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The synthesis of a new palladacycle catalyst. Development of a high performance catalyst for Heck reactions

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Abstract

The new palladacycle catalyst **5** was synthesized, and this Pd catalyst showed high catalytic activity with turnover numbers of up to 8 900 000 (mol product per mol Pd) and turnover frequencies of up to 400 000 (mol product per mol Pd per h) in the coupling of aryl halides with olefins. This is the highest catalytic activity of all Heck reactions reported to date.

Keywords: Pd catalysts; Heck reactions.

Heck reactions are one of the most important C–C bond-forming reactions known to date. Generally, these reactions require fairly high catalyst concentrations (1–10 mol%) because of the formation of palladium deposits at high temperature. This limits their attractiveness for large scale commercial applications. Recently, some groups reported high performance Heck reactions with palladacycle catalysts where elemental palladium was formed either not at all, or only in trace amounts.[1–5] Among them, Milstein's catalysts **1** and **2**[2] are very attractive. Considering generality of substrates and synthetic utility, this has proven to be the most effective catalyst for Heck reactions. However, in terms of the practical use of Heck reactions, there are still several problems such as the facile synthesis of the catalysts **1** and **2** and the catalytic activity when aryl halides with electron donating groups are used as substrates. Quite recently, Bedford et al. synthesized the catalyst **3**[4] by changing a phosphine part of the catalyst **4** to a phosphite part, resulting in improvement of the synthetic accessibility and catalytic activity of the catalyst **4**.[1] So we envisioned and synthesized the catalyst **5** which was found to be very efficient to overcome the above-mentioned problems (Fig. 1).

The catalyst **5** was prepared by the method shown in Scheme 1.[7,8] This catalyst was synthesized by a one-pot reaction from 2-iodoresorcinol,[9] constituting an easier preparation of **5** than Milstein's catalysts.[2] The catalyst **5** has been characterized by satisfactory elemental analysis, ^{1}H, ^{13}C, ^{31}P NMR,[6] and single crystal X-ray analysis (Fig. 2),[11] and can be purified by silica gel column chromatography. Moreover, solid **5** shows remarkable stability to air and moisture.

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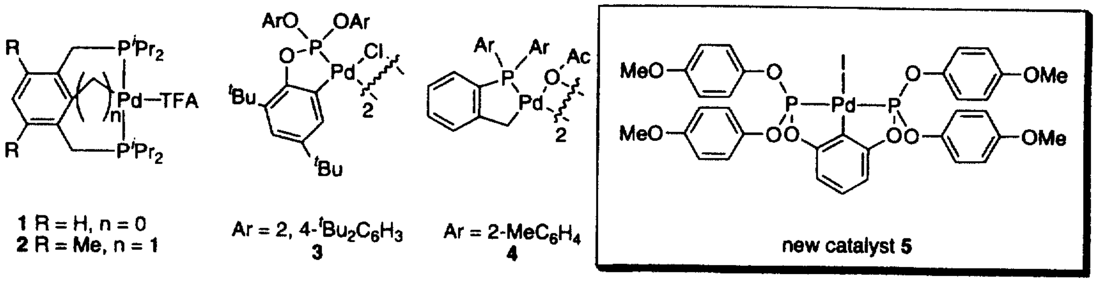


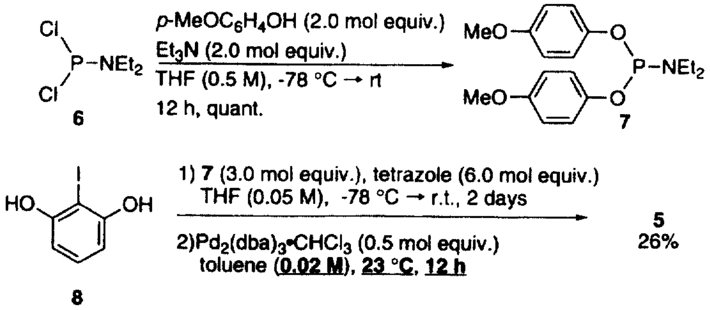
1 R = H, n = 0
2 R = Me, n = 1

Ar = 2, 4-^{t}Bu$_2$C$_6$H$_3$
3

Ar = 2-MeC$_6$H$_4$
4

new catalyst **5**

Figure 1.



Scheme 1.

