Highly efficient C–C coupling reactions using metallated benzylphosphine complexes of palladium

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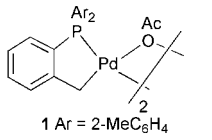
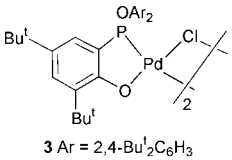
Phosphapalladacyclic complexes synthesised from *ortho*-bromobenzylphosphine ligands are effective catalysts for carbon–carbon bond forming reactions, exhibiting activity that compares with, and in several examples exceeds, that of existing systems.

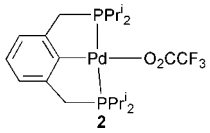
Outstandingly active catalysts for the Heck (Scheme 1) and Suzuki (Scheme 2) coupling reactions using palladacyclic compounds have been reported by Herrmann *et al.* (**1**, turnover numbers (TON, mol (mol Pd)$^{-1}$) for Heck reactions up to 1 M),[1,2] Milstein and coworkers (**2**)[3] and Bedford and coworkers (**3**, TON for Heck up to 5.75 M, but substantial formation of polystyrene occurred and TON to product was not reported).[4]



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



3 Ar = 2,4-Bu$^t_2$C$_6$H$_3$



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We were interested in whether the nature of the Pd–C bond was important in determining catalyst efficiencies, so we attempted the synthesis of a complex similar to that of Herrmann *et al*., but with a metallated benzyl ligand.

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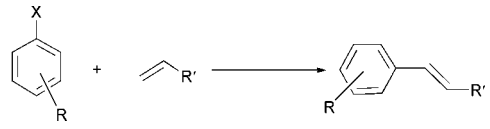
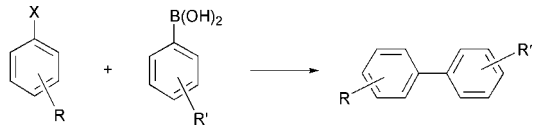
Tertiary *o*-bromobenzylphosphine ligands **4** undergo metallation with [Pd$_2$(dba)$_3$] (dba = dibenzylideneacetone) to yield the palladacycle complexes **5** (Scheme 3) which also exhibit efficient cross-coupling catalytic activity. In common with the studies of Herrmann *et al.*, we have found that aryl groups on the phosphine moiety of the palladacyclic complex give superior catalytic performance than electron-donating alkyl groups,[5] so we have concentrated on complex **5a** (Table 1).

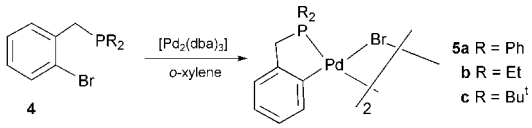
The reaction of 4-bromoacetophenone with *n*-butyl acrylate consistently resulted in reasonable yields of 85–90% when 2×10^{-4} mol% of **5a** was used. As expected, longer reaction times were required to achieve the same yield when a lower reaction temperature was used (entry 2). It is noted that higher



Scheme 1 Heck coupling reaction.



Scheme 2 Suzuki reaction.



Scheme 3 Synthesis of new palladium metallocycles.

Table 1 Heck coupling reactions catalysed by new palladium complexes[a]

