COMMUNICATIONS

Palladacycles as Precatalysts in Heck and Cross-Coupling Reactions

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Abstract: A variety of palladacycles are shown to catalyze Heck alkenylations with similar efficiencies. The new oxapalladacycle **1** was shown to insert and transmetalate under mild conditions with *n*-butyl acrylate and vinyltributylstannane, respectively. This palladacycle acts as an active (pre)catalyst for cross-coupling and Heck reactions.

The use of bulky and electron-rich phosphines allows one to perform palladium-catalyzed cross coupling and Heck reactions with the least reactive organic electrophiles.[1,2,3] Certain palladacycles are also excellent catalysts for these types of processes. In particular, the phospa-palladacycles developed by Herrmann have found application in a wide variety of palladium-catalyzed transformations.[4,5] In addition, *ortho*-palladated triaryl phosphites,[6] as well as *ortho*-metalated imines,[7] oximes,[8] and benzyl thioethers[9] have been found to be stable yet active catalysts for Heck and cross-coupling reactions. In many cases TONs[10] as high as 10^5–10^6 have been achieved for Heck alkenylations, as well as Suzuki and Stille coupling reactions.

Recently, Shaw has proposed a mechanism for the Heck reaction catalyzed by the metallacycles based on a Pd(II)–Pd(IV) cycle,[5b,11] that is different from that generally accepted for these reactions based on a Pd(0)–Pd(II) catalytic cycle. In this new mechanism, a Pd(II) intermediate was proposed to react with the aryl halide by oxidative addition giving rise to a Pd(IV) complex. However, it is important to note that although Pd(II) complexes with N-donor ligands react readily with alkyl halides to form Pd(IV) complexes,[12] there is no direct evidence for the oxidative addition of an aryl halide to Pd(II).[13,14] In this context, it has been shown that, under the reaction conditions, phospha-palladacycles are reduced to Pd(0) complexes,[15] which probably are the actual catalysts.

We have synthesized the new oxapalladacycles dimers **1** and **2** (Figure 1)[16] to explore their potential as new catalysts for Heck and cross-coupling reactions. These palladacycles bear an alkoxo ligand, which might enhance the reactivity of the Pd center towards organic electrophiles.[17] Herein we report that, although these palladacycles react with alkenes and stannanes under mild conditions, they nevertheless act as active (pre)-catalysts for Heck and cross-coupling reactions. We have also found that other palladium complexes such as the oxapalladacycle **3**,[18] palladated *N,N*-dimethylhydrazones **4–7**,[19] the tetramer **10**,[16] and the palladacycle **11**[20] catalyze cross-coupling or Heck reactions under conditions that are comparable to those reported when using other palladacycle complexes. We also include in this study palladated oxime **8**[8] as well as oximato Pd(II) complex **9**,[21] which may suffer palladation under the conditions of the Heck reactions to afford a palladacycle (Figure 1).[8]

