, G. C.; Hooper, A. D. *Appl. Catal., A* **2000**, *191*, 69. (b) Miyazaki, A.; Balint, I.; Aika, K.-i.; Nakano, Y. *J. Catal.* **2001**, *204*, 364. (c) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4538. (d) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 1480.

Table 2. Heck-Type Olefination of Aryl and Alkenyl Halides Using Ru/Al₂O₃ Catalyst^a

$\text{R}_1\text{-X} + \text{CH}_2=\text{CH-R}_2 + \text{NaOAc} \xrightarrow[\text{DMF, 12 h}]{\text{Ru/Al}_2\text{O}_3 (5 \text{ wt } \%), (5 \text{ mol } \%)} \text{R}_1\text{-CH=CH-R}_2$				
entry	R ₁ -X	R ₂	T (°C)	yield (%) ^b
1	C ₆ H ₅ I	CO ₂ Et	115	94
2	C ₆ H ₅ I	CONMe ₂	115	63
3 ^c	C ₆ H ₅ I	PO(OEt) ₂	115	84
4	C ₆ H ₅ I	CN	115	99 ^d
5 ^e	C ₆ H ₅ I	C ₆ H ₅	135	91
6	C ₆ H ₅ I	CO ₂ H	115	57
7	4-AcC ₆ H ₄ I	CO ₂ Et	115	70
8	4-AcC ₆ H ₄ I	CONMe ₂	115	89
9 ^e	4-MeC ₆ H ₄ I	C ₆ H ₅	135	94
10		CO ₂ Et	115	70
11		CN	115	89 ^d
12		CO ₂ Et	115	75
13		CO ₂ Et	115	83
14		CO ₂ Et	115	99 ^f

^a Iodobenzene (0.5 mmol), olefin (1.5 mmol), 5 wt % Ru/Al₂O₃ (5 mol %), and NaOAc (1.0 mmol) in DMF (0.5 mL). ^b Isolated yield. ^c Cs₂CO₃ as a base. ^d E/Z = 3:1. ^e KOAc was used as a base and the reaction time was 8 h. ^f Product is 3-bromo-*trans*-ethyl cinnamate.

wide range of olefins were reacted with aryl iodides, providing good to excellent yields of olefinated products at temperatures 115–135 °C. It should be noted that whereas the olefination of iodobenzene with vinyl phosphonate was inert with [RuCl₂(*p*-cymene)]₂ catalyst even at temperatures above 150 °C for long reaction times (24 h), the reaction went smoothly at 115 °C using the supported ruthenium catalyst to afford vinylated phosphonate in good yield (entry 3). When acrylonitrile was allowed to react with iodobenzene, both selectivity (E/Z = 3:1) and yield (99%, 115 °C) were significantly improved with the supported catalyst (entry 4), compared to that with [RuCl₂(*p*-cymene)]₂ catalyst (1:1, 54%, 135 °C, entry 5 in Table 1). Whereas acrylic acid did not react at all with iodobenzene using [RuCl₂(*p*-cymene)]₂ catalyst, the corresponding product, (*E*)-cinnamic acid, was obtained with the immobilized catalyst albeit in moderate yield (entry 6). In addition, 1-iodonaphthalene, which is a poor substrate with the homogeneous precatalyst (<20% yield at 135 °C, 12 h), was readily reacted with ethyl acrylate and acrylonitrile to afford the corresponding coupled naphthalene derivatives (entries 10 and 11). In addition, the supported Ru/Al₂O₃ system exhibited a complete chemoselectivity with iodo over bromo group, as demonstrated in entry 14. In contrast to terminal olefins that afforded high yields of olefinated products, reactions with internal olefins were sluggish, resulting in lower product yields. For example, when iodobenzene was allowed to react with ethyl crotonate under the same

conditions, ethyl *trans*-β-methylcinnamate was obtained in 43% yield using the supported ruthenium catalyst.