Entry	Aryl bromide	Alkene	[Pd](mol%)	*T*/°C	*t*/h	Conv (%)[b]	Yield (%)[c]	TON/mol product (mol Pd)$^{-1}$
1	4-Bromoacetophenone	Butyl acrylate	0.0002	170	20	85.5	85.1	425 300
2	4-Bromoacetophenone	Butyl acrylate	0.0002	130	143	88.9	88.4	442 250
3	4-Bromoacetophenone	Butyl acrylate	0.00002	160	48	63.2	49.3	2464 800
					144	81.6	71.8	3590 400
4	4-Bromoacetophenone	Butyl acrylate	0.000002	160	72	41.5	2.1	1037 500
5	4-Bromobenzaldehyde	Butyl acrylate	0.00001	150	96	37.2	37.2	3720 000
6	Bromobenzene	Butyl acrylate	0.004	130	175	84.5	84.5	21 100
7	4-Bromoanisole	Butyl acrylate	0.004	130	175	67.6	67.6	16 900
8	4-Bromo-*N*,*N*-dimethylaniline	Butyl acrylate	0.02	130	24	19.3	19.3	1 930
9	4-Bromoacetophenone	MMA[d]	0.002	130	48	96.4	96.4[e]	48 200
10	4-Bromophenol	Butyl acrylate	0.02	130	24	21.1	20.0	1 000
11	4-Bromoaniline	Butyl acrylate	0.02	130	48	97.6	2.0	97
12	2-Bromo-6-methoxynaphthalene	Ethene (20 bar)	0.05	140	11	68.0	68.0	1 360
13[f]	4-Bromoacetophenone	Butyl acrylate	0.02	130	24	98.6	98.1	4 900

[a] *Reaction conditions*: 50 mmol aryl bromide, 70–100 mmol alkene, 55 mmol NaOAc, 50 cm^3 *N*,*N*-dimethylacetamide. [b] Based on aryl bromide consumed determined by GC-MS. [c] Of product, determined by GC-MS. [d] Methyl methacrylate. [e] Three products formed. [f] Complex **5c** used.

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Table 2 Suzuki coupling reactions catalysed by new palladium complexes[a]

Entry	Aryl halide	[**5a**](mol%)	*T*/°C	*t*/h	Yield (%)[b]	TON/mol product (mol Pd)$^{-1}$
1	4-Bromoacetophenone	0.002	130	20	100	49 750
2	4-Bromoacetophenone	0.001	130	24	97	96 600
3	4-Bromoacetophenone	0.0002	130	24	67	334 500
4	4-Chloroacetophenone	0.02	130	48	0	0
5	4-Chlorobenzaldehyde	0.01[c]	130	24	27.2[d]	2 724

[a] *Reaction conditions*: 50 mmol aryl halide, 75 mmol phenylboronic acid, 100 mmol K_2CO_3, 150 cm^3 *o*-xylene. [b] Determined by GC-MS. [c] Catalyst **5c**. [d] Conversion is 83.4%, other products are 1-(4-chlorophenyl)-1-phenylmethanol (37.4%) and 1-4-biphenyl-1-phenylmethanol (19%).

temperature (170 °C, entry 1) is required to achieve activity comparable to the Herrmann system (1000 000 TON in 24 h at 130 °C),[5] but no additive/promoting salts (*e.g.* NBu_4Br) are required. In fact we have not observed any increase in activity or catalyst stability when such salts are added to our system. As the catalyst concentration is decreased, higher turnover numbers, in excess of 3×10^6, are achieved at the expense of product selectivity (entries 3 and 4). Indeed, when bromoacetophenone was used as the substrate, Michael addition to the alkene was a competing side reaction, which predominated with higher temperatures and lower catalyst concentration. The Michael addition is reversible so that the selectivity to the coupled product increases with time (Fig. 1). Michael addition was not observed when 4-bromobenzaldehyde was used (entry 5), as the aldehyde proton is less acidic than the α protons of the acetophenone, and a TON of 3.7×10^6 was achieved with good selectivity. There is also evidence to suggest that complex **5a** is deactivated more quickly due to palladium metal aggregation when higher catalyst concentrations are used, resulting in incomplete reaction. Product decomposition at prolonged high reaction temperatures has also proven a problem with certain substrates.