Palladacycle dimer **1** reacted with acrylate **12** in DMF at 60 °C to give cinnamate **13** (89%), after aqueous workup. Complex **1** also reacted readily with vinyltributylstannane in THF at 23 °C to afford styrene **14**[22] in 71% yield by Pd(II)/Sn(IV) transmetalation followed by reductive elimination (Scheme 1). In these reactions, an unstable, highly coordinatively unsaturated Pd(PPh₃) is formally produced. Therefore, we assayed the performance of **1** as a precatalyst for cross-coupling reactions. Indeed, coupling of iodoarenes **15** and **16** with vinyltributylstannane in the presence of 1 mol % of palladacycle dimer **1** proceeded at 23 °C to afford styrenes **17** (67%) and **18** (42%) (Scheme 2). Although these yields are only
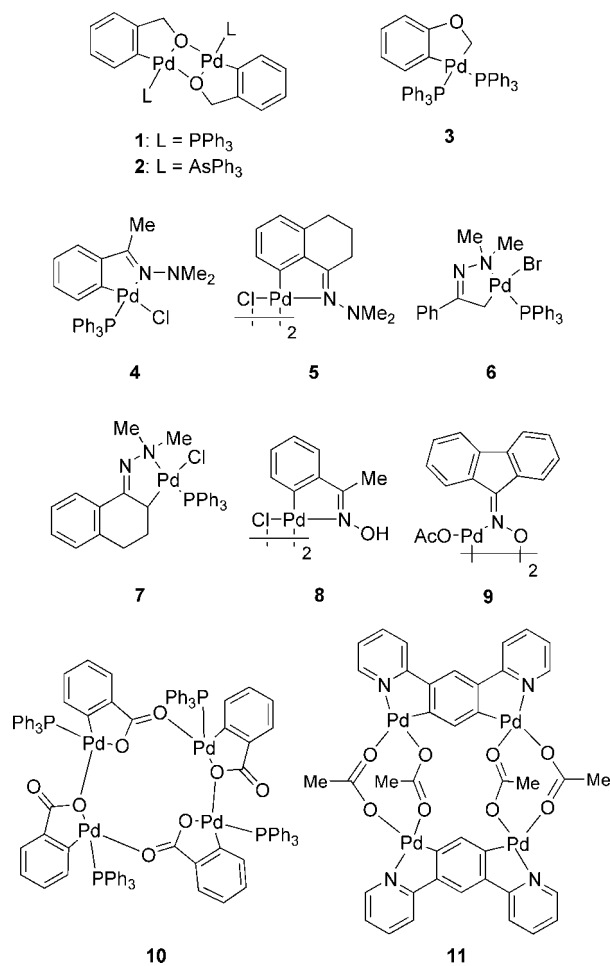
Figure 1. Structures of compounds **1–11**.

plexes **2**, **3**, and **5** (Table 1, entries 2–4). Suzuki reaction of aryl iodide **16** with phenylboronic acid yielded the biphenyl **20** in good to excellent yield (Table 1, entries 5–7). Similarly, phenylation of **15** and **16** under Stille conditions led to **19** and **20**, respectively, by using complexes **2** and **5** as the catalysts (Table 1, entries 8–10).

Scheme 1.

Scheme 2.

moderate, it is noteworthy that the reactions proceed under very mild conditions. Similarly, Suzuki coupling with phenylboronic acid took place at 40 °C to give the biphenyl **19** (Table 1, entry 1). Coupling of phenylboronic acid with **15** also proceeded with com-
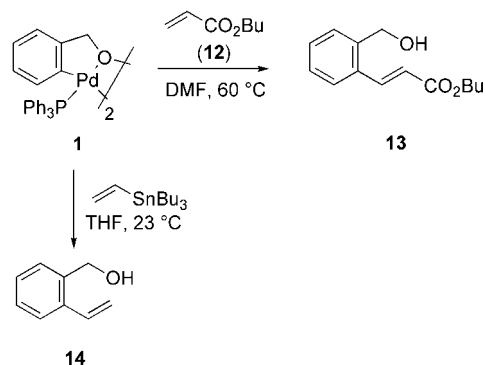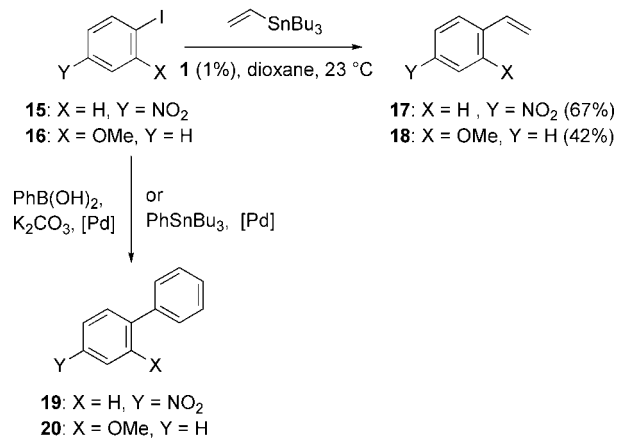
Table 1. Suzuki and Stille reactions of aryl iodides with $PhB(OH)_2$ or $PhSnBu_3$ catalyzed by palladium complexes **1–3**, and **5** (Scheme 2).[a]

