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Expression of the Reaction Selectivity and the Substituent Effect in Coupling Reactions by Reducing the Catalyst Loading

Misa Kawase [1], Tomohiro Shibata [1], Shohei Masuu [1], Masaki Yamaguchi [1], Yoshimasa Matsumura [1], Osamu Shimomura [1] and Atsushi Ohtaka [1,*]

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Abstract: The control of stereo-, regio-, and chemo-selectivity in transition-metal-catalyzed coupling reactions is a key topic in organic synthesis. Several methods for controlling selectivity have been reported thus far. On the other hand, the reduction of the catalyst loading in the reaction is one of the most important issues in organic synthesis from the standpoint of green sustainable chemistry. As another advantage of reducing the catalyst loading, the expression of the reaction selectivity and the substituent effect caused by the reduction of the catalyst loading to the parts-par-million (ppm) level in various catalytic reactions is presented herein.

Keywords: selectivity control; catalyst loading; ppm

1. Introduction

The control of stereo-, regio-, and chemo-selectivity in transition-metal-catalyzed coupling reactions is a key topic in organic synthesis. Several methods for controlling selectivity have been reported thus far. For example, stereoselectivity has been controlled using chiral ligands in most cases [1–5]. In the control in the regioselectivity [6–14], Yudin et al. have reported the control of regioselectivity in allylic amination with and without the base [13]. Catalyst-dependent regioselective reactions have also been reported, and Fairlamb et al. achieved site-selective cross-coupling of 2,4-dibromopyridine using specific types of catalysts, such as mononuclear, clusters, or nanoparticles [6]. Regioselective reactions by ligands are the most extensively studied, and it has been reported that the existence or type of ligand affects regioselectivity [8–12,14]. With regard to chemoselectivity [15–22], Newman et al. achieved the selective cross-coupling reaction of phenyl esters with alkyl boranes by controlling decarbonylation with the ligand [16]. In addition, the selectivity control of Ni catalyzed-Ullmann coupling reaction with and without of Pd [17], the control of Suzuki and Buchwald-Hartwig coupling reactions by aryl halides [18], and the control of Hiyama and Ullmann coupling reactions by the valence of the Pd nanoparticles [19] have been reported to date. This study reports the expression of selectivity by reducing the Pd content to the parts-par-million (ppm) level.

Typically, catalytic activity increases with decreasing catalyst concentration in reactions that are catalyzed by molecular catalysts, *in situ*-generated metal nanoparticles, and metal nanoparticles which acts as a reservoir of an active form of the catalyst [23–30], probably because the aggregation of metal species is more likely to occur by increasing the metal content in the reaction solution. Therefore, it is possible to select the reaction field in the solution and on the surface of the nanoparticles by changing the metal content. That is, in the case of a high amount of Pd, Pd easily aggregates and the reaction occurs on the surface of the Pd aggregates. In contrast, the reaction occurs in the solution phase in the case of a low amount of Pd. Indeed, we observed the expression of the substrate-dependent selectivity at mol ppm level of Pd loading in allylic arylation (Scheme 1) [31]. In this previous paper, it is proposed that the reaction with the blanch-type substrate proceeds in solution phase and the linear-type substrate reacts on the surface of the nanoparticle.