Although it is too early to give an exclusive explanation for the observation that the supported ruthenium catalyst shows higher catalytic activity and selectivity in the Heck-type reaction compared to the homogeneous precursor, [RuCl₂(*p*-cymene)]₂, it may be again closely related to our postulation that the reaction is catalyzed by ruthenium colloids of zero oxidation state.⁴⁰ The supported catalyst was quantitatively recovered at the end of the reaction by a simple centrifugation, and it could be reused for the following runs with constancy reactivity (1st, 2nd, and 3rd runs; 94, 91, 92%, respectively).⁴¹ When the reaction mixture was filtered through a micropore filter, no residual Ru was detected from the filtrate by ICP analysis (<1 ppm), implying that leaching of Ru from the support is negligible. In addition, no conversion was observed when a substrate and a base were added to a filtered solution under the same reaction conditions. Crude products were readily isolated in most cases with more than 95% purity from the reaction mixture by a simple workup of the filtrate solution. It should be noted that this represents a rare example of ruthenium-catalyzed heterogeneous Heck-type olefination with a reusability.⁴²

The *external ligand-free* ruthenium catalyst supported on alumina was next successfully utilized to Suzuki–Miyaura cross coupling, one of the most efficient and practical C–C bond-forming reactions (Table 3).⁴³ It was found that the immobilized ruthenium system was highly efficient and selective for the coupling of a wide range of aryl iodides with boron compounds using as low as 1 mol % of the catalyst in either a biphasic or monophasic reaction medium. The ruthenium-catalyzed coupling was carried out at ~60–90 °C, depending on the electronic nature of the employed substrates with electron-donating substituents being slower. Both boronic acids and boronate esters were equally efficiently coupled with iodoarenes, although most data presented in Table 3 are those from reactions with the former reactants.

Coupling of phenylboronic acid with 4'-iodoacetophenone was complete within 12 h at 60 °C, using the supported ruthenium catalyst (1 mol %) to give 4-acetylphenyl in quantitative yield in a cosolvent of 1,2-dimethoxyethane/water (1:1, v) (Table 3, entry 1). In the case of boronic acid derivatives, NaOH was chosen as a practical base although other commonly used ones also gave similar results: KOH (60 °C, 12 h, 95%) and *t*-BuOK (60 °C, 12 h, 96%). However, carbonate bases turned out to be less effective for the conversion: K₂CO₃ (120 °C, 12 h, 50%) and Na₂CO₃ (120 °C, 12 h, 28%). Whereas a biphasic medium consisting of 1,2-dimethoxyethane/water (1:



(40) No catalytic activity for the olefination was observed even with stoichiometric alumina in the absence of ruthenium under otherwise identical conditions.

(41) For selected recent examples of reusable Pd catalytic systems for Heck reactions, see: (a) Turlan, D.; U. E. P.; Navarro, R.; Royo, C.; Menéndez, M.; Santamaría, J. *Chem. Commun.* **2001**, 2608. (b) de Vries, A. H. M.; Parlevliet, F. J.; de Vondervoort, L. S.; Mommers, J. H. M.; Henderickx, H. J. W.; Walet, M. A. M.; de Vries, J. G. *Adv. Synth. Catal.* **2002**, *344*, 996. (c) Nair, D.; Scarpello, J. T.; Vankelecom, I. F. J.; Santos, L. M. F. D.; White, L. S.; Kloetzing, R. J.; Welton, T.; Livingston, A. G. *Green Chem.* **2002**, *4*, 319.

(42) The reaction scope of a single report (ref 14) on the homogeneous Ru-(COD)(COT)-catalyzed olefination is rather narrow, working only with alkenyl halides, and to our best knowledge, no heterogeneous ruthenium-catalyzed Heck-type reaction has been published.

(43) For recent reviews on the Pd-catalyzed Suzuki reaction, see: (a) Suzuki, A. J. *Organomet. Chem.* **2002**, *653*, 83. (b) Miyaura, N. J. *Organomet. Chem.* **2002**, *653*, 54. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

Table 3. Suzuki–Miyaura-Type Cross Coupling Reaction of Aryl Iodides with Boron Compounds Using Ru/Al₂O₃ Catalyst^a