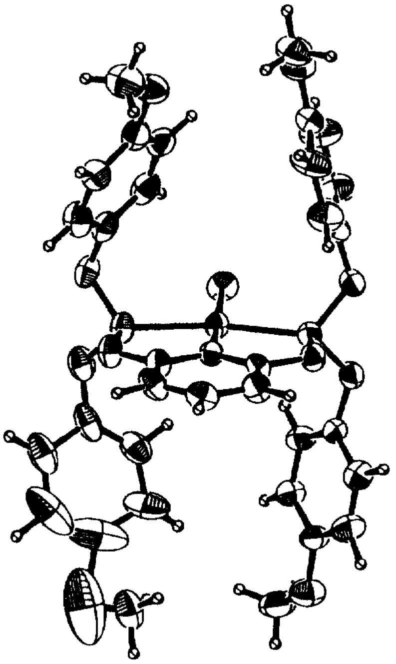


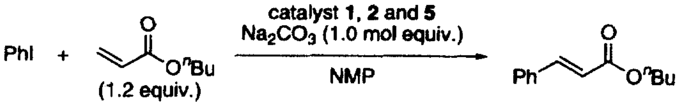
Figure 2. X-Ray crystal structure of 5

Table 1
Heck reactions using 1.0 ppm of the catalyst **5**

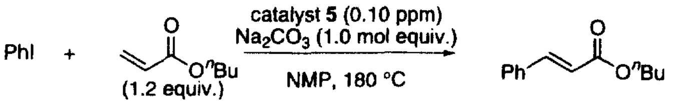
run	conc. (M)	additive	catalyst (ppm)	temp. (°C) /time (h)	yield (%)[b] (S.M. recov.)	TON/TOF (mol product per mol Pd. /mol product per mol Pd per h)
1[a]	-	-	1 (7.0)	140/40	4[c]	5650/140
2[a]	-	-	2 (7.0)	140/64	100[c]	142900/2200
3	2.0	-	5 (1.0)	140/88	20 (68%)	200000/2300
4	1.0	-	5 (1.0)	140/40	43	430000/11000
5	0.50	-	5 (1.0)	140/40	65 (30%)	650000/16000
6	0.25	-	5 (1.0)	140/96	51 (48%)	520000/5400
7	0.50	HQ[d] (1.0 mol %)	5 (1.0)	140/40	68 (30%)	680000/17000
8	0.50	-	5 (2.0)	140/126	43 (46%)	210000/1700
9	1.0	-	5 (1.0)	180/18	95	950000/53000

[a]See the ref. 2. [b]Isolated yield. [c]Determined by GC. [d]HQ is hydroquinone.

The coupling reactions of iodobenzene with *n*-butyl acrylate using 1.0 ppm of the catalyst **5** are summarized in Table 1. First of all, substantial quantities of polyolefins were found to be formed when using the catalyst **5** in this Heck reaction.[4] To prevent this polymerization, optimization of the concentration of the reaction mixture was examined. However, excellent chemical yields were not obtained (up to 65% in run 3–6 of Table 1). To obtain further improvement, we then used hydroquinone (1.0 mol%) as an additive, however without much improvement in chemical yield (68%, run 7, Table 1). In addition, chemical yield could not be improved even when 2.0 ppm of the catalyst **5** was used (run 8, Table 1). Finally, we were pleased to find that nearly quantitative chemical yield (95%) was obtained when the reaction temperature was increased from 140°C to 180°C (run 9, Table 1).



The coupling reactions of iodobenzene with *n*-butyl acrylate using 0.10 ppm of the catalyst **5** at 180°C are summarized in Table 2.[10] Initially we tried the Heck reaction with 0.10 ppm of the catalyst **5** at 180°C (run 1, Table 2), and only moderate chemical yield (60%) was obtained. To improve this yield, 1 mol% of hydroquinone was added to the reaction mixture as an additive, and the chemical yield was moderately improved from 60% to 79% (run 1 and 2, Table 2). To obtain further improvement, the concentration of the reaction mixture was optimized (run 2–4, Table 2). As a result, the highest chemical yield (89%) was obtained when the concentration was 1.5 M (run 3, Table 2). This is the highest catalytic activity of all Heck reactions reported to date with turnover frequencies of 400 000 and turnover numbers of 8 900 000. The best turnover number previously reported for the Heck reaction was 5 750 000 in the coupling of *p*-bromoacetophenone with styrene.[4]



