Combinatorial Libraries with P-Functionalized Aminopyridines: Ligands for the Preparation of Efficient C(Aryl)–Cl Activation Catalysts**

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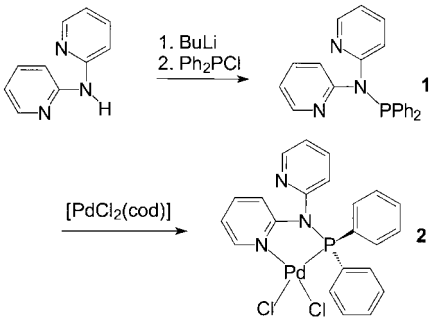
Today the principles of combinatorial chemistry are used routinely by pharmaceutical companies for the discovery of lead structures.[1] Recently, these methods have started to find use in such areas as materials science[2] and catalysis research.[3] Both in biochemistry and in materials science the methods used have led to an increase in efficiency: by combination of amino acids or nucleotides a plethora of compounds has been generated[1] with the help of a diverse method repertoire,[4] and the parallelization or miniaturization of materials-science libraries has resulting in considerable time-saving.[5] However, in catalyst research the preparation of homogeneous-catalyst libraries with the synthetic strategies of organometallic chemistry gives rise to problems. We report here on a new class of ligands, the P-functionalized aminopyridines, which can be prepared efficiently and in great diversity by use of parallel synthesis under the exclusion of air. These ligands form C(aryl)–Cl activation catalysts for the Suzuki reaction with Group 10 metals.

Di(2-pyridyl)amine reacts with BuLi and chlorodiphenylphosphane to form **1** in high yields (Scheme 1). According to the NMR spectrum, the reaction of **1** with $[PdCl_2(cod)]$ (cod = cyclooctadiene) occurs almost quantitatively to form the complex **2**, the molecular structure of which was determined by X-ray crystallography (Figure 1).[6] Compound **1** coordinates with the palladium atom to form a five-membered ring. The bond lengths and angles determined for **2** are in agreement with those of other P,N-ligand–dichloropalladium complexes.[7] Ligands, such as **1** and complexes or precatalysts, such as **2** should be accessible simply and in large diversity by parallel synthesis.[8] Many bipyridylamines, 2-aminopyridines,[9] or similar N-heterocyclic amines can be prepared from primary amines by palladium-catalyzed arylamination.[10] These may be P-functionalized in parallel in simple synthetic steps and treated with metal salts to form complexes (such as, **1** in Scheme 1). In this way 60 different catalyst systems were synthesized[11] and tested in parallel in the preparation of 4-cyanobiphenyl from 4-chlorobenzonitrile and phenylboronic acid by the Suzuki coupling.[12] Selected results are summarized in Table 1. The abbreviations for the ligands used are explained in the box below. One of the best ligands in the palladium-complex-catalyzed Suzuki coupling[13] is TtBP,[14] which is reproducibly surpassed by B4MPm.[15]



Scheme 1. Synthesis of **1** and **2**.

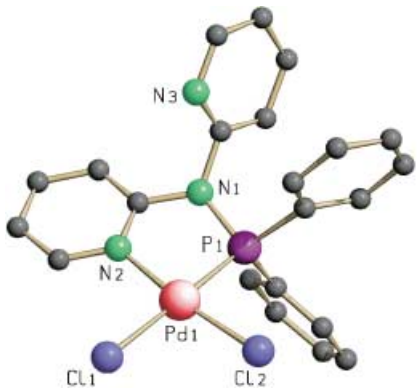


Figure 1. Molecular structure of **2**. Selected bond lengths [Å] and angles [°]: N1-P1 1.702(5), N2-Pd1 2.053(5), P1-Pd1 2.1951(15), Cl1-Pd1 2.3731(14), Cl2-Pd1 2.303(2); N2-Pd1-P1 83.15(14), P1-Pd1-Cl2 89.52(6), N2-Pd1-Cl1 95.00(14), Cl2-Pd1-Cl1 92.36(6).

Table 1. Conversions of selected catalyst systems (Suzuki reaction, synthesis of 4-cyanobiphenyl). In total 60 systems were tested.

Entry	Base	Ligand	Catalyst precursor[a]	Yield [%]
1	K_2CO_3	B4MPm	$[Pd_2(dba)_3]$	quant
2	NaO*t*Bu	BPyPy	$[Pd_2(dba)_3]$	quant
3	NaO*t*Bu	B4MPm	$[Pd_2(dba)_3]$	quant
4	K_2CO_3	BPyPy	$[Pd_2(dba)_3]$	83
5	K_2CO_3	TtBP	$[Pd_2(dba)_3]$	80
6	K_3PO_4	BPy_2(o-P)Py	$Pd(OAc)_2$	78
7	NaO*t*Bu	DtBPCl	$[Pd_2(dba)_3]$	76
8	K_3PO_4	PPmPm	$[Ni(cod)_2]$	65

[a] dba = dibenzylidenacetone.

