

Palladium–tetraphosphine catalysed cross coupling of aryl bromides with arylboronic acids: remarkable influence of the nature of the ligand

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The *cis,cis,cis*-1,2,3,4-Tetrakis(diphenylphosphinomethyl)cyclopentane–[PdCl(C₃H₅)₂] system catalyses the cross coupling of aryl bromides with arylboronic acids with very high substrate–catalyst ratios in good yields; a turnover number of 28 000 000 can be obtained for the addition of 4-bromobenzophenone to benzenboronic acid in the presence of this catalyst.

Biaryl compounds are fundamental building blocks in organic synthesis and their preparation is an important industrial goal.¹ The cross coupling reaction is an efficient method for the synthesis of these compounds.² The classical method of performing this reaction is to employ aryl halides and organometals containing zinc, magnesium or boron in the presence of palladium catalysts. These palladium complexes are generally associated with the triphenylphosphine ligand.² Even if the catalyst formed by association of this ligand with palladium complexes is efficient in terms of yield of adduct, the efficiency in terms of substrate–catalyst ratio is usually low. In general 1–10% of the catalyst must be used. Recently a few bulky monodentate ligands have been successfully used for this reaction.³ One of the most efficient catalytic systems uses a palladium–phosphite complex. The nature of the phosphite ligand has an important effect on the yield of the reaction, and only hindered phosphites such as P(O-2,4-*t*Bu₂C₆H₃)₃ or P(O-*i*Pr)₃ are useful ligands.⁴ A carbene ligand also leads to the formation of palladium catalysts that are more efficient than those of triphenylphosphine for this reaction. With this complex the reaction can be performed with as little as 0.0004% catalyst.⁵ Finally, a very efficient catalyst for this reaction has been prepared with the bulky ligand (*o*-biphenyl)P(*t*-Bu)₂.⁶ If bulky monodentate ligands have been successfully used for this reaction, to our knowledge, the efficiency of bulky polydentate ligands has not yet been demonstrated.

The nature of the phosphine ligand on complexes has a tremendous influence on the rate of catalysed reactions.⁷ In order to find more efficient palladium catalysts we have prepared a new tetrapodal phosphine ligand, *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane or Tedicyp **1**⁸ (Fig. 1) in which the four diphenylphosphino groups are stereospecifically bound to the same face of the cyclopentane ring. The presence of four phosphines close to the metal centre should increase the coordination of the ligand to the metal centre and therefore increase the stability of the catalyst. We have reported recently the first results obtained in allylic substitution using **1** as ligand.⁸ For example, a TON of 680 000 for the addition of dipropylamine to allyl acetate had been observed. In this paper, we wish to report on the superiority of Tedicyp **1** over other

diarylphosphines in the cross coupling of arylboronic acid with aryl bromides.

First, we tried to evaluate the importance of the presence of phosphine ligands on the complex. So we performed the reaction with [PdCl(C₃H₅)₂] as catalyst in the absence of ligand. We observed that the coupling of 2,4-dimethoxybromobenzene **2** or 3-bromothiophene **3** with benzenboronic acid **12** in the presence of 4% catalyst led to the biaryl adducts in low yield (Scheme 1 and 2) (Table 1, entries 1 and 2). Next, we tried to evaluate the difference of efficiency between mono, di and polydentate ligands bearing diphenylphosphino groups for this reaction. For this we compared the rate of the reaction in the presence of a monophosphine PPh₃, a diphosphine dppe, and with our tetraphosphine.⁹ Addition of 3-bromothiophene **3** to benzenboronic acid **12** in the presence of 0.0002% catalyst, led to the addition product in 2% conversion when PPh₃ was used as ligand and 61% conversion with dppe (Table 1, entries 3 and 5). With Tedicyp the yield was 91% in the presence of 0.00002% catalyst (substrate–catalyst ratio of 5 000 000) (Table 1 entry 7) and 16% in the presence of 0.000002% catalyst (Table 1, entry 9). A similar tendency was observed for the addition of 2,4-dimethoxybromobenzene **2** to benzenboronic acid **12**. In the presence of 0.0002% catalyst, only 2% conversion was observed with PPh₃ (Table 1, entry 4). With Tedicyp, in the presence of 0.00002% catalyst, the conversion was 28% (Table 1, entry 6).

