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Carbonylative Suzuki–Miyaura Coupling Reactions of Aryl Iodides with Readily Available Polymer-Immobilized Palladium Nanoparticles
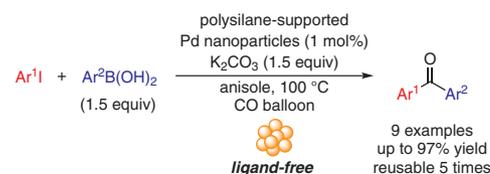
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Dedicated to Professor Barry M. Trost to celebrate his great contributions to organic synthesis

Ar^1I + $Ar^2B(OH)_2$ (1.5 equiv)

polysilane-supported Pd nanoparticles (1 mol%)
K_2CO_3 (1.5 equiv)
anisole, 100 °C
CO balloon

ligand-free

Ar^1—C(=O)—Ar^2

9 examples
up to 97% yield
reusable 5 times

Abstract Polysilane/alumina-supported palladium nanoparticle catalyzed carbonylative Suzuki–Miyaura coupling reactions under ligand-free conditions have been developed to synthesize diaryl ketones. High yields and selectivities were achieved even with low catalyst loading under atmospheric pressure of CO gas. A variety of aryl iodides and aryl-boronic acids could be utilized to afford the diaryl ketones in excellent yields. Moreover, the ligand-free immobilized palladium nanoparticles could be recovered by simple filtration and the catalytic activity could be maintained for several runs.

Diaryl ketones are important building blocks that are present in a variety of molecules, such as pharmaceuticals,[1] bioactive natural products,[1,2] and photosensitizers.[3] These compounds are conventionally accessed from acyl halides via Friedel–Crafts reaction;[1,4] however, the low regioselectivity and requirement for a stoichiometric amount of Lewis acid are significant drawbacks. Among the known methodologies for the synthesis of diaryl ketones, palladium-catalyzed three-component coupling of aryl halides, arylboronic acids, and carbon monoxide offers a promising, potentially ideal, option. Although these reactions have been well documented since the pioneering work by Suzuki and co-workers,[5] several drawbacks remain, including the requirement for high loading of expensive palladium catalysts and ligands, and elevated temperature and pressure.[6]

Heterogeneous catalysts have several advantages over homogeneous catalysts because they are easy to separate from products and are generally reusable. In carbonylative

coupling reactions, the presence of an excess amount of carbon monoxide, which works as a π-acidic ligand, tends to prevent an oxidative addition process and cause metal leaching and aggregation. To address these issues, electron-rich ligand moieties, such as amine,[7] phosphine,[8] thiol,[9] and *N*-heterocyclic carbene,[10] have often been introduced to the support to activate and stabilize Pd species. However, tedious multistep functionalization of the support is necessary for this strategy, and nonfunctionalized carbon-supported Pd catalysts show lower activity and require high-pressure conditions.[11] Therefore, the development of readily accessible heterogeneous Pd catalysts with high catalytic activity and selectivity toward noncarbonylative coupling remains an important challenge.[12]

To convert homogeneous catalysis into the corresponding heterogeneous form, immobilization of metal nanoparticles on a solid support is of great interest because of the reusability, robustness, and high catalytic activity that such systems can offer.[13] Our group developed poly(dimethyl)silane-immobilized metal nanoparticles with alumina as a second support, and the resulting catalysts have been utilized in several reactions, such as hydrogenation[14] and asymmetric 1,4-addition.[15] High catalytic activity, robustness, and reusability were observed in previous reports. These supports are readily available and this catalyst (PPD-100) itself is commercially available. Herein, we examined the use of PPD-100 and readily available polysilane/Al_2O_3-immobilized Pd nanoparticles, in carbonylative Suzuki–Miyaura coupling reactions.