The coupling reactions of *p*-iodoanisole with olefins are summarized in Table 3. In general, it's very difficult to obtain high catalytic activity by palladacycle catalysts when aryl halides with electron donating groups are used as substrates. So we tried to optimize the conditions of the Heck reaction using *p*-iodoanisole and catalyst **5**. Initially 1.0 ppm of the catalyst **5** was used, but satisfactory chemical yield was not obtained (run 3, Table 3). To improve the chemical yield, 5.0 ppm of the catalyst **5** was used, but unexpectedly only slightly improved chemical yield was obtained (run 2, Table 3). These results suggest

Table 2
Heck reactions using 0.10 ppm of the catalyst **5**

run	conc. (M)	additive	time (h)	yield (%)[a] (S.M. recov.)	TON/TOF (mol product per mol Pd /mol product per mol Pd per h)
1	1.7	-	40	60	6000000/150000
2	1.7	HQ[b] (1.0 mol %)	40	79 (10%)	7900000/200000
3	1.5	HQ[b] (1.0 mol %)	22	89	8900000/400000
4	1.2	HQ[b] (1.0 mol %)	62	86	8600000/140000

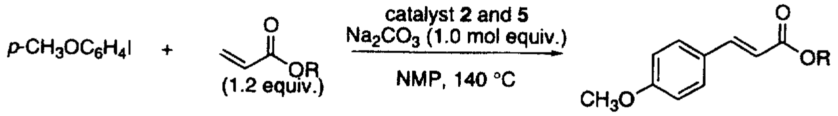
[a] Isolated yield. [b] HQ is hydroquinone.

Table 3
Heck reactions using *p*-iodoanisole as a substrate

run	conc. (M)	R	additive	catalyst (ppm)	time (h)	yield (%)[b] (S.M. recov.)	TON/TOF (mol product per mol Pd /mol product per mol Pd per h)
1[a]	-	Me	-	2 (7.0)	16	100[c]	142900/8900
2	1.0	*n*-Bu	-	5 (5.0)	72	66 (16%)	130000/1800
3	1.0	*n*-Bu	-	5 (1.0)	72	44	440000/6100
4	0.50	*n*-Bu	-	5 (1.0)	72	52 (48%)	520000/7200
5	0.25	*n*-Bu	-	5 (1.0)	96	43 (43%)	430000/4500
6	0.50	*n*-Bu	HQ[d] (1.0 mol %)	5 (1.0)	72	98	980000/14000

[a] See the ref. 2. [b] Isolated yield. [c] Determined by GC. [d] HQ is hydroquinone.

that substantial quantities of polyolefins are formed by the catalyst **5**.[4] To prevent this polymerization, optimization of the concentration of the reaction mixture was again needed, and the best concentration was found to be 0.5 M (when 1.0 ppm of the catalyst **5** was used), giving 52% chemical yield (run 4, Table 3). In order to improve it further, hydroquinone (1.0 mol%) was again used as an additive. As a result, the highest chemical yield (98%) was obtained (run 6, Table 3) with turnover frequencies of 14 000 and turnover numbers of 980 000. This is also the highest activity of all Heck reactions by palladacycle catalysts using aryl halides with electron donating groups as a substrate. The previous highest turnover number for any Heck reaction by palladacycle catalysts using aryl halides with electron donating groups was 142 900 (run 1, Table 3).



Comparing run 7 in Table 1 with run 6 in Table 3, it is obvious that *p*-iodoanisole is more reactive than iodobenzene. This result suggests that the rate-determining step in the Heck reaction of aryl iodide is not the oxidative addition to the actual palladium catalyst, but rather the insertion of the olefins into the aryl palladium intermediate. This assumption is further supported by the Herrmann's comments.[1] The issue of a possible Pd(II)/Pd(IV) cycle in Heck catalysis is currently under debate, particularly for palladacycles.[1–3] We believe that the major pathway in Heck reaction by palladacycle catalyst is Pd(II)/Pd(IV) cycle, because the catalyst **1–5** shows different reactivities. If active species in Heck reaction by palladacycle catalysts is Pd(0), generated from the catalysts **1–5**, these catalysts should show the same reactivity.