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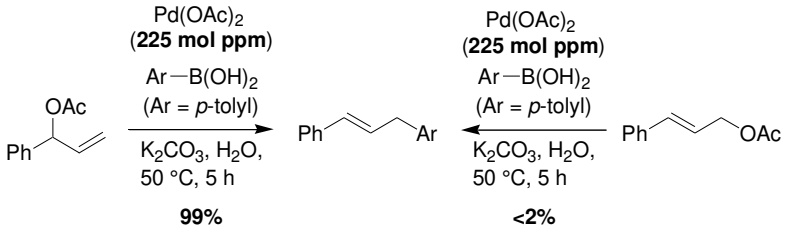
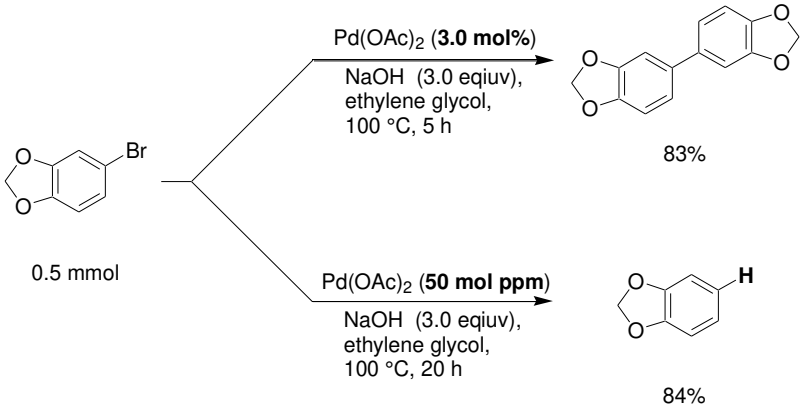


Scheme 1. The substrate-dependent selective allylic arylation at mol ppm level of Pd loading.

2. Results and Discussion

Based on the above-mentioned assumption, we first investigated the chemoselectivity in the reaction of aryl halide. When 15 μmol of $Pd(OAc)_2$ (3.0 mol% relative to the aryl bromide) was heated in ethylene glycol in the presence of NaOH at 100 °C for 5 h and subsequently 5-bromo-1,3-benzodioxole was added and heated at 100 °C for 5 h, Ullmann coupling reaction occurred to give 5,5′-bi-1,3-benzodioxole in 83% yield. 5,5′-Bi-1,3-benzodioxole was obtained in 88% yield even in the presence of dibenzo[a,e]cyclooctene (DCT, 6.0 mol% relative to the aryl bromide), indicating that the Ullmann coupling reaction proceeded on the surface of the Pd aggregates (Crabtree test). In contrast, hydrodebromination afforded 1,3-benzodioxole after heating aryl bromide in the presence of 50 mol ppm of $Pd(OAc)_2$ (Scheme 2). No 1,3-benzodioxole was obtained in the presence of DCT, indicating that the hydrodebromination proceeds in solution phase.



Scheme 2. Chemoselectivity by the catalyst loading.

On the other hand, the lower the catalyst concentration used, the slower the reaction rate, because the reaction rate depends on the collision frequency. That is, a subtle difference in the reaction rate is expected to become more observable by decreasing the catalyst concentration, thereby allowing the expression of selectivity in the reaction. To confirm the aforementioned scenario, the Suzuki coupling reaction with bromobenzene or phenyl trifluoromethanesulfonate was selected as a model reaction because it is well known that the reactivity of these substrates are similar [32]. When the Suzuki coupling reaction was performed in the presence of 2.0 mol% of $Pd(OAc)_2$ and PCy_3 (1.2 equiv relative to Pd) in THF at 50 °C for 24 h [21], quantitative formations of the coupling product were achieved in both cases. In contrast, when the Pd loading was decreased to 150 mol ppm, the coupling reaction occurred smoothly only in the case of bromobenzene, indicating that the reaction selectivity can be controlled by changing the catalyst concentration (Scheme 3a). This result would be derived from the difference in rate of transmetalation step because the oxidative addition of aryl triflate to Pd(0) species is faster than that of aryl bromide [33]. Indeed, the coupling reaction with 4-methylphenylboronic acid took place smoothly in the case of *p*-dibromobenzene to give 4,4′′-dimethyl-1,1′:4′,1′′-terphenyl in 85% yield. While only 4′-methylbiphenyl-4-yl triflate was obtained in 11% yield in the case of 4-bromophenyl trifluoromethanesulfonate (Scheme 3b), suggesting that the transmetalation did not proceed after the oxidative addition in C-OTf bond occurred preferentially. Furthermore, when the reaction of 4-bromophenyl trifluoromethanesulfonate with 4-