To start our investigation, we selected *p*-iodotoluene (**1a**) and phenylboronic acid (**2a**) as model substrates. The initial reaction was conducted in the presence of PPh$_3$ using a CO gas balloon (Table 1, entry 1) under reported reaction

conditions.[16] The desired product could be afforded with excellent yields and the competitive Suzuki–Miyaura coupling product was only observed in a trace amount. However, a significant amount of Pd leached to the solution, which might be caused by the coordination with PPh$_3$ ligand. Hence, a ligand-free reaction was examined (entry 2). A decreased but acceptable yield was obtained and the amount of metal leached out was dramatically suppressed. The inclusion of organic base, such as Et$_3$N, was detrimental in terms of both yield and metal leaching (entry 3).
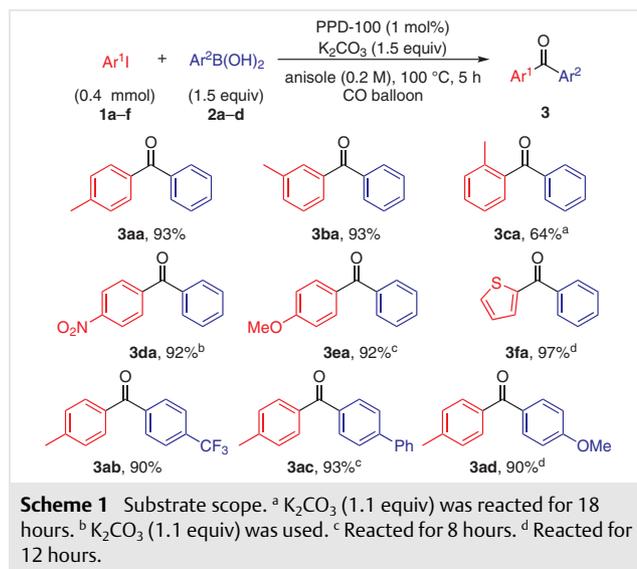
Table 1 Optimization of Reaction Conditions
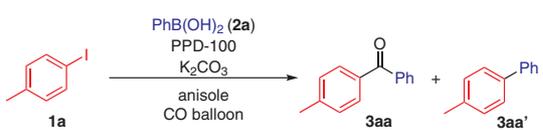
Entry	PPD-100 (mol%)	Conv. (%)[a]	3aa (%)[a]	3aa' (%)[a]	Pd leaching (%)[b]
1[c,d]	3	96	98	trace	24.7
2[c]	3	84	78	7	0.3
3[c,e]	3	58	20	0	15.1
4[f]	1	95	74	21	0.2
5[f,g]	1	full	95	7	0.6
6[f,g,h]	1	full	97	6	–
7[f,g,i]	0.5	full	93	7	–
8[f,g,i]	0.25	99	86	15	–

[a] Determined by gas chromatography (GC) analysis with 1,3,5-trimethoxybenzene as internal standard.
[b] Determined by inductively coupled plasma analysis of the reaction solution after filtration ('–' not determined).
[c] Conditions A: PhB(OH)$_2$ (1.1 equiv), K$_2$CO$_3$ (3.0 equiv), 0.167 M concentration, 80 °C for 5 hours with 0.1 mmol scale.
[d] With PPh$_3$ (3.3 mol%).
[e] Et$_3$N was used instead of K$_2$CO$_3$.
[f] Conditions B: PhB(OH)$_2$ (1.5 equiv), K$_2$CO$_3$ (1.5 equiv), 0.2 M concentration, reacted at 100 °C for 18 hours with 0.4 mmol scale.
[g] CO gas was introduced into the liquid phase by bubbling from a CO balloon.
[h] Reacted for 5 hours.
[i] Reacted for 12 hours.

