Palladium Catalysed Cross-Coupling of Aryl Chlorides with Arylboronic Acids in the Presence of a New Tetraphosphine Ligand

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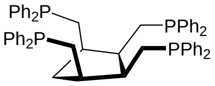
Abstract: *Cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)-cyclo pentane/[$PdCl(C_3H_5)]_2$ system catalyses the cross-coupling of aryl chlorides with arylboronic acids with high ratios substrate/catalyst. A turnover number of 6800000 has been obtained for the addition of the activated 2-chloro-5-(trifluoromethyl)nitrobenzene to benzeneboronic acid in the presence of this catalyst.

Key words: catalysis, palladium, tetraphosphine, arylboronic acids, aryl chlorides

Biaryl compounds are fundamental building blocks in organic synthesis and their preparation is an important industrial goal.[1] The Suzuki cross-coupling reaction is one of the most efficient methods for the synthesis of these compounds.[2] The general procedure to perform this reaction is to employ aryl iodides or bromides and a boronic acid in the presence of palladium catalysts. However, from an industrial point of view, the use of cheaper aryl chlorides is important.[3] Since a few years several ligands have been tested for the coupling of these relatively inert substrates.[4–6] The nature of the ligand has an important effect on the yield of the reaction, and only hindered electron rich ligands led to the coupling adducts in good yields. The most efficient catalytic systems use bulky monodentate ligands such as (*o*-biphenyl)P(*t*-Bu)$_2$,[4b,c] P(O-2,4-*t*$Bu_2C_6H_3)_3$[4g] or P(*t*-Bu)$_3$.[4h] To our knowledge the most efficient ligand for this reaction is PBu(adamantyl)$_2$.[4i] With this ligand a TON (turnover number) of 69000 has been obtained for the coupling of 2-chlorobenzonitrile with benzeneboronic acid.[6] A few bidentate ligands such as dppp,[5c] dppb,[5a] P(o-tolyl)$_3$,[5b] an aminophosphine[5d] or a bis carbene[5e] have also been used, however they seem in general less efficient than bulky monodentate ligands. If monodentate or bidentate ligands have been used for the coupling of aryl chlorides, to our knowledge, the efficiency of tetradentate ligands has not yet been demonstrated.

The nature of the phosphine ligand has an important effect on the rate of transition-metal catalysed reactions. In order to find more efficient palladium catalysts we have prepared a new tetrapodal[7] phosphine ligand, *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphino-methyl)cyclopentane or Tedicyp **1**[8a] (Figure) 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 seems to 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[8] and in Suzuki cross-coupling[9] using **1** as ligand. For example, a TON of 28000000 for the coupling of 4-bromobenzaldehyde with benzeneboronic acid had been observed. Here, we wish to report on the catalysed cross-coupling of arylchlorides with Tedicyp **1** as ligand.



Tedicyp 1

Figure

First, we have investigated the Suzuki reaction of several *para* substituted aryl chlorides with benzeneboronic acid in the presence of the system [$PdCl(C_3H_5)]_2$ / 2 tedicyp in xylene at 130 °C. The results presented in the Table unfold a strong substituent effect on the reaction rate. Electron-withdrawing groups in the aryl chloride support the Suzuki reaction, while electron-donating groups are unfavourable. Turnover numbers of 2500-13000 can be achieved with this catalyst for activated substrates such as 4-chloroacetophenone, 4-chlorobenzaldehyde, 4-chlorobenzonitrile, 1-chloro-4-(trifluoromethyl)benzene and 4-chloronitrobenzene (Scheme, Table). In the presence of the very activated substrate 2-chloro-5-(trifluoromethyl)nitrobenzene an extremely high TON has been obtained: 6800000. On the other hand, with deactivated 4-chloroanisole we obtained a TON of 21.

Next we studied the influence of an *ortho* substituent on the aryl chloride, but no significant steric effect was observed on the rate of the reaction. 2-Chloroacetophenone, 2-chlorobenzaldehyde, 2-chlorobenzonitrile and 1-chloro-2-(trifluoromethyl)benzene led to similar TON's than *para* substituted aryl chlorides.

We also tried to evaluate the importance of the presence of a tetradentate phosphine ligand on the complex. For this we compared the rate of the reaction in the presence of electronically similar ligands: PPh$_3$, dppe, dppb. For the coupling of 4-chloroacetophenone in the presence of 0.1% [$PdCl(C_3H_5)]_2$ / 4 PPh$_3$ only traces of product were observed. The same reaction performed with dppe or dppb led to higher TON's: 220 and 260, respectively. With **1**

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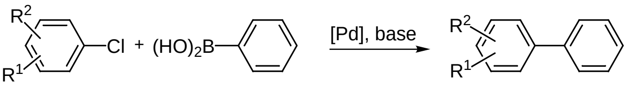
the TON was 2600. The coupling of several other substrates has also been performed using dppe and we observed in all cases that **1** associated to $[PdCl(C_3H_5)]_2$ lead to the formation of a palladium catalyst that is in general more efficient than those of dppe or dppb by a factor of ten. Palladium-tedicyp complex is extremely robust and the reactions can be performed at high temperature without decomposition of the catalyst. The results obtained with activated aryl chlorides using **1** as ligand compare favourably with those reported using bulky electron rich monodentate phosphine ligands. Moreover, Tedicyp is less air-sensitive than these electronically rich phosphines and therefore easier to handle.