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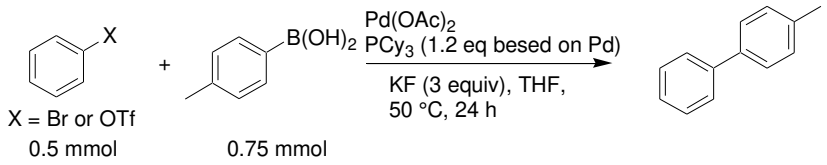
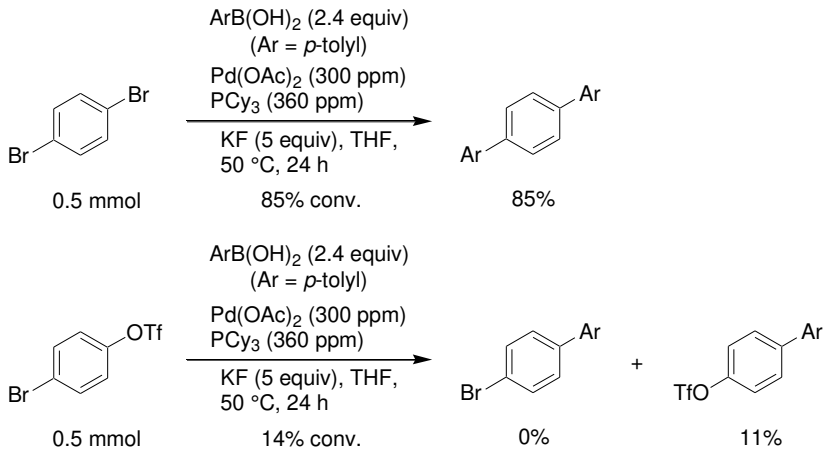
methylphenylboronic acid was performed using 2.0 mol% of $Pd(OAc)_2$ and PCy_3 (1.2 equiv relative to Pd) in THF at 50 °C for 24 h, 4′-methylbiphenyl-4-yl triflate and 4,4′′-dimethyl-1,1′:4′,1′′-terphenyl were obtained in 91% and 4% yields, respectively, whereas at 60 °C, the yields were 75% and 25%, respectively. These results are consistent with the assumption that the transmetalation of Pd-OTf bond is difficult to proceed.

(a) Difference in the reactivity between aryl bromide and aryl triflate at ppm level of Pd.



entry	amount of Pd	X	conv.	yield
1	2 mol%	Br	99%	99%
2		OTf	99%	98%
3	150 ppm	Br	99%	99%
4		OTf	<1%	<1%

(b) Selective synthesis of terphenyl.



Scheme 3. Expression of the substrate-dependent selectivity at ppm level of Pd.

These data prompted us to consider that important information about the reaction mechanism could be obtained by decreasing the catalyst concentration. To confirm the above-mentioned assumption, the Suzuki coupling reaction in aqueous KOH solution was selected as a model reaction because this reaction occurs smoothly using mol ppm Pd content (Table S1). When 1.0 mol% of $Pd(OAc)_2$ was used in the Suzuki coupling reaction of several aryl bromides with arylboronic acids, quantitative yields of the products were obtained even when a substituent was introduced to either the aryl bromide or the arylboronic acid (Table 1, entries 1-5). No substituent effect of aryl bromide was observed, even at 40 mol ppm of $Pd(OAc)_2$ (entries 6-8). In contrast, at 40 mol ppm of $Pd(OAc)_2$, the reaction did not proceed smoothly using the arylboronic acid with an electron-withdrawing group although the coupling product was obtained in a quantitative yield by the reaction with arylboronic acids with electron-donating groups at 40 mol ppm (entries 6-10), which is consistent with the fact that transmetalation with arylboronic acid is the rate-determining step in the Suzuki coupling reaction of aryl bromides [34]. When the competitive reaction was performed using 4-methoxyphenylboronic acid and 4-(trifluoromethyl)phenylboronic acid, 4-methoxybiphenyl and 4-(trifluoromethyl)biphenyl were obtained in 99% and 46% yields, respectively. In the reaction of 4-bromotoluene with 4-(trifluoromethyl)phenylboronic acid to give 4-methyl-4′-

