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Practical synthesis of new and highly efficient ligands for the Suzuki reaction of aryl chlorides

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A practical synthesis of a novel class of phosphine ligands, phosphino substituted *N*-aryl pyrroles (PAP ligands), has been developed. These ligands are applied in the palladium-catalyzed coupling of a variety of aryl and heteroaryl chlorides with phenylboronic acid showing exceedingly high turnover numbers at mild reaction temperatures and even at room temperature.

Biaryls constitute important building blocks for the synthesis of biologically active substances, *e.g.* pharmaceuticals and herbicides.[1] Currently, the most versatile method for the synthesis of substituted biaryls is the cross-coupling reaction of aryl halides and arylboronic acids (Suzuki reaction).[2] Suzuki cross-coupling reactions of aryl halides have been extensively studied in organic synthesis and the methodology has been significantly enlarged in the last decade. Recently, even catalyst-free Suzuki reactions of aryl bromides and iodides were developed using microwave technology.[3] However, less reactive chloroarenes, which are easily accessible with a variety of substituents and are often the most economically interesting substrates do not react under these conditions. Notable catalyst developments for the use of aryl chlorides[4] have been reported by Bedford,[5] Buchwald,[6] Fu,[7] Herrmann,[8] Nolan,[9] us[10] and others.[11] Our main interest is concerned with the practical application of palladium-catalyzed coupling reactions.[12] In this respect the most active ligands for Suzuki reactions, which are composed of sterically demanding basic phosphines, still have significant drawbacks such as the high sensitivity towards oxygen and/or the price (availability) of the ligand. Therefore the development of more efficient ligands, which lead to highly active catalyst systems and can easily be prepared and modified on a larger scale, is still an important topic in this area. Here, we describe for the first time the synthesis and application of new 2-**p**hosphino-1-**a**ryl**p**yrrole ligands **1–6** (PAP ligands, Fig. 1), which fulfil these criteria.

Faigl and co-workers have shown that *N*-aryl pyrroles can be deprotonated selectively at the α-position to the nitrogen atom.[13] We thought that reaction of these carbanions with chlorophosphines should give access to novel ligands, which would be sterically demanding because of their biaryl backbone and electron rich, if suitable chlorophosphines were chosen. Indeed lithiation of different *N*-aryl pyrroles, with *n*-BuLi/TMEDA and subsequent reaction with chlorodiphenylphosphine, chlorodicyclohexylphosphine, di-1-adamantylchlorophosphine and di-*tert*-butylchlorophosphine gave the PAP ligands **1–6** directly in one step. Initially, ligands **1–3** were tested in the coupling of 2-chlorotoluene with phenylboronic acid under various reaction conditions.

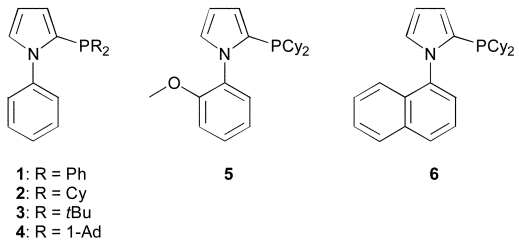
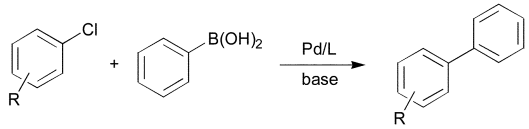


Fig. 1 A novel ligand family: PAP ligands.

The screening of PAP–Ph (**1**), PAP–Cy (**2**) and PAP-*t*-Bu (**3**) in the presence of 0.1 mol% $Pd(OAc)_2$ or 0.05 mol% Pd_2dba_3 (L/Pd = 2/1, toluene) and different bases demonstrates the importance of basic substituents on the phosphorus atom: almost no yield (and conversion) is observed if **1** is applied as ligand. On the other hand, with **2** and **3** as ligands high yields (> 90%) have been observed. Advantageously, best yields have been obtained using potassium phosphate or cheap potassium carbonate as base.