		Ru/Al ₂ O ₃ (5 wt%)					
		Base					
R ₁ -I + R ₂ -B(OR ₃) ₂		DME/H ₂ O (1:1)		→		R ₁ -R ₂	
entry	R ₁	R ₂	R ₃	T(°C)/h	cat ^b	yield(%) ^c	
1	4-AcC ₆ H ₄	C ₆ H ₅	H	60 (12)	1	99	
2 ^d	4-AcC ₆ H ₄	C ₆ H ₅	(CH ₂) ₂	60 (12)	1	99	
3 ^e	4-AcC ₆ H ₄	C ₆ H ₅	cate	80 (12)	1	98	
4	4-AcC ₆ H ₄	4-ClC ₆ H ₄	H	80 (8)	1	82	
5	4-AcC ₆ H ₄	4-MeOC ₆ H ₄	H	60 (12)	5	93	
6	4-AcC ₆ H ₄	(E)-PhCH=CH	H	90 (12)	1	91	
7	C ₆ H ₅	C ₆ H ₅	H	60 (12)	5	96	
8	C ₆ H ₅	4-ClC ₆ H ₄	H	90 (12)	1	88	
9	C ₆ H ₅	4-MeOC ₆ H ₄	H	90 (12)	1	83	
10	4-MeC ₆ H ₄	C ₆ H ₅	H	90 (24)	1	76	
11	4-MeOC ₆ H ₄	C ₆ H ₅	H	90 (24)	5	93	
12 ^d	4-O ₂ NC ₆ H ₄	C ₆ H ₅	(CH ₂) ₂	90 (24)	1	96	
13		C ₆ H ₅	H	90 (20)	5	66	
14		C ₆ H ₅	H	90 (36)	1	92	
15	4-HCOC ₆ H ₄	C ₆ H ₅	H	90 (12)	5	87	
16	4-HOCH ₂ C ₆ H ₄	C ₆ H ₅	H	90 (12)	5	97	

^a Iodoarene (1.0 mmol), boron compound (1.5 mmol), and base (2 equiv) in solvent (1 mL). Base was NaOH except entries 2, 3, and 12. ^b Used ruthenium catalyst in mol %. ^c Isolated yield. ^d K₃PO₄ was used as a base. ^e K₂CO₃ was used.

1) turned out to be the most suitable, other cosolvent systems were less effective under otherwise same conditions. For example, reactions of iodobenzene with phenylboronic acid in DMF/water (5% conversion) and toluene/water (12%) resulted in poor yields. Meanwhile, coupling in various monophasic organic solvents was almost ineffective (e.g., in DME or DMF, <5% conversion). Boronate esters were also coupled with aryl iodides to afford high yields of products (entries 2 and 3). In these cases, certain weak inorganic bases such as K₂CO₃ or K₃PO₄ turned out to be more effective than NaOH. While various boronic esters could be readily employed, 2-phenyl-1,3-dioxaborolane was more readily coupled with iodobenzene under milder conditions than catechol-derived boronate (compare entries 2 and 3). Alkenylboronic acid was also smoothly reacted with iodoarene to afford olefinic product in high yield with complete retention of double-bond geometry (entry 6). In general, introduction of electron-donating groups in iodoarenes slowed the reaction, and higher loadings of catalyst up to 5 mol % were necessary to obtain satisfactory yields at elevated

temperatures with longer reaction times (entries 10 and 11). 1-Iodonaphthalene turned out to be slow-reacting and was coupled with phenylboronic acid to afford product in moderate yield (entry 13). The ruthenium-catalyzed Suzuki coupling was also similarly operated with a heteroaromatic substrate (entry 14). Some functional groups such as nitro, formyl, and free hydroxyl moiety were tolerated under the developed reaction conditions (entries 12, 15, and 16, respectively). In contrast to iodobenzene derivatives, bromo- and chloroarenes were unreactive under the present conditions.

The supported ruthenium catalyst used in this study could be easily removed by a simple filtration of the reaction mixture through a pad of Celite and silica gel after basic workup, and the coupled products were isolated in >98% purity without any further purification process such as silica gel column chromatography. No significant residual ruthenium contents (<1 ppm) were detected from the filtrate by an ICP analysis. The Suzuki reaction can be readily scaled up to a few grams without any practical problems. For example, reaction of 4'-iodobenzyl alcohol (2.3 g, 10.0 mmol) with phenylboronic acid (1.8 g, 15.0 mmol) gave the desired coupled product in 88% yield with the use of Ru/Al₂O₃ (202 mg, 1.0 mol %) under the standard conditions. Also noteworthy is that this represents, to the best of our knowledge, the first example of ruthenium-catalyzed heterogeneous Suzuki-type cross coupling.⁴⁴