After intensive screening of the reaction time, temperature, and equivalents of reagents (see Table S1 in the Supporting Information for the full entries), almost full conversion of **1a** could be achieved in larger scale reactions with decreased catalyst loading and base equivalents (entry 4). However, the selectivity dropped, which might be caused by the decreased mixing efficiency between gaseous CO and the liquid phase with the increased reaction scale. Hence, a needle was connected to a CO gas balloon and dipped into the reaction mixture to directly introduce CO gas into the liquid phase by bubbling. With this modified technique, the desired product was afforded with excellent yield and selectivity without a significant amount of metal leaching (entry 5). The desired product could still be afforded with excellent yields with either shorter reaction time (entry 6) or decreased amounts of catalyst (entries 7 and 8).

To our knowledge, these are the lowest reported catalyst loadings to achieve high yield and selectivity under atmospheric pressure of CO gas (Table S2 in the Supporting Information).

With the optimized conditions in hand, a range of aryl iodides (**1a–f**) with different steric and electronic properties were utilized to study the generality of the developed method (Scheme 1). When the effect of substituents on the aryl ring at different positions (**1a**, **1b**, and **1c**) was examined, decreased yields and selectivities towards Suzuki–Miyaura coupling were observed in the case of *ortho*-substituted substrate. Both electron-deficient (**1d**) and electron-rich (**1e**) aryl iodides were tolerated, affording the desired products in excellent yields. Moreover, heteroaryl iodide **1f** was investigated, and an excellent yield could be achieved. Furthermore, the scope of the reaction with arylboronic acids **2a–d** was also explored under the optimized conditions. Despite the different electronic properties, the desired products could be obtained in excellent yields while utilizing slightly modified reaction conditions.

Scheme 1 Substrate scope. [a] K$_2$CO$_3$ (1.1 equiv) was reacted for 18 hours. [b] K$_2$CO$_3$ (1.1 equiv) was used. [c] Reacted for 8 hours. [d] Reacted for 12 hours.

To examine the robustness of PPD-100 catalyst towards the carbonylative Suzuki–Miyaura coupling reactions, the recovery and reuse of catalysts was conducted with the model reaction (Table 2). Upon reactivation with H$_2$ at 100 °C, the catalytic activity of PPD-100 could be maintained with a slight loss in yields within five runs.

In summary, we have developed a carbonylative Suzuki–Miyaura coupling reaction with readily available PPD-100 catalyst.[17] Excellent yields and selectivities could be observed for a variety of substrates under ambient pressure with low catalyst loading without using any ligands. The catalysts could be reused for several runs without significant loss in catalytic activity.

Table 2 Recovery and Reuse of Catalysts

Run	Scale (mmol)	3aa (%)[a]
1	0.80	96
2	0.79	94
3	0.77	93
4	0.76	92
5	0.74	88

[a] Determined by GC analysis with 1,3,5-trimethoxybenzene as internal standard.

Funding Information

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707243.

References and Notes

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(16) Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726.
(17) **Carbonylative Suzuki–Miyaura Coupling Reaction; Typical Procedure (Table 1, Entry 6):** Phenylboronic acid (73.2 mg, 0.6 mmol, 1.5 equiv), K_2CO_3 (82.9 mg, 0.6 mmol, 1.5 equiv), and PPD-100 (40.0 mg with 0.1 mmol/g loading of Pd, 0.004 mmol, 1 mol%) were combined in a two-neck glass tube equipped with a magnetic stirring bar. *p*-Iodotoluene (87.2 mg, 0.4 mmol, 1.0 equiv) was dissolved in anisole (2.0 mL, 0.2 M) and the resulting solution was added to the glass tube using a syringe. A balloon of carbon monoxide, equipped with rubber band and a two-way stopcock, was connected to the glass tube through a needle, and the bubbling of CO was started by opening the two-way stopcock. After starting to input CO, the mixture was stirred for 5 hours at 100 °C. After cooling to room temperature, the reaction mixture was diluted and washed with diethyl ether and the solid catalysts were filtrated off with a membrane filter. The mixture was concentrated, and purified with preparative TLC to afford the desired product, phenyl(*p*-tolyl)methanone, in 93% yield.