In summary, we have synthesized the new palladacycle catalyst **5**, which can be prepared very efficiently. Its catalytic activity is so high that the highest turn over numbers (8 900 000) of all Heck reactions reported to date were obtained when iodobenzene was used as a substrate. The highest turn over numbers (980 000) were also obtained in any Heck reaction by palladacycle catalysts even when *p*-iodoanisole was used as a substrate. Further studies are currently under investigation to improve the yield for other substrates.[12]

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6. Data of **5**: ^{1}H NMR (500.00 MHz, d_6-DMSO): δ 6.42 (1H, dd, J=7.9Hz), 6.34 (8H, d, J=8.9 Hz), 6.06 (8H, d, J=8.9 Hz), 6.01 (2H, d, J=7.9 Hz), 2.91 (12 H,s); ^{31}P NMR (202.35 MHz, d_6-DMSO): 139.5 (s); ^{13}C NMR (125.65 MHz, d_6-DMSO) δ 158.0, 156.6, 142.6, 131.9, 123.0, 115.9, 108.6, 100.4, 56.28.; Anal. calcd for $C_{34}H_{31}IO_{10}P_2Pd$, C; 45.63, H; 3.49. Found, C; 45.91, H; 3.26.
7. The synthesis of **7** is as follows. To a solution of diethylphosphoramidous dichloride **6** (0.836 ml, 5.75 mmol) in THF (5.75 ml), a solution of triethylamine (1.6 ml, 11.5 mmol) and *p*-methoxyphenol (1.43 g, 11.5 mmol) in THF (5.75 ml) was added at −78°C. The resulting mixture was then warmed to room temperature and stirred overnight. The reaction mixture was filtered and the residue was rinsed with hexane. Concentration of the filtrate under reduced pressure gave the desired product **7** (2.00 g, quant.).
8. The synthesis of **5** is as follows. To an anhydrous solution of 2-iodoresorcinol **8** (1.82 g, 7.71 mmol) in THF (76.8 ml), an anhydrous solution of **7** (6.49 ml, 23.1 mmol) and tetrazole (3.23 g, 46.3 mmol) in THF (76.8 ml) was added at −78°C. The resulting mixture was then warmed to room temperature and stirred for 2 days. Evaporation of the solvent under reduced pressure gave a crude mixture of the ligand. To the mixture, CH_2Cl_2 was added and then the resulting mixture was filtered to remove the salt of tetrazole, and the filtrate was evaporated under reduced pressure. To the residue, toluene (385 ml) and $Pd_2(dba)_3\cdot CHCl_3$ (4 g, 3.86 mmol) were added and then the reaction mixture was stirred for 12 h at 23°C. The catalyst **5** was directly purified by silica gel column chromatography (first, hexane only; second, 3:1 hexane:ethyl acetate) to give the desired product (1.82 g, 26%) as a white powder.
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10. The typical procedures are as follows. To a suspension of Na_2CO_3 (6.36 g, 60 mmol) and hydroquinone (66 mg, 0.60 mmol) in NMP (40 ml), iodobenzene (6.71 ml, 60 mmol) was added. Then the mixture was degassed by freeze–pump–thaw cycles (×3). To the degassed mixuture was added *n*-butyl acrylate (10.3 ml, 72 mmol) and then the whole was warmed to 180°C. To this reaction mixture, 0.05 ml of catalyst solution (the catalyst **5** (5.4 mg) in toluene (50 ml)) degassed by freeze–pump–thaw cycles (×3) was added and then the whole was stirred at the same temperature for 22 h. The reaction was quenched with 1000 ml of water and the product was extracted with diethyl ether. The organic extract was dried (K_2CO_3) and concentrated, and the residual oil was purified by flash chromatography (silica gel, hexane:EtOAc (3:1)), furnishing the desired product (11 g, 53 mmol, 89%).
11. Crystal data for **5**: $C_{34}H_{31}O_{10}IP_2Pd$, m=894.86, orthorhombic, $P2_12_12_1$, a=17.172(9), b=18.829(9), c=11.075(6) Å, V=3580(2) Å^3, Z=4, Dc=1.660 g cm^{-1}, μ Mo-K)=15.25 cm^{-1}. The refinement (434 variables) based on F converged with R=0.050 and Rw=0.053 using 3301 unique reflections (I >2.00 $\delta(I)$).
12. We cannot obtain the good results when other substrates like bromobenzene, chlorobenzene and styrene are used.