It should be mentioned that the Suzuki coupling was much less effective when a homogeneous ruthenium precursor was used as a catalyst.⁴⁵ For example, 4'-iodoacetophenone was coupled with phenylboronic acid only in low yield (18%) when [RuCl₂(*p*-cymene)]₂ was used as a catalyst (5 mol %) under otherwise identical conditions (60 °C, 12 h, compare this with entry 1 of Table 3). This result may be attributed to the relatively low reaction temperatures, at which generation of ruthenium colloids of zero oxidation state is difficult from the used homogeneous precursor. Indeed, it was observed that ruthenium nanoparticles are generated from the precursor only at temperatures above 130 °C upon addition of certain bases. No ruthenium colloids were found to form in situ from the homogeneous precursor under the Suzuki conditions (60–90 °C). This observation led us once again to affirm that the ruthenium-catalyzed Heck and Suzuki reaction proceed by ruthenium colloids.⁴⁶

Conclusions

“Is it homogeneous or heterogeneous?” is not a trivial question that can be answered by simple investigations in metal-catalyzed reactions. Studies on certain reactions with homogeneous catalyst precursors reveal that the true catalytic species are heterogeneous nanoparticles or insoluble metal clusters instead of the supposed homogeneity. On the other hand, it turns out that long time believed heterogeneous systems with

(44) A full description on this Ru-catalyzed Suzuki reaction will be submitted with regard to the scope and limitations of the present procedure.

(45) No catalytic activity was observed for the Suzuki coupling reaction with stoichiometric alumina in the absence of ruthenium under otherwise identical conditions.

(46) For selected recent examples of using Pd nanoparticles for Suzuki reactions, see: (a) Reetz, M. T.; Breinbauer, R.; Wanninger, K. *Tetrahedron Lett.* **1996**, *37*, 4499. (b) Li, Y.; Hong, X. M.; Collard, D. M.; El-Sayed, M. A. *Org. Lett.* **2000**, *2*, 2385. (c) Kim, S.-W.; Kim, M.; Lee, W. Y.; Hyeon, T. *J. Am. Chem. Soc.* **2002**, *124*, 7642. (d) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *J. Am. Chem. Soc.* **2002**, *124*, 11858. (e) Strimbu, L.; Liu, J.; Kaifer, A. E. *Langmuir* **2003**, *19*, 483.

supported catalysts serve simply as a reservoir for homogeneous catalytic species in some cases. Herein, we have shown that olefination of aryl and alkenyl (pseudo) halides can be efficiently and selectively carried out with ruthenium catalyst systems with the use of both a homogeneous precatalyst and heterogeneous supported catalyst. Detailed investigations on the nature of the reaction led us to assume that catalytically active species are ruthenium colloids with zero oxidation state even when a homogeneous complex precursor such as $[\text{RuCl}_2(p\text{-cymene})]_2$ is employed. Induction periods were observed from the reaction with homogeneous precursor, and ruthenium colloids were generated quantitatively under the reaction conditions, which were followed by ^1H NMR spectroscopy, XPS, and TEM as well as color change of the reaction mixture. Isolated ruthenium colloids from the reaction mixture displayed measurable catalytic activity in the olefination albeit with lower turnovers compared to the employed homogeneous precatalyst presumably due to a surface contamination of the rather naked particles. Independently prepared ruthenium nanoparticles having amine stabilizers exhibited excellent catalytic activity and reusability in the Heck reaction. Mercury poisoning experiments showed that the olefination was completely inhibited by the addition of mercury regardless of ruthenium sources employed, which would be a vital evidence for the heterogeneity. These results led us to develop a highly efficient, user-friendly, reusable, and *external ligand-free* heterogeneous ruthenium catalyst, $\text{Ru}/\text{Al}_2\text{O}_3$, for both the olefination and Suzuki-type coupling reactions. Further studies on the detailed mechanistic cycles and synthetic application of the presently explored catalyst system would be expected to follow immediately.