Entry[a]	Aryl iodide	Reagent	Pd complex	Solvent	T [°C]	Product	Yield[b] [%]
1	15	$PhB(OH)_2$	1	acetone	40	19	71
2	15	$PhB(OH)_2$	2	DMF	80	19	71
3	15	$PhB(OH)_2$	3	DMF	80	19	74
4	15	$PhB(OH)_2$	5	acetone	56	19	68
5	16	$PhB(OH)_2$[c]	2	DMF	80	20	100
6	16	$PhB(OH)_2$	3	DMF	80	20	86
7	16	$PhB(OH)_2$ [c]	5	DMF	80	20	99
8	15	$PhSnBu_3$	2	DMF	60	19	61
9	15	$PhSnBu_3$	5	DMF	60	19	95
10	16	$PhSnBu_3$	2	DMF	60	20	80

[a] Unless otherwise stated, the couplings of iodides were performed for 15 h with 1 equiv of boronic acid or stannane, 1 mol % palladium complex as the catalyst.
[b] Yield of isolated product.
[c] 2 equiv of boronic acid were used.

We also examined the Heck reaction of *o*-iodoanisole (**16**) and iodobenzene (**21**) with *n*-butyl acrylate (**12**) and styrene (**22**) in *N*-methylpyrrolidone (NMP) with several palladacycles as catalysts (Scheme 3). Remarkably, alkenylation products **23–25** were obtained in all cases with all palladium complexes examined. Selected results are summarized in Table 2.

21: X = H   **12**: Y = CO₂Bu
16: X = OMe   **22**: Y = Ph

23: X = H, Y = CO₂Bu
24: X = H, Y = Ph
25: X = OMe, Y = CO₂Bu
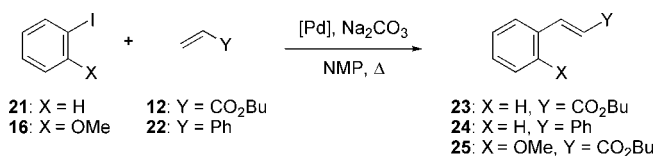
Scheme 3.

Palladacycle **1** catalyzed the formation of *n*-butyl *trans*-cinnamate (**23**) with a TON as high as 7.2×10^5 (Table 2, entry 2). A similar result was obtained with the analogous palladacycle **2** (Table 2, entry 7). Oxa-palladacycle **3**, bearing two PPh₃ ligands, is also an active catalyst for the formation of **23** (Table 2, entries 9–14). Figure 2 shows the formation of **23** as a function of time by using oxapalladacycle **3** as the source of palladium. Although an induction period was not clearly observed in the reactions performed at 80 and 130 °C, in the first case the time dependence for formation of **23** was sigmoidal, indicating the formation of an active catalytic species from precatalyst **3**.