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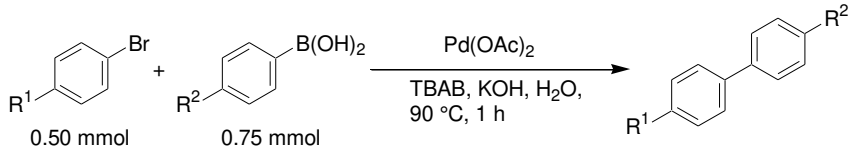
(trifluoromethyl)biphenyl in 15% yield, 85% of 4-bromotoluene was recovered and no other by-product was observed. These results are consistent with the assumption that the transmetalation is the rate-determining step. Furthermore, little effect of steric hindrance was observed. Indeed, at 40 mol ppm of $Pd(OAc)_2$, quantitative yields of the products were obtained even when a methyl group was introduced at *ortho*-position to either the aryl bromide or the arylboronic acid. Interestingly, when the Pd concentration was reduced to 10 mol ppm, the substituent effect of the aryl bromide was also observed (entries 11-13). In contrast, 4-methoxy-4′-methylbiphenyl and 4-(trifluoromethyl)-4′-methylbiphenyl were obtained in 44% and 94% yields, respectively, by the competitive reaction using 4-bromoanisole and 4-bromobenzotrifluoride as the substrate. Although the reason why the reaction of 4-bromobenzotrifluoride proceeded smoothly is unclear now, the results of non-competitive and competitive experiments, as in Schmidt's paper [35], are thought to reflect the rate-determining step and the rate of oxidative addition which is the first step in the reaction, respectively. 4-Methoxy-4′-(trifluoromethyl)biphenyl was obtained in 29% yield by the reaction of 4-benzotrifluoride with 4-methoxyphenylboronic acid using 10 mol ppm of $Pd(OAc)_2$, suggesting that the impurities in 4-benzotrifluoride did not retard the reaction. In addition, this result is consistent with the assumption that the non-competitive experiment reflects the rate-determining step. The observed substituent effect of aryl bromides at 10 mol ppm of $Pd(OAc)_2$ may originate from the rate of transmetalation step or the reductive elimination step [36,37]. These results suggested that the change of the rate-determining step depending on the substrate combination could be confirmed by reducing the catalyst loading.

Table 1. The substituent effect in Suzuki coupling reaction at different Pd amounts.[1]



Entry	Amount of Pd	R^1	R^2	Yield[2]
1	1 mol%	H	Me	99%
2		MeO	Me	99%
3		CF_3	Me	95%
4		H	MeO	99%
5		H	CF_3	99%
6	40 mol ppm	H	Me	91%
7		MeO	Me	97%
8		CF_3	Me	98%
9		H	MeO	99%
10		H	CF_3	26%
11	10 mol ppm	H	Me	65%
12		MeO	Me	41%
13		CF_3	Me	8%[3]
14		H	MeO	84%
15		H	CF_3	7%

[1] The reaction was performed with aryl bromide (0.5 mmol), arylboronic acid (0.75 mmol), TBAB (0.5 mmol), KOH (1.5 mmol), $Pd(OAc)_2$, and H_2O (1 mL) at 90 °C for 1 h. [2] NMR yield. [3] 4-Bromobenzotrifluoride was recovered in 83% yield.

A similar trend was observed for the Hiyama coupling reaction in propylene glycol [38]. When 1.0 mol% of $Pd(OAc)_2$ was used for the Hiyama coupling reaction of several aryl bromides with aryltrimethoxysilanes in propylene glycol, the reaction proceeded smoothly although the yields varied slightly (Table 2, entries 1-5). In contrast, at 100 mol ppm of $Pd(OAc)_2$, the reaction hardly proceeded using 4-fluorophenyltrimethoxysilane, although the coupling product was obtained in