During the course of our studies, we also examined several different bases for this reaction. K_2CO_3, Na_2CO_3 and Cs_2CO_3 were found to be the most effective bases. Other bases such as KOH, NaOH or ^{t}BuOK were substantially less effective. In all cases, we also observed the formation of a small amount of homocoupling of the boronic acid.



Scheme

In conclusion, the advantage of this Tedicyp/palladium complex lies in the formation of stable active species and in the length of time it remains stable even at high temperature, a property that is still essential for the activation of chloroarenes. This catalyst is much more stable than the complexes formed with triphenylphosphine ligands or simple diphosphines such as dppe or dppb. This efficiency probably comes from the presence of the four diphenylphosphinoalkyl groups stereospecifically bound to the same face of the cyclopentane ring which probably increase the coordination of the ligand to the metal and prevent precipitation of the catalyst. The Suzuki cross-coupling of electron deficient chloroarenes can be performed with as little as 0.01-0.0001% catalyst. However, this system is not very active for non-activated chloroarenes. For these substrates, a tetraphosphine electronically similar to $P(t\text{-}Bu)_3$ or $PBu(adamantyl)_2$ should lead to better results.

Table Palladium-Tedicyp catalysed cross-coupling[11]

R^1	R^2	Ligand	Ratio substrate/ catalyst	Turnover frequencies (h^{-1})[a]	Yield (%)
4-MeO	H	dppe	100	–	0[b]
”	”	**1**	100	1	21
2-MeCO	H	dppe	1 000	–	0[b]
”	”	**1**	1 000	48	97[b]
”	”	“	10 000	125	25
4-MeCO	H	PPh_3	1 000	–	<2[b]
”	”	dppe	1 000	11	22[b]
”	”	dppb	1 000	13	26
”	”	**1**	1 000	47	95[b]
”	”	**1**	10 000	130	26
2-HCO	H	dppe	1 000	4	8
”	”	**1**	10 000	440	88
4-HCO	H	dppe	1 000	10	21
”	”	**1**	10 000	125	25
2-CN	H	**1**	1 000	44	88
”	”	**1**	50 000	1 450	58
4-CN	H	**1**	10 000	450	90
”	”	**1**	10 000	235	47[c]
”	”	**1**	10 000	50	10[d]
”	”	**1**	100 000	650	13
$2\text{-}CF_3$	H	**1**	1 000	50	100[b]
$4\text{-}CF_3$	H	**1**	1 000	50	100[b]
”	”	**1**	10 000	125	25
$2\text{-}CF_3$	$4\text{-}CF_3$	**1**	1 000	50	100[b]
”	”	**1**	10 000	90	18
$4\text{-}NO_2$	H	**1**	1 000	39	79[b]
”	”	**1**	10 000	235	47[e]
”	”	**1**	100 000	1 200	24
$2\text{-}NO_2$	$3\text{-}NO_2$	**1**	1 000	40	81[b]
”	”	**1**	10 000	250	50
”	”	**1**	100 000	1 150	23
$2\text{-}NO_2$	$4\text{-}CF_3$	**1**	100 000	4 750	95
”	”	**1**	1 000 000	42 000	84
”	”	**1**	10 000 000	340 000	68
”	”	**1**	100 000 000	100 000	2[b]

Conditions: catalyst see ref 10, ArCl (1 eq.), $ArB(OH)_2$ (2 eq.), K_2CO_3 (2 eq.), xylene, 130 °C, 20 h. [a]TOF calculated between initial time and 20 hours. [b]GC yield. [c]Na_2CO_3 was used as base. [d]Cs_2CO_3 was used as base, [e]60 h.

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(10) *Cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclo pentane / $[PdCl(C_3H_5)]_2$ complex was prepared by stirring under argon the tetraphosphine **1** (140 mg, 162 μmol) with $[PdCl(C_3H_5)]_2$ (30 mg, 81 μmol) in dry THF (10 mL) during 10 minutes at room temperature. ^{31}P NMR (162 MHz, $CDCl_3$) δ 25 (w = 80 Hz), 19.4 (w = 110 Hz).

(11) As a typical experiment, the reaction of 2-chloro-5-(trifluoromethyl)nitrobenzene (1.13 g, 5 mmol), benzeneboronic acid (1.22 g, 10 mmol) and K_2CO_3 (1.38 g, 10 mmol) at 130 °C during 20 h in dry xylene (10 mL) in the presence of the *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenyl-phosphinomethyl)-cyclopentane / $[PdCl(C_3H_5)]_2$ complex ($5\ 10^{-6}$ mmol) under argon affords the corresponding biaryl adduct after evaporation and filtration on silica gel in 95% (1.4 g) isolated yield.

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