Experimental Section

General. NMR spectra were obtained on Bruker AVANCE 300 and AVANCE 400 spectrometers (^1H at 300 MHz, 400 MHz and ^{13}C at 75 MHz, 100 MHz, respectively). Chemical shifts are reported in ppm, using TMS as an internal standard and CDCl_3 as a solvent. ^{13}C NMR spectra are reported in ppm relative to the center line of a triplet at 77.0 ppm of CDCl_3 . IR spectra were recorded with a FT-IR (EQUINOX 55) spectrometer. GC data and mass spectra were obtained on a VG AUTOSPEC Ultima GC/MS system using direct insertion probe (DIP) and electron impact (EI) (70 eV) method. Column chromatography was carried out using silica gel 60 (230–400 mesh, ASTM, Merck). Ruthenium catalysts including $[\text{RuCl}_2(p\text{-cymene})]_2$ and Ru on alumina (5 wt %), haloarenes, olefins, boronic acids, boronate esters, bases, and solvents were purchased from Aldrich or TCI and used as such without further purification. CDCl_3 was obtained from Cambridge Isotope Laboratories, Inc. TEM data were obtained with a Hitachi H9000-NAR high-resolution TEM operating at 300 kV. X-ray photoelectron spectra were recorded on a VG Sci. ESCA Lab200R with dual anode (Mg and Al) apparatus using Mg $K\alpha$ anode. The pressure in the spectrometer was about 10^{-10} Torr. For energy calibration, the alumina 1s photoelectron line was used, and the alumina 1s binding energy was taken to be 74.0 eV.

Activation Experiment of Iodobenzene with $[\text{RuCl}_2(\text{benzene})]_2$. A mixture of $[\text{RuCl}_2(\text{benzene})]_2$ (12 mg, 0.024 mmol) and NaOAc (79 mg, 0.96 mmol) in DMF-*d*₇ (0.5 mL) was stirred at 135 °C for 2 h, followed by the addition of iodobenzene (7 mg, 0.04 mmol). The ^{13}C NMR spectrum of the reaction mixture immediately showed a set of signals in the aromatic region at $\delta = 126.0, 128.9, 129.6$, which are attributed to arise from an activated ruthenium aryl species in analogy with the Pd cases (ref 19), and they are distinctly different from those of iodobenzene ($\delta = 94.9, 128.4, 130.4, 138.1$ ppm). But a quaternary carbon center bound to Ru was not detected by the ^{13}C NMR spectroscopy.

Screening of Various Ruthenium Catalysts for the Heck-Type Reaction of Iodobenzene with Styrene. To a solution of iodobenzene (50 mg, 0.25 mmol) in DMF (0.2 mL) was added styrene (78 mg, 0.75 mmol) and KOAc (49 mg, 0.50 mmol), followed by a chosen ruthenium catalyst (5 mol %). The reaction mixture was stirred at 150 °C for 8 h in a screw-capped vial. Conversion and crude yields were calculated by ^1H NMR based on an internal standard (anisole).

Base Screening in the Olefination of Iodobenzene with Styrene. To a solution of iodobenzene (50 mg, 0.25 mmol) in DMF (0.2 mL) was added styrene (78 mg, 0.75 mmol) and $[\text{RuCl}_2(p\text{-cymene})]_2$ (7.7 mg, 5 mol %), followed by a chosen base (0.50 mmol). The reaction mixture was stirred at 150 °C for 8 h in a screw-capped vial. Conversions were calculated by ^1H NMR based on an internal standard (anisole).

Representative Heck-Type Olefination Reaction Using $[\text{RuCl}_2(p\text{-cymene})]_2$ as a Catalyst. To a solution of iodobenzene (102 mg, 0.5 mmol) in DMF (0.5 mL) was added ethyl acrylate (150 mg, 1.5 mmol) and NaOAc (82 mg, 1.0 mmol), followed by $[\text{RuCl}_2(p\text{-cymene})]_2$ (15.3 mg, 5 mol %). The reaction mixture was stirred at 135 °C for 12 h either in a screw-capped vial or in a round-bottom flask. In the case of using a flask, the reaction was carried out under N_2 atmosphere. The crude product was extracted with ethyl acetate, washed with water, and dried (MgSO_4). After removal of organic solvent under reduced pressure, the residue was purified by column chromatography on silica gel (10% ethyl acetate/hexane) to afford ethyl *trans*-cinnamate (84 mg, 95%) as a colorless liquid.