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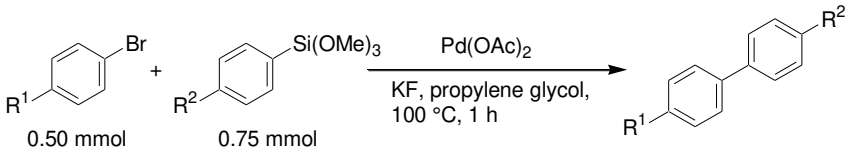
high yield by the reaction with 4-methoxyphenyltrimethoxysilane (entries 9 and 10). This result is consistent with the general trend that transmetalation with arylsilane is the rate-determining step in the Hiyama coupling reaction of aryl bromides [38,39]. At 10 mol ppm of $Pd(OAc)_2$, the Hiyama coupling reaction of 4-bromobenzotrifluoride did not proceed smoothly (entries 11-13). 4-Methylbiphenyl and 4-(trifluoromethyl)biphenyl were obtained in 6% and 24% yields, respectively, in the competitive reaction using 4-bromotoluene and 4-bromobenzotrifluoride. As in the Suzuki coupling reaction, opposite tendencies were observed between competitive and non-competitive reactions. Because the transmetalation of arylsilanolate with arylpalladium species bearing electron-withdrawing groups is faster than that with arylpalladium species bearing electron-donating groups [40], the observed difference may originate from the rate of the reductive elimination step to produce the coupling product [37]. In allylic arylation, although similar yields were obtained at 100 mol ppm level of Pd, the substituent effect of arylboronic acid was become observable at 40 mol ppm of Pd loading (Table 3).

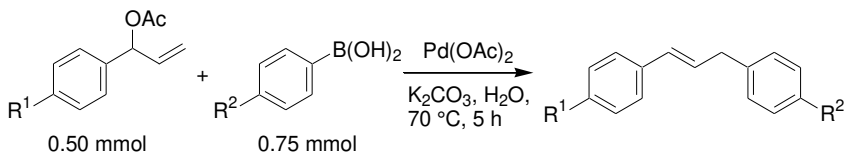
Table 2. The substituent effect in Hiyama coupling reaction in propylene glycol at different Pd amounts [1].



Entry	Amount of Pd	R^1	R^2	Yield[2]
1	1 mol%	Me	H	81%
2		MeO	H	99%
3		CF_3	H	69%
4		Me	MeO	70%
5		Me	F	72%
6	100 mol ppm	Me	H	99%
7		MeO	H	99%
8		CF_3	H	93%
9		Me	MeO	86%
10		Me	F	<1%[3]
11	10 mol ppm	Me	H	90%
12		MeO	H	87%
13		CF_3	H	2%[4]
14		Me	MeO	93%
15		Me	F	0%[3]

[1] The reaction was performed with aryl bromide (0.5 mmol), aryltrimethoxysilane (0.75 mmol), KF (1.5 mmol), $Pd(OAc)_2$, and propylene glycol (1 mL) at 100 ^{0}C for 1 h. [2] NMR yield. [3] 4-Bromotoluene was recovered quantitatively. [4] 4-Bromobenzotrifluoride was recovered in 90% yield.

Table 3. The substituent effect in allylic arylation at low Pd loading [1].



Entry	Amount of Pd	R^1	R^2	Yield[2]
1	100 mol ppm	H	Me	66%
2		MeO	Me	71%
3		CF_3	Me	58%
4		H	MeO	86%

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5		H	CF_3	40%
6	40 mol ppm	H	Me	17%
7		MeO	Me	21%
8		CF_3	Me	20%
9		H	MeO	58%
10		H	CF_3	0%[3]

[1] The reaction was performed with allylic substrate (0.5 mmol), arylboronic acid (0.75 mmol), K_2CO_3 (1.5 mmol), $Pd(OAc)_2$, and H_2O (1 mL) at 70 °C for 5 h. [2] NMR yield. [3] Allyl acetate was recovered in 68% yield.

3. Materials and Methods

3.1. General Comments

All chemicals were commercially available and used without further purification unless otherwise mentioned. ^1H NMR spectra in $CDCl_3$ were recorded with a JEOL ECZ400s spectrometer. Chemical shifts of ^1H NMR are reported in δ ppm referenced to an internal tetramethylsilane standard (δ = 0).