The general usefulness of our new catalyst systems is shown in Table 1. 15 different aryl and heteroaryl chlorides gave the corresponding biaryls in good to excellent yield (74 to > 99%) at low catalyst concentration (0.05 mol% Pd or below). While a number of substrates have been tested in the presence of all synthesized ligands, most often PAP–*t*-Bu (**3**) gave the best results. For example *para*-substituted chloroarenes are coupled efficiently in the presence of only 0.01 mol% palladium and 0.02 mol% **3**. Utilizing **3** electron rich aryl chlorides (entries 5 and 7; 80–99%) are coupled as smoothly as electron deficient ones (entries 1 and 2; > 99%). Consistently, chlorobenzene yields biphenyl in 96% yield under the same conditions (entry 3). Noteworthy are the mild reaction conditions (60 °C) under which the different coupling reactions proceed. Even at room temperature good yields of biaryl products can be obtained in the presence of 0.1 mol% Pd. To the best of our knowledge the obtained turnover number of 800 for the coupling of a non-activated aryl chloride (4-chlorotoluene; entry 4) at room temperature is the highest ever reported. When the reaction temperature is increased to 100 °C the catalyst concentration can be reduced to 0.005 mol% without any decrease in yield, resulting in a TON of almost 20,000 (entry 6). However, when the catalyst concentration is further lowered (0.001 mol% of catalyst) the activity breaks down and product yields are generally below 40%.

In the case of *ortho*-substituted aryl chlorides the catalytic efficiency is strongly dependent on the bulk of the substituent. Relatively large or rigid groups result in the need of a higher catalyst concentration (0.05 mol%) or higher reaction temperatures (100 °C) in order to obtain good yields even if the electronic nature of the substituent leads to a formal activation of the substrate (acetyl, cyano, trifluoromethyl groups; entries 8–11). *Ortho*-substituents that do not interfere with the metal complex, *e.g.* fluoro or methoxy groups (entries 12 and 13), have no detrimental effect on the reaction outcome. However, when two *ortho*-methyl substituents are present in the chloroarene, dicyclohexylphosphino substituted ligands, especially **2**, result in more efficient catalysts than the more bulky *tert*-butyl or adamantyl derivatives (entries 14–18).



Scheme 1 Suzuki coupling of aryl chlorides with phenylboronic acid.

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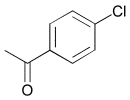
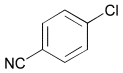
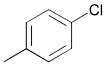
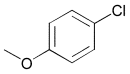
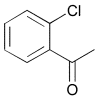
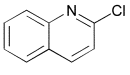
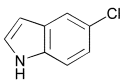
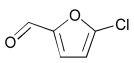
Heteroaryl chlorides can also be arylated efficiently using the new PAP ligands. For example, 3-chloropyridine yields 99% of 3-phenylpyridine in the presence of 0.01 mol% catalyst (entry 19). 2-Chloroquinoline requires some more catalyst (0.05 mol%) to be coupled well (87%, entry 20), because of a supposed dimerization of the oxidative addition product *via* coordination of the nitrogen atom to a second palladium center. For the coupling of 5-chloroindole and 5-chlorofurfural, respectively, the reaction temperature needs to be increased to 100 °C. Then, almost quantitative yields (> 97%) are obtained (entries 21 and 22).

In summary, we have shown that monodentate 2-phosphino-1-arylpyrrole ligands **1–6** (PAP ligands) can be prepared directly from *N*-aryl pyrroles. Hence, ligand synthesis of the PAP family is comparably easy and the shown PAP ligands will be commercially available on the 100 g-scale.[14] The new ligand family allows highly efficient coupling reactions of electron rich as well as electron poor aryl chlorides with phenylboronic acid under mild conditions. In general, excellent yields are obtained at very low catalyst concentrations.

Table 1 Suzuki coupling of aryl and heteroaryl chlorides with phenylboronic acid

Entry	Aryl chloride	Ligand	Cat. conc. [mol%]	Temp. [°C]	Yield [%]	TON
1		**3**	0.01	60	> 99	10,000
2		**3**	0.01	60	> 99	10,000
3		**3**	0.01	60	96	9600
4		**3**	0.1	r.t.	80	800
5		**3**	0.01	60	99	9900
6		**3**	0.005	100	98	19,600
7		**3**	0.01	60	80	8000
8		**3**	0.05	60	80	1600
9		**3**	0.05	60	> 99	10,000
10		**3**	0.05	60	90	1800
11		**3**	0.01	100	91	9100
12		**3**	0.01	60	97	9700
13		**3**	0.01	60	97	9700
14		**2**	0.05	60	72	1440
15		**3**	0.05	60	16	320
16		**4**	0.05	60	15	300
17		**5**	0.05	60	55	1100
18		**6**	0.05	60	35	700
19		**3**	0.01	60	99	9900
20		**3**	0.05	60	87	1740
21		**3**	0.05	100	97	1940
22		**3**	0.05	100	99	1980

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