(E)-Ethyl 3-(3,4,5,6-tetrahydro-2-pyridinyl)-2-propenoate. ^1H NMR (CDCl_3 , 300 MHz): δ 6.94 (td, 1H, $J = 15.7, 6.5$ Hz), 5.85 (d, 1H, $J = 15.7$ Hz), 4.15 (m, 4H), 2.50 (m, 2H), 1.27 (m, 7H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 172.2, 166.3, 146.4, 122.3, 60.4, 60.1, 32.5, 27.2, 14.1, 14.0. IR (neat): 2963, 1713, 1638, 1202 cm^{-1} . HRMS (EI): calcd for $\text{C}_{10}\text{H}_{15}\text{NO}_2$, 181.1103 (M^+); found, 181.1097.

Experiments for in Situ Preparation of Ruthenium Colloids.
Method A. A mixture of $[\text{RuCl}_2(p\text{-cymene})]_2$ (30.6 mg, 0.050 mmol) and NaOAc (164 mg, 2.0 mmol) in DMF (1.0 mL) was stirred for 2 h at 135 °C, and the sample was directly deposited on carbon film coated with TEM grids by dip-coating without workup, so that the process can be reviewed as an “in situ” TEM analysis. The rest of the sample was diluted with EtOH (40 mL), and formed ruthenium colloids were separated by centrifugation and dried in a vacuum. To a solution of iodobenzene (71 mg, 0.35 mmol) in DMF (0.35 mL) was added ethyl acrylate (105 mg, 1.05 mmol) and NaOAc (57 mg, 0.70 mmol), followed by the in situ generated ruthenium colloids (7 mg) which were obtained by previous procedure. The reaction mixture was stirred at 135 °C for 12 h in a screw-capped vial. The crude product was extracted with ethyl acetate, washed with water, and dried (MgSO_4). After removal of organic solvent under reduced pressure, the residue was purified by column chromatography on silica gel (10% ethyl acetate/hexane) to afford ethyl *trans*-cinnamate (15 mg, 24%) as a colorless liquid.

Method B. To a solution of iodobenzene (204 mg, 1.00 mmol) in DMF (1.0 mL) was added ethyl acrylate (300 mg, 3.0 mmol) and NaOAc (164 mg, 2.0 mmol), followed by $[\text{RuCl}_2(p\text{-cymene})]_2$ (30.6 mg, 0.050 mmol). The reaction mixture was stirred for 3 h at 135 °C in a screw-capped vial. The samples were directly deposited on a carbon film coated with TEM grids by dip-coating without workup, so that the process can be reviewed as an “in situ” TEM analysis. The rest of the sample was diluted with EtOH (40 mL), and formed ruthenium colloids were separated by centrifugation and dried in a vacuum. Samples for X-ray photoelectron spectra were prepared as $\gamma\text{-Al}_2\text{O}_3$ pellets.

Preparation of Amine-Stabilized Ru Nanoparticles. A solution of tetraoctylammonium bromide (472 mg, 0.72 mmol) in toluene (20 mL) was added to a stirred solution of $\text{RuCl}_3\cdot 3\text{H}_2\text{O}$ (100 mg, 0.48 mmol) in water (20 mL). After stirring the mixture for 12 h at room temperature, a solution of dodecylamine (266.9 mg, 1.44 mmol) in

toluene (20 mL) was added, and the reaction mixture was stirred for additional 1 h at room temperature. To the above mixture was added a solution of NaBH₄ (163 mg, 4.3 mmol) in water (20 mL), and the resulting mixture was stirred at room temperature for 2 h and then stirred for an additional 2 h at 100 °C. A homogeneous dark brown solution was evaporated under reduced pressure to about 5 mL, and the residue was diluted with EtOH (30 mL). The nanoparticles were separated by centrifugation and dried in a vacuum to afford 46 mg, which was microanalyzed to be Ru: 48%, N: 52%.

Heck-Type Reaction of Iodobenzene with Ethyl Acrylate with Stabilized Ru Nanoparticles as a Catalyst. To a solution of iodobenzene (102 mg, 0.5 mmol) in DMF (0.5 mL) was added ethyl acrylate (150 mg, 1.5 mmol) and NaOAc (82 mg, 1.0 mmol), followed by Ru nanoparticles (48 wt %, 10 mg, 10 mol %). The reaction mixture was stirred at 115 °C for 12 h either in a screw-capped vial or in a round-bottom flask. The crude product was extracted with ethyl acetate, washed with water, and dried (MgSO₄). After removal of organic solvent under reduced pressure, the residue was purified by column chromatography on silica gel (10% ethyl acetate/hexane) to afford ethyl *trans*-cinnamate (83 mg, 94%) as a colorless liquid.