3.2. Procedure for the selective reaction of 5-bromo-1,3-benzodioxole.

5-Bromo-1,3-benzodioxole (100 mg, 0.5 mmol), NaOH (60 mg, 1.5 mmol), ethylene glycol (1 mL), and THF solution of $Pd(OAc)_2$ (1.0 mM, 25 μL, 50 mol ppm) were added to a screw caped vial (No. 02, Maruemu Co., Osaka, Japan) with stirring bar. After stirring at 100 °C for 20 h, the reaction mixture was extracted eight times with diethyl ether. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was analyzed by ^1H NMR and the yield of 1,3-benzodioxole was calculated to be 84%.

3.3. Procedure for the substrate-dependent Suzuki coupling reaction.

Bromobenzene (87.5 mg, 0.5 mmol), 4-methylphenylboronic acid (102 mg, 0.75 mmol), KF (87.2 mg, 1.5 mmol), THF (1 mL), and THF solution of $Pd(OAc)_2$ and PCy_3 (Pd: 1.0 mM, 75 μL, 150 mol ppm; phosphine: 1.2 mM, 75 μL, 180 mol ppm) were added to a screw caped vial (No. 02, Maruemu Co., Osaka, Japan) with stirring bar. After stirring at 50 °C for 24 h, the reaction mixture was extracted eight times with chloroform. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was analyzed by ^1H NMR and the yield of 4,4′′-dimethyl-1,1′:4′,1′′-terphenyl was calculated to be 85%.

3.4. General procedure for Suzuki coupling reaction at mol ppm level of Pd loading.

Bromobenzene (78 mg, 0.5 mmol), 4-methylphenylboronic acid (102 mg, 0.75 mmol), TBAB (161 mg, 0.5 mmol), aqueous KOH solution (1.5 M, 1 mL), and THF solution of $Pd(OAc)_2$ (0.5 mM, 20 μL, 20 mol ppm) were added to a screw caped vial (No. 02, Maruemu Co., Osaka, Japan) with stirring bar. After stirring at 90 °C for 1 h, the reaction mixture was extracted eight times with diethyl ether. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was analyzed by ^1H NMR and the yield of 4-methylbiphenyl was calculated to be 90%.

3.5. General procedure for Hiyama coupling reaction at mol ppm level of Pd loading.

4-Bromotoluene (85 mg, 0.5 mmol), trimethoxyphenylsilane (149 mg, 0.75 mmol), KF (87 mg, 1.5 mmol), propylene glycol (1 mL), and THF solution of $Pd(OAc)_2$ (0.5 mM, 20 μL, 20 mol ppm) were added to a screw caped vial (No. 02, Maruemu Co., Osaka, Japan) with stirring bar. After stirring at 100 °C for 1 h, the reaction mixture was extracted eight times with diethyl ether. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was analyzed by ^1H NMR and the yield of 4-methylbiphenyl was calculated to be 88%.

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3.6. General procedure for Allylic Arylaton at mol ppm level of Pd loading.

α-Vinylbenzyl acetate (0.088 g, 0.5 mmol), 4-methylphenylboronic acid (102 mg, 0.75 mmol), aqueous K_2CO_3 solution (1.5 M, 1 mL), and THF solution of $Pd(OAc)_2$ (1.0 mM, 50 μL, 100 mol ppm) were added to a screw caped vial (No. 02, Maruemu Co., Osaka, Japan) with stirring bar. After stirring at 70 °C for 5 h, the reaction mixture was extracted eight times with diethyl ether. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was analyzed by ^{1}H NMR and the yield of (*E*)-3-(4-methylphenyl)-1-phenylpropene was calculated to be 66%.

3.7. Compounds Data

5,5′-bi-1,3-benzodioxole [CAS: 4791-89-3]: ^{1}H NMR (CDCl3) δ = 6.96-6.99 (m, 4 H), 6.85 (d, *J* = 7.6 Hz, 2 H), 5.99 (s, 4 H); ^{13}C NMR (CDCl3) δ 148.1, 146.8, 135.4, 120.4, 108.6, 107.6, 101.2.