The electronic properties of the ligand are certainly of importance for this reaction, as most triarylphosphines are not sufficiently electron-rich to promote a fast oxidative addition of aryl bromides.² However, previous studies have shown that electron-rich trialkylphosphines such as PCy₃ are also rather inefficient ligands for this reaction.¹⁰ In contrast *t*-Bu₂P(biphenyl) is an effective ligand for the Suzuki coupling.⁶ Although electron-rich ligands such as P(Cy)₃ facilitate oxidative addition, they also decrease the rate of the reductive elimination process. These observations indicate that the combination of both steric bulk and electronics is important. The complex formed by association of Tedicyp and [PdCl(C₃H₅)₂] seems to possess a fine balance of steric and electronic properties, which allow a fast catalytic process.

Next we tried to evaluate the scope and limitations of the Tedicyp–palladium complex for this reaction. A survey of

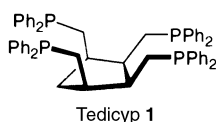
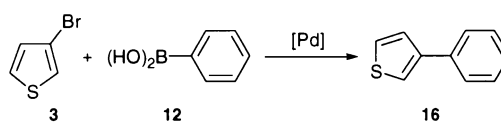
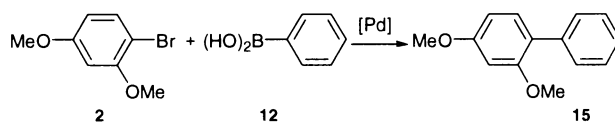


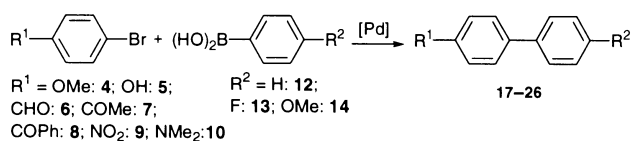
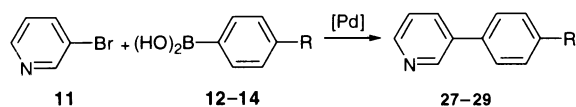
Fig. 1

Table 1 Palladium-catalysed cross-coupling with **12**: influence of the ligand

Entry	Substrate	Ligand	T/h	Substrate-catalyst ratio	Yield (%)
1	3-Bromothiophene	No ligand	24	25	33
2	2,4-Dimethoxybromobenzene	No ligand	48	25	16
3	3-Bromothiophene	PPh ₃	96	500 000	2
4	2,4-Dimethoxybromobenzene	PPh ₃	24	500 000	2
5	3-Bromothiophene	dppe	24	500 000	61
6	2,4-Dimethoxybromobenzene	1	20	5 000 000	28
7	3-Bromothiophene	1	24	5 000 000	91
8	3-Bromothiophene	1	20	100 000 000	34
9	3-Bromothiophene	1	24	500 000 000	16

Conditions: catalyst [Pd(C₃H₅)Cl]₂/ligand 1/1; 3-bromothiophene 1 eq.; benzeneboronic acid **12** 1.5 eq.; K₂CO₃ 2 eq.; 130 °C; xylene.