Recovery and Reuse of Ruthenium Nanoparticles in the Heck-Type Olefination Reaction. To a solution of iodobenzene (204 mg, 1.0 mmol) in DMF (1.0 mL) was added ethyl acrylate (300 mg, 3.0 mmol) and NaOAc (165 mg, 2.0 mmol), followed by Ru nanoparticles (48 wt %, 21 mg, 10 mol %). The reaction mixture was stirred at 115 °C for 12 h in a screw-capped vial. After completion, the Ru nanocatalyst was separated by centrifugation. The filtrate was evaporated in a vacuum, and the crude product was purified by column chromatography on silica gel to give ethyl *trans*-cinnamate. The separated Ru nanoparticles were washed with MeOH (40 mL × 2) and water and dried in a vacuum before using for the next runs.

Representative Olefination Reaction Using Ru/Alumina as a Catalyst. To a solution of iodobenzene (102 mg, 0.50 mmol) in DMF (0.5 mL) was added ethyl acrylate (150 mg, 1.5 mmol) and NaOAc (82 mg, 1.0 mmol), followed by Ru/Al₂O₃ (5 wt %, 50.5 mg, 5 mol %). The reaction mixture was stirred at 115 °C (135 °C with styrene) for 12 h either in a screw-capped vial or in a round-bottom flask. The crude product was extracted with ethyl acetate, washed with water, and dried (MgSO₄). After removal of organic solvent under reduced pressure, the residue was purified by column chromatography on silica gel (10% ethyl acetate/hexane) to afford ethyl *trans*-cinnamate (83 mg, 94%) as a liquid.

Determination of Conversion versus Time in the Reaction of Iodobenzene with Styrene Using [RuCl₂(*p*-cymene)]₂ as a Catalyst. The course of the reaction was monitored by taking samples periodically

and analyzing them by ¹H NMR spectroscopy from the olefination reaction of styrene with iodobenzene at 150 °C in DMF using [RuCl₂(*p*-cymene)]₂ catalyst under the standard conditions.

Mercury Poisoning Experiment. To a solution of iodobenzene (102 mg, 0.50 mmol) in DMF (0.5 mL) was added styrene (156 mg, 1.5 mmol), KOAc (98 mg, 1.0 mmol), [RuCl₂(*p*-cymene)]₂ (15.3 mg, 5 mol %), and mercury (15 mg, 0.075 mmol). The reaction mixture was stirred at 150 °C for 8 h in a screw-capped vial. Conversion of the reaction was checked using ¹H NMR with an internal standard (anisole). In another experiment, mercury was added after 4 h instead of adding from the start, and conversion of the reaction was checked using the same method.

Suzuki-Type Reactions Using Ru/Alumina as a Catalyst. To a solution of 4'-iodoacetophenone (246.1 mg, 1.0 mmol) in 1,2-dimethoxyethane/water (v, 1:1, 1.0 mL) was added phenylboronic acid (182.9 mg, 1.5 mmol), NaOH (80.0 mg, 2.0 mmol), and Ru/Al₂O₃ (5 wt %, 20.2 mg, 0.01 mmol). The reaction mixture was stirred at 60 °C, and the progress of the reaction was monitored by TLC until 4'-iodoacetophenone disappeared completely. After 12 h, the reaction mixture was diluted with EtOAc (10 mL), followed by water (10 mL). The organic layer was separated, washed with aqueous NaHCO₃ and NaOH solution (5%) several times, and then dried over anhydrous MgSO₄. The organic layer was filtered through a pad of silica gel. After removal of organic solvent under reduced pressure, the residue was purified by flash column chromatography (ethyl acetate/hexane, 1:20) to give 4-phenylacetophenone (184 mg, 99%).

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Supporting Information Available: Copies of spectral data in the ruthenium-mediated activation of iodobenzene, new compounds obtained in this study, TEM images of aggregated ruthenium nanoparticles after recycles in olefination, as well as experimental procedure of the control test in mercury poisoning experiments (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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