1,3-benzodioxole [CAS: 274-09-9]: ^{1}H NMR (CDCl3) δ 6.86-6.81 (m, 4 H), 5.95 (s, 2 H); ^{13}C NMR (CDCl3) δ 147.5, 121.7, 108.8, 100.7, 31.1.

4-Methylbiphenyl [CAS: 644-08-6]: ^{1}H NMR (CDCl3) δ 7.60-7.55 (m, 2 H), 7.50-7.47 (m, 2 H), 7.43-7.39 (m, 2 H), 7.33-7.29 (m, 1 H), 7.25-7.20 (m, 2 H), 2.38 (s, 3 H); ^{13}C NMR (CDCl3) δ 141.1, 138.3, 136.9, 129.4, 128.7, 128.7, 126.9, 21.1.

4,4′′-dimethyl-1,1′:4′,1′′-terphenyl [CAS: 97295-31-3]: ^{1}H NMR (CDCl3) δ 7.64 (s, 2 H), 7.53 (d, *J* = 7.6 Hz, 2 H), 7.26 (d, *J* = 8.8 Hz, 3 H), 2.39 (s, 3 H); ^{13}C NMR (CDCl3) δ 137.9, 137.2, 134.0, 129.6, 127.4, 127.0, 21.3.

4-Methoxybiphenyl [CAS: 613-37-6]: ^{1}H NMR (CDCl3) δ 7.58-7.51 (m, 4 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 3.85 (s, 3 H); ^{13}C NMR (CDCl3) δ 159.1, 140.7, 133.7, 128.6, 128.0, 126.6, 126.6, 114.2, 55.3.

4-Trifluoromethylbiphenyl [CAS: 398-36-7]: ^{1}H NMR (CDCl3) δ 7.76-7.68 (m, 4 H), 7.68-7.58 (m, 2 H), 7.51-7.38 (m, 3 H); ^{13}C NMR (CDCl3) δ 144.7, 139.7, 129.3 (q, *J* = 32.3 Hz), 129.0, 128.2, 127.6, 127.4, 127.3, 125.6 (q, *J* = 3.2 Hz), 124.3 (q, *J* = 272.1 Hz).

4-Methoxy-4′-methylbiphenyl [CAS: 53040-92-9]: ^{1}H NMR (CDCl3) δ 7.51 (d, *J* = 9.0 Hz, 2 H), 7.45 (d, *J* = 8.1 Hz, 2 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 6.96 (d, *J* = 9.0 Hz, 2 H), 3.84 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR (CDCl3) δ 158.9, 137.9, 136.3, 133.7, 129.4, 127.9, 126.6, 114.2, 55.3, 21.0.

4-Fluoro-4′-methylbiphenyl [CAS: 72093-43-7]: ^{1}H NMR (CDCl3) δ 7.62-7.53 (m, 4 H), 7.51-7.42 (m, 2H), 7.37-7.33 (m, 1 H), 7.16-7.10(m, 2 H); ^{13}C NMR (CDCl3) δ 163.8, 161.3, 140.3, 137.4 (d, *J* = 3.9 Hz), 128.9, 128.8 (d, *J* = 8.7 Hz), 127.4, 127.1, 115.9, 115.7 (d, *J* = 28.8 Hz).

4-Methyl-4′-(trifluoromethyl)biphenyl [CAS: 97067-18-0]: ^{1}H NMR (CDCl3) δ 7.67 (m, 4 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 2.41 (s, 3 H); ^{13}C NMR (CDCl3) δ 144.6, 138.1, 136.8, 129.7, 129.2 (q, *J* = 32.3 Hz), 127.2, 127.1, 125.6 (q, *J* = 4.2 Hz), 124.3 (q, *J* = 271.7 Hz), 21.1.

