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Pyrazole and benzothiazole palladacycles: stable and efficient catalysts for carbon–carbon bond formation

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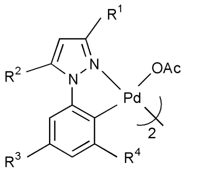
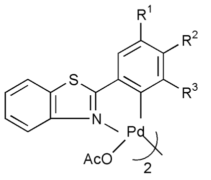
Cyclopalladated phosphine free pyrazole complexes 1 and benzothiazole complexes 2 are excellent catalysts for the Heck vinylation of aryl iodides and termolecular queuing cascades, leading to turnover numbers of > 10^6 in some cases, at moderate temperatures; these catalysts show high thermal stability and are not sensitive to moisture and air.

Palladium salts/complexes are exceptionally versatile and robust catalysts for the construction of carbon–carbon and carbon–heteroatom bonds. Recently a number of novel phosphapalladacycles[1–7] as well as cyclometallated imine complexes[8] have been used in the Heck coupling of aryl halides and acrylates with TONs (turnover numbers) of 10^5–10^6. Suzuki[1,5,8,9] and Stille cross couplings[1,5] have also been performed using some of these palladacycle catalysts with varying TONs of 10^2–10^6. These catalysts exhibit higher air and thermal stability compared with conventional Pd(0) catalysts *e.g.* $Pd(PPh_3)_4$.

The use of phosphine free, nitrogen based ligands in the Heck reaction is a neglected area. We report here that palladacycles **1** and **2**[10] are outstanding catalysts for the Heck reaction and TONs of > 10^6 can be achieved at 70–110 °C. Palladium complexes **1** and **2** are easily prepared, show high thermal stability and are not sensitive to moisture or air. Recently Milstein and coworkers reported non-phosphine cyclopalladated imine complexes for Heck reactions.[8]

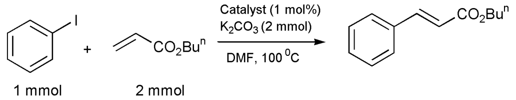


a R^1 = Me, R^2 = Me, R^3 = F, R^4 = H
b R^1 = CF$_3$, R^2 = Me, R^3 = F, R^4 = H
c R^1 = Me, R^2 = CF$_3$, R^3 = F, R^4 = H
d R^1 = Me, R^2 = Me, R^3 = F, R^4 = F
e R^1 = CF$_3$, R^2 = Me, R^3 = F, R^4 = F
f R^1 = Me, R^2 = CF$_3$, R^3 = F, R^4 = F



a R^1 = F, R^2 = H, R^3 = H
b R^1 = H, R^2 = OMe, R^3 = H
c R^1 = F, R^2 = H, R^3 = F
d R^1 = CF$_3$, R^2 = H, R^3 = H
e R^1 = CF$_3$, R^2 = H, R^3 = F
f.R^1 = OMe, R^2 = H, R^3 = H

Initially we explored the Heck reaction between iodobenzene and *n*-butyl acrylate (Scheme 1) in the presence of 1 mol% catalyst in DMF at 100 °C (Table 1).



Scheme 1

Table 1 Heck coupling of iodobenzene with *n*-butyl acrylate using pyrazole and benzothiazole palladacycles at 100 °C in DMF

Entry	Catalyst (1 mol %)	*T*/°C	*t*/min	Conversion[a] (%)
1	**1a**	100	60	100
2	**1b**	100	15	100
3	**1c**	100	90	100
4	**1d**	100	45	100
5	**1e**	100	15	100
6	**1f**	100	60	100
7	**2a**	110	180	95
8	**2b**	110	180	93
9	**2c**	100	30	100
10	**2f**	110	180	100

[a] Conversion estimated by NMR spectroscopy.

Introducing fluorine (−I and π donor) substituents in the heterocyclic ligand *para* and/or *ortho* to the C–Pd bond increases the rate of the reaction (Table 1, entries 1, 4 and 9). Dual *o*- and *p*-fluoro substituents enhance this trend (Table 1, entries 4 and 9). Exchanging the R^1 and R^2 methyl groups for an electron withdrawing trifluoromethyl group in **1** also perturbs the rate. Thus replacing the C(3) methyl group in **1a** by CF$_3$ results in a more active catalyst (Table 1, entries 1 and 2; entries 4 and 5) whilst replacing the C(5) methyl group does not produce rate acceleration (Table 1, entries 1 and 3; entries 4 and 6). The role of the fluoro and trifluoromethyl substituents is to perturb the C–Pd covalent bond, and N–Pd dative bond. When these substituents are optimally located they facilitate a controlled breakdown of the Pd(II) complexes **1** and **2** furnishing the active catalytic species. These palladacycles could operate *via* a Pd(II)/Pd(IV)[12] or Pd(0)/Pd(II) catalytic cycle. It appears probable, on our current evidence that the active species are Pd(0) nanoparticles.[13,14]

Next we briefly studied the effects of base in the Heck reaction employing milder conditions. These results are summarised in Table 2.