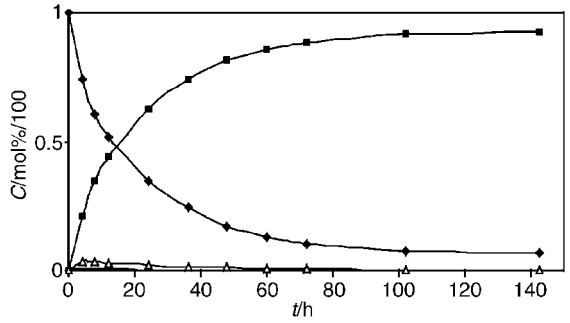

Fig. 1 Diagram of the concentration (*C* in mol%/100) *vs*. reaction time of the Heck reaction of 4-bromoacetophenone (◆) with *n*-butyl acrylate at 130 °C to form *n*-butyl (*E*)-4-acetylcinnamate (■): catalyst **5a** (0.0001 mol%, 0.0002 mol% Pd). Michael addition by-products (△) and (□) are also formed.

Non-activated and deactivated (electron donating) substrates, such as bromobenzene, 4-bromoanisole and 4-bromo-*N*,*N*-dimethylaniline (entries 6–8) require higher catalyst concentrations and reaction times to obtain reasonable yields, but the turnover numbers compare favourably with other palladacyclic systems.[5] Even 4-bromophenol reacted to give 20% of *n*-butyl-(*E*)-4-hydroxycinnamate, but 4-bromoaniline gave almost exclusively Michael addition products. The industrially important reaction of ethene with 2-bromo-6-methoxynaphthalene also occurs with excellent selectivity and good activity (entry 12).

Although the observations of Herrmann that aryl donating groups on the phosphino moiety give higher activity than alkyl groups have been confirmed, complex **5c** catalyses the coupling of 4-bromoacetophenone and *n*-butyl acrylate with excellent selectivity when 0.02 mol% Pd is used (entry 13).

In addition to being an effective Heck catalyst, complex **5a** also exhibits catalytic activity towards the Suzuki coupling, and, to a lesser extent, the Stille coupling (35% yield from 4-bromoacetophenone and Me_3PhSn in 6 h at 110 °C, 3528 turnovers) and the hydroarylation reaction[6] (57% conversion of norbornene to phenylnorbornane using **5a** and bromobenzene in 12 h at 130 °C, 9500 turnovers).

The Suzuki reaction is the coupling of aryl halides with arylboronic acids (Scheme 2). It is mechanistically similar to the Heck reaction, and both the Herrmann[1b] and Bedford[7] complexes have also been reported as active catalysts for this reaction. Some results for the coupling of alkyl halides with phenylboronic acid are displayed in Table 2.

Excellent conversions and selectivities are observed with catalyst concentrations down to 0.001 mol% Pd, after which longer reaction times are required. In contrast to the results of Bedford and coworkers, little activity is observed when toluene is used as the reaction solvent (Bedford obtains 1000 000 TON in toluene in 2.25 h).[7] No activity is observed with aryl chlorides when using complex **5a**, but using the more electron donating **5c** activities higher than those reported by Fu and coworkers[8] using Pd/PBu^t_3 complexes (maximum TON = 200) or than those recently reported by Beller and coworkers[9] using unmetallated monophosphine palladium complexes (maximum TON < 2000) are obtained in the coupling of 4-chlorobenzaldehyde with phenylboronic acid. The major side products of this reaction are 1-(4-chlorophenyl)-1-phenylmethanol and 1-(4-biphenyl)-1-phenylmethanol. Since the latter arises from coupling of the Suzuki product to the boronic acid, the overall turnovers to Suzuki products are *ca.* 4600, which is similar to the best results obtained by Buchwald using di-*tert*-butylphosphinobiphenyl.[10] Other highly active catalysts for Suzuki coupling, which have been reported since the submission of this communication, show very low activities for coupling of chloroaromatics with aryl boronic acids.[11,12]

In conclusion, we have developed an underligated palladium catalyst system that shows comparable activity to existing palladacycle systems but does not require promoting salts. By making the P atom strongly electron donating (Bu^t_2P groups), a catalyst which shows very high activity for coupling of Suzuki chloroaromatic compounds is obtained.

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