The reaction also proceeds with the less reactive *o*-iodoanisole (**16**) (Table 2, entry 15). It is also interest-
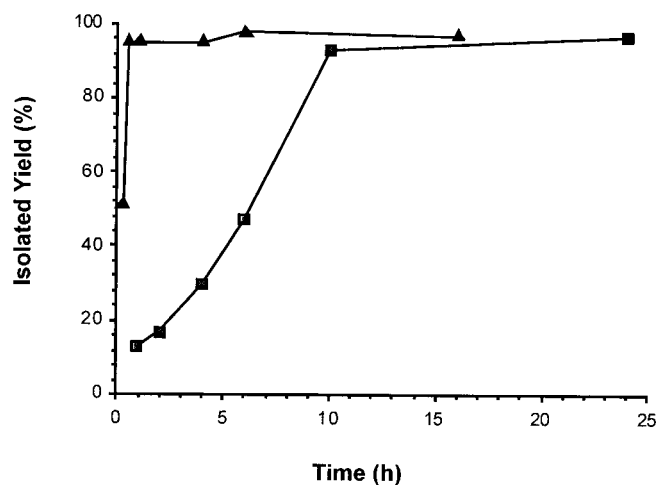
Figure 2. Formation of **23** vs time at 80 °C (■) and 130 °C (▲) catalyzed by palladium complex **3** (1 mol %).

ing to note that the results with aryl- or alkyl-palladated *N,N*-dimethylhydrazones **4–7** (entries 16–20) were very similar to those obtained with the palladated oxime **8**[8] (Table 2, entry 21) and oximato complex **9** (Table 2, entry 22).[25] Heating **1–4** in NMP with Na₂CO₃ at 80 °C for 2 h gave black solutions,[24] that catalyzed the reaction of **21** with efficiencies similar to those of the palladacycles under the same reaction conditions (Table 2, entries 4, 8, 14, and 17). Palladacycles **10** and **11** also led to catalysts for the formation of **23** (Table 2, entries 23–25).

Table 2. Heck reaction of aryl iodides catalyzed by palladium complexes **1–11** (Scheme 3).[a]

Entry	Pd complex	Mol %	T [°C]	Time [h]	Product	Yield[b] [%]
1	**1**	1	130	16	**23**	91
2	**1**	1.0×10^{-4}	160	8	**23**	72[c]
3	**1**	1	60	48	**24**	82
4	**1**[d]	1	80	6	**23**	49
5	**1**	1	80	10	**23**	93
6	**2**	1	130	16	**23**	93
7	**2**	1.0×10^{-4}	160	168	**23**	62
8	**2**[d]	1	80	6	**23**	60
9	**3**	1	80	6	**23**	47
10	**3**	1	130	0.25	**23**	51
11	**3**	1	130	0.5	**23**	95
12	**3**	7.0×10^{-4}	150	18	**23**	59
13	**3**	1.0×10^{-4}	160	168	**23**	71
14	**3**[d]	1	80	6	**23**	56
15	**3**	1	130	6	**25**	79
16	**4**	1	130	16	**23**	100
17	**4**[d]	1	80	6	**23**	56
18	**5**	0.5	130	16	**23**	98
19	**6**	1	130	16	**23**	92
20	**7**	1	130	16	**23**	88
21	**8**	0.5	130	16	**23**	100
22	**9**	0.4	130	16	**23**	99
23	**10**	0.5	130	16	**23**	98
24	**10**	1.0×10^{-4}	160	8	**23**	23
25	**11**	7.0×10^{-4}	160	8	**23**	68[e]

[a] The aryl iodide (**16** or **21**) was allowed to react with 1.8 mol equiv of **12** or **22**.
[b] Isolated yields; [c] 13:1 *E/Z*.
[d] The palladium complex was first heated in NMP with Na₂CO₃ for 2 h at 80 °C.
[e] 4 : 1 *E/Z*.

Additionally, neither **1, 2,** nor **3**[25] reacted with aryl iodides or bromides under stoichiometric conditions. These results, along with the catalysis of Heck, Stille, and Suzuki reaction by complexes that react with the alkenes[26] or organometallic nucleophiles point to catalysis of these reactions by Pd(0) clusters formed *in situ* from the precatalysts.[27] This conclusion is also supported by the fact that structurally diverse palladium complexes **1–11** catalyze Heck reactions with similar efficiencies. Therefore, at least with the palladacycles that we have examined, there is no need to propose Pd(IV) intermediates since the normally accepted mechanism based on Pd(0)–Pd(II) is in accord with the observed results.