catalytic cross coupling of aryl bromides with arylboronic acids is provided in Table 2. A wide variety of functional groups are tolerated. Coupling of 4-bromoanisole **4**, 4-bromophenol **5**, 4-bromobenzaldehyde **6**, 4-bromoacetophenone **7** and 4-bromobenzophenone **8** with benzeneboronic acid **12** in the presence of 0.00001% of Tedicyp–palladium complex led to the coupling products in 25, 74, 15, 96 and 98% yields, respectively. A turnover number of 28 000 000 has been obtained for the addition of 4-bromobenzophenone **8** to benzeneboronic acid **12**. Lower TON were observed in the course of the coupling of 1-bromo-4-nitrobenzene **9** and 4-bromo-*N,N*-dimethylaniline **10** with **12**. Coupling of 4-bromoacetophenone **7** with the substituted 4-fluorobenzeneboronic acid **13** and 4-methoxybenzeneboronic acid **14**, in the presence of 0.0001% catalyst, led to the coupling products **25** and **26** in 97% and 80% yield (Scheme 3). When we used 3-bromopyridine **11** in the presence of 0.0001% catalyst a complete conversion was observed for the coupling with benzeneboronic acid **12**. Turnover numbers of 75 000 and 96 000 have also been obtained for the coupling of 3-bromopyridine **11** with 4-methoxybenzeneboronic acid **14** and 4-fluorobenzeneboronic acid **13** respectively (Scheme 4). These results seem to indicate that in general electron-poor aryl bromides can be reacted at higher TON than electron-rich aryl bromides. In contrast, substituents on the arylboronic acid seem to have a minor effect. In all cases, only traces (<1%) of homocoupling products were observed with this catalyst. The best results were usually obtained with K₂CO₃ as base in toluene or xylene as solvents. Use of biphasic solvent systems generally gave inferior results compared to reactions run without added water.

**Scheme 3****Scheme 4**

In conclusion, the use of the tetradentate ligand Tedicyp associated with a palladium complex provides a convenient catalyst for the cross coupling of aryl bromides with arylboronic acids. This catalyst is much more efficient than the complex formed with the triphenylphosphine ligand. This efficiency probably comes from the presence of the four diphenylphosphinoalkyl groups stereospecifically bound to the same face of the cyclopentane ring which probably increases the coordination of the ligand to the metal and prevents precipitation of the catalyst. The complex seems also to possess a fine balance of steric and electronic properties which allow a fast catalytic process. The reaction can be performed with as little as

Table 2 Tedicyp–Pd catalysed cross-coupling¹¹

Aryl bromide	Boronic acid	Product	Substrate-catalyst ratio	Yield (%)
4	12	17	100 000	93 ^a
			10 000 000	25 ^f
5	12	18	1 000 000	98 ^b
			10 000 000	74 ^a
6	12	19	10 000 000	15 ^d
7	12	20	10 000 000	96 ^f
8	12	21	10 000 000	98 ^c
			100 000 000	28 ^a
9	12	22	100 000	26 ^b
10	12	23	100 000	92 ^a
5	13	24	20 000 000	95 ^a
7	13	25	1 000 000	97 ^e
7	14	26	1 000 000	80 ^a
11	12	27	1 000 000	98 ^e
11	13	28	100 000	96 ^d
11	14	29	100 000	75 ^d

Conditions: catalyst see ref. 9; ArX 1 eq; ArB(OH)₂ 1.5 eq.; K₂CO₃ 2 eq.; xylene; 130 °C.

^a 24 h, ^b 48 h, ^c 72 h, ^d 90 h, ^e 115 h, ^f 135 h.

0.000005% catalyst without further optimisation of the reaction conditions. These results represent an inexpensive, efficient, and environmentally friendly synthesis.

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- As a typical experiment, the reaction of 4-bromoacetophenone **7** (1.03 g, 5.2 mmol), benzeneboronic acid **12** (0.92 g, 7.6 mmol) and K₂CO₃ (1.38 g, 10 mmol) at 130 °C for 24 h in dry xylene (10 mL) in the presence of *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane–[PdCl(C₃H₅)₂] complex (5.2 10⁻⁷ mmol) under argon affords the corresponding biaryl adduct **20** after evaporation and filtration on silica gel in 96% (0.98 g) isolated yield.