(*E*)-3-(4-methylphenyl)-1-phenylpropene [CAS: 134539-86-9]: ^{1}H NMR (CDCl3) δ 7.13-7.37 (m, 9 H), 6.45 (dt, *J* = 15.2 Hz, 1 H), 6.34 (dt, *J* = 16 Hz, 1 H) 3.51 (d, *J* = 6.4 Hz, 2 H), 2.33 (s, 3 H); ^{13}C NMR (CDCl3) δ 137.6, 137.1, 135.8, 130.9, 129.6, 129.3, 128.7, 128.6, 127.2, 126.2, 39.1, 21.2.

(*E*)-1-(4-methoxyphenyl)-3-phenylpropene [CAS: 35856-80-5]: ^{1}H NMR (CDCl3) δ 7.35 (d, *J* = 7.6 Hz, 2 H), 7.29 (t, *J* = 12.8 Hz, 2 H), 7.22-7.19 (m, 1 H), 7.16 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.43 (d, *J* = 15.6 Hz, 1 H), 6.34 (ddt, *J* = 6.4, 9.2, 12.8 Hz, 1 H), 3.80 (s, 3 H), 3.49 (d, J = 6.4 Hz, 2 H); ^{13}C NMR (CDCl3) δ 158.1, 137.6, 132.3, 130.8, 129.8, 129.7, 128.6, 127.2, 126.2, 114.0, 55.4, 38.6.

(*E*)-3-phenyl-1-(4-trifluoromethylphenyl)propene [CAS: 723341-12-6]: ^{1}H NMR (CDCl3) δ 7.56 (d, *J* = 8.4 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 7.2 Hz, 2 H), 7.31 (t, *J* = 6.8 Hz, 2 H), (t, *J* = 6.8 Hz, 2 H), 6.45 (d, *J* = 16 Hz, 1 H), 6.32 (tt, *J* = 13.6 Hz, 1H), 3.60 (d, *J* = 6.8 Hz, 2 H); ^{13}C NMR (CDCl3) δ 144.4, 137.2, 132.0, 129.1, 128.7, 128.5, 128.0, 127.5, 126.3, 125.8, 125.5 (q, J = 15.2 Hz), 39.2.

(*E*)-1-(4-methoxyphenyl)-3-(4-methylphenyl)propene [CAS:183621-28-5]: ^{1}H NMR (CDCl3) δ 7.28 (d, *J* = 8.8 Hz, 2 H), 7.13 (s, 4 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 6.34 (d, *J* = 15.6 Hz, 1 H), 6.23-6.16 (m, 1 H),

3.79 (s, 3 H), 3.48 (d, *J* = 6.8 Hz, 2 H), 2.33 (s, 3 H); ^{13}C NMR (CDCl3) δ 158.8, 137.4, 135.7, 130.4, 130.2, 129.3, 128.7, 127.4, 127.3, 114.0, 55.4, 39.0, 21.2.

(*E*)-3-(4-methylphenyl)-1-(4-trifluoromethylphenyl)propene [CAS: 1669332-26-6]: ^{1}H NMR (CDCl3) δ 7.54 (d, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.14 (s, 2 H), 6.46 (t, *J* = 3.6 Hz, 1 H), 3.54 (d, *J* = 4.4 Hz, 1 H), 2.34 (s, 2 H); ^{13}C NMR (CDCl3) δ 141.0, 136.5, 136.0, 132.5, 129.6, 129.4, 128.7, 126.9, 126.3, 125.5 (q, *J* = 15.2 Hz), 39.0, 21.2.

4. Conclusions

In summary, the expression of several selectivity in various catalytic reactions was confirmed by reducing the catalyst concentration. In the reaction catalyzed by *in situ*-generated Pd nanoparticles, the catalytic reaction on the Pd surface and in the solution phase can be controlled by changing the catalyst loading. A slight difference in the reaction rate was confirmed by the decrease in catalyst concentration. Moreover, the substituent effect was confirmed using the Pd catalyst at the mol ppm level, and the rate-determining step in the catalytic reaction could be predicted. Therefore, reducing the catalyst concentration is crucial not only in terms of environmental aspects and industrial applications, but also for synthetic chemistry [41,42]. The investigation in other catalytic reactions is now in progress to extend the versatility of this concept.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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