Although in some cases competitive reduction of the aryl iodide bond was observed, the use of sodium and potassium formate was found to accelerate the rate of the reaction. When potassium carbonate was employed as the base, the product was furnished in 80% isolated yield (entry 5) after 2 h. However lower isolated yields of product (65–70%) were obtained after

Table 2 Effect of base on the Heck coupling of iodobenzene with *n*-butyl acrylate using pyrazole and benzothiazole palladacycles at 70 °C in DMF

Entry	Catalyst (1 mol%)	Base (2 eq.)	*t*/h	Conversion[a] (%)
1	**1b**	HCO_2Na	1	100
2	**1b**	K_2CO_3	2	61
3	**1b**	HCO_2K	1	100
4	**1b**	$MeCO_2Na$	1	29
5	**1e**	K_2CO_3	2	93
6	**1e**	HCO_2Na	1	100
7	**1e**	HCO_2K	1	100

[a] Conversion estimated by NMR spectroscopy.

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Table 3 Heck coupling of iodobenzene (1 mmol) with *n*-butyl acrylate (2 mmol) using pyrazole and benzothiazole palladacycles for 48 h at 90–110 °C in DMF

Entry	Catalyst/mmol	Base (2 mmol)	*T*/°C	Conversion[a] (%)	TON[b]	Yield[c] (%)
1	**1b** (5×10^{-7})	HCO_2Na	100	75	1.5×10^6	—
2	**1b** (5×10^{-7})	$MeCO_2Na$ or $MeCO_2Cs$	100	< 10	—	—
3	**1e** (5×10^{-7})	HCO_2Na	100	74	1.48×10^6	—
4	**1e** (5×10^{-7})	$MeCO_2Na$	100	0	—	—
5	**1f** (5×10^{-7})	HCO_2Na	100	93	1.8×10^6	—
6	**1a** (5×10^{-7})	HCO_2Na	100	100	2×10^6	50
7	**1a** (5×10^{-7})	K_2CO_3	110	100	2×10^6	78
8	**2c** (1×10^{-6})	K_2CO_3	90	78	7.8×10^5	—
9	**2b** (1×10^{-5})	K_2CO_3	90	98	9.8×10^4	—
10	**2e** (1×10^{-5})	K_2CO_3	90	98	9.8×10^4	—
11	**2f** (1×10^{-5})	K_2CO_3	90	100	1×10^5	—

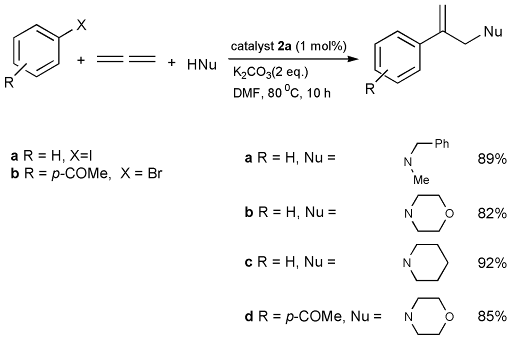
[a] Conversion estimated by NMR spectroscopy. [b] TON based on consumption of iodobenzene. [c] Isolated yields.

1 h when either sodium or potassium formate were used (entries 1, 3, 6 and 7). Sodium acetate was the least effective of the bases evaluated (entry 4), with only 29% conversion after 1 h.

Turnover numbers are summarised in Table 3 for the Heck reaction of iodobenzene (1 mmol) and *n*-butyl acrylate (2 mmol) using either HCO_2Na (2 mmol) or K_2CO_3 (2 mmol) as base in DMF at 90–110 °C for 48 h.

Although TONs of up to 2×10^6 can be achieved when employing sodium formate as base (entry 6) competitive reduction of the aryl iodide bond results in lower isolated yield of Heck product (50%). Employing potassium carbonate as base resulted in a TON of 2×10^6 (entry 7) and 78% isolated yield.

Finally we have briefly explored the scope of these catalysts in a three-component cascade process.[15] Typical examples are shown in Scheme 2.



Scheme 2

In conclusion, we have developed a range of non-phosphine palladacycles which are efficient catalysts with high TONs for Heck reactions under mild conditions and with relatively short reaction times. Studies on other Heck substrates and the mechanism are in progress.

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