Experimental Section

Synthesis of Palladium Complex 9

A mixture of fluorenone oxime (100 mg, 0.51 mmol) and $Pd(OAc)_2$ (116 mg, 0.51 mmol) in HOAc (2 mL) was heated under reflux for 2 h. After cooling, the reaction mixture was filtered and washed with MeOH and Et_2O to furnish the product as an orange solid; Yield: 180 mg (98%); ^{1}H NMR (300 MHz ÇDCl$_3$): δ = 11.35 (d, $J = 8.2$ Hz, 1 H), 7.68 (td, $J = 7.4$, 1.3 Hz, 1 H), 7.61–7.52 (m, 2 H), 7.38 (d, $J = 7.1$ Hz, 1 H), 7.27 (d, $J = 7.6$ Hz, 1 H), 7.07 (td, $J = 7.6$, 1.2 Hz, 1 H), 6.53 (t, $J = 7.6$ Hz, 1 H), 2.23 (s, 3 H), 2.10 (s, 1 H) (the signal at 2.10 ppm disappears upon addition of D_2O); ^{13}C NMR (75 MHz, CDCl$_3$; DEPT): δ = 184.97 (C), 155.65 (C), 140.13 (C), 139.19 (C), 130.92 (C), 130.76 (CH), 130.56 (CH), 128.01 (CH), 127.98 (CH), 127.60 (CH), 123.23 (CH), 120.06 (CH), 119.06 (CH), 23.28 (CH$_3$) (one signal is not observed due to overlapping); anal.: calcd for $C_{50}H_{22}N_2O_6Pd_2 \cdot H_2O$: C 48.87, H 3.28, N 3.80; found: C 48.82, H 3.15, N 3.64.

Cross-Coupling Reactions

A mixture of the aryl iodides **15** or **16** (0.25 mmol) and palladium complex (1 mol %) and either vinyltributylstannane (0.37 mmol), phenylboronic acid (0.26 or 0.50 mmol), or phenyltributylstannane (0.26 mmol) was stirred at the stated temperature for 17 h in the stated solvent (1.25 mL) (see Scheme 2 or Table 1 for reaction temperature, palladium catalyst and amount of organometallic nucleophile). The mixtures were partitioned between Et_2O and aqueous 10% HCl solution. After the usual extractive work-up and chromatography (hexane-EtOAc mixtures), styrenes **17** (67%),[28] **18** (42%),[29] and biphenyls **19**, and **20** were obtained. The NMR data of **19** and **20** were identical to those described.[30] *Caution:* Biphenyl **19** is a carcinogenic compound.[31]

Heck Reactions

The aryl iodide (0.49 mmol), alkene (0.88 mmol), Na_2CO_3 (93 mg, 0.88 mmol), palladium catalyst and hydroquinone (5 mg, 0.05 mmol) were heated in NMP (2.5 mL) (see Scheme 3 and Table 2 for reaction time and temperature).

After being cooled to room temperature, extractive work-up and chromatography gave **23–25**. With the exception of the reaction of entries 2 and 25, **23** was isolated as the pure *E*-isomer.

Acknowledgements

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[23] A palladium complex of unknown structure formed by reaction of fluorenone oxime and PdCl₂ also catalyzed the formation of **23** from **12** (92% yield, 16 h, 130 °C).

[24] The black solutions could be filtered through Celite under Ar without a loss in their catalytic activity.

[25] Similarly, oxapalladacycles related to **3** with other ligands (AsPh₃, COD, phen, dppf)[19] were also unreactive towards iodobenzene or arylbromides bearing electron-withdrawing groups at the *para* position.

[26] Palladacycle **3** reacted with **12** in DMF (60 °C, 72 h) to give *n*-butyl cinnamate (26%) as the major compound. This product presumably arises from a phosphonium salt formed by reductive elimination of **3**.[1d]

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