Nomenclature of the compounds $R_2PNR'R''$

R = phenyl (P), cyclohexyl (C), *tert*-butyl (B)
R′, R″ = 2-pyridyl (Py), 3-methyl-2-pyridyl (3M), 4-methylpyridyl (4M), 6-methyl-2-pyridyl (6M), 4,6-dimethyl-2-pyridyl (4,6M), 6-methoxypyridinyl (Mx), 2-pyrimidyl (Pm), pyrazinyl (Pa), trimethylsilyl (Si), 4-methylquinolin-2-yl (L), 2-(*N*,*N*-di-2-pyridyl)phenyl (Py_2(o-P))

Further ligands: tri(*tert*-butyl)phosphane (TtBP), *rac*-2,2'-bis(diphenylphosphanyl)-1,1′-binaphthyl (binap), 1,3-bis(diphenylphosphanyl)propane (bdpp), di(*tert*-butyl)chlorophosphane (DtBPCl), triphenylphosphane (PPh_3)

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In addition to palladium, other metals are also attracting increasing interest for use in C–C coupling, for example, nickel, which is relatively reduction-stable and less expensive.[16] Thus, the activity of the novel catalysts was also investigated in the nickel-complex-catalyzed coupling of non-activated *p*-chloroanisole with phenylboronic acid to form 4-methoxybiphenyl. Selected results of the 84 screening experiments are summarized in Table 2.[11] Here too the P-functionalized aminopyridines in combination with nickel and palladium are, under screening conditions, superior to the known catalyst systems.[14, 17] Remarkably, ligands which in combination with nickel salts act as catalysts show almost no catalyst activity or selectivity with palladium salts and vice versa.[18]

Table 2. Conversions of selected catalyst systems (Suzuki reaction, synthesis of 4-methoxybiphenyl).

Entry	Base	Ligand	Yield [%][a]	Yield [%][b]
1	K_3PO_4	C46MMx	14	53
2	K_2CO_3	BPmPm (1 equiv)	53	0
3	K_3PO_4	BPmSi	19	31
4	K_3PO_4	TtBP	4	6
5	K_3PO_4	PPh_3	1	38

[a] With $[Pd_2(dba)_3]$. [b] With $[Ni(cod)_2]$.

The following may be concluded from these investigations: palladium or nickel complexes which are stabilized by P-functionalized aminopyridines can activate C(aryl)–Cl bonds efficiently and possess a stable metal–ligand bond (formation of a five-membered ring chelate, see Figure 1). This property allows such catalyst systems to couple non-activated chloroarenes with problematic functional groups, that is those which can poison the catalyst. A summary of the 48 screening experiments[11] on the coupling of 3-chloropyridine to 3-phenylpyridine with phenylboronic acid is shown in Table 3. Complexes with ligands which have established

Table 3. Activation of 3-chlorpyridine (Suzuki reaction, synthesis of 3-phenylpyridine). In total 48 systems were tested.

Entry	Base	Ligand	Catalyst precursor	Yield [%]
1	K_3PO_4	B4MPm	$Pd(OAc)_2$	90
2	K_3PO_4	B4MPm	$[Pd_2(dba)_3]$	89
3	K_3PO_4	BPyPy	$[Pd_2(dba)_3]$	86
4	K_3PO_4	BPaPa	$[Pd_2(dba)_3]$	79
5	K_3PO_4	B4MPm (0.5%)	$[Pd_2(dba)_3]$ (0.5%)	76
6	K_3PO_4	B4MPm (0.25%)	$[Pd_2(dba)_3]$ (0.25%)	69
7	K_2CO_3	BPyPy	$[Pd_2(dba)_3]$	58
8	K_3PO_4	TtBP	$[Pd_2(dba)_3]$	5
9	K_3PO_4	*rac*-binap	$[Pd_2(dba)_3]$	1
10	K_3PO_4	bdpp	$[Pd_2(dba)_3]$	0

themselves with non-activate chloroarenes (TtBP) or with activated pyridines (2- or 4-chloropyridine; binap, bdpp)[10] exhibit lower activity than B4MPm or, in some cases, even none. A similar situation occurs in the reaction of 2-chloro-4,6-dimethoxytriazine to 2,4-dimethoxy-6-phenyltriazine with phenylboronic acid (Table 4).

Table 4. Activation of 2-chloro-4,6-dimethoxytriazine (Suzuki reaction, synthesis of 2,4-dimethoxy-6-phenyltriazine, catalyst precursor: $[Pd_2(dba)_3]$). In total 19 systems were tested.

Entry	Base	Ligand	Yield [%]
1	K_3PO_4	CPmPm	89
2	K_3PO_4	BPaPa	79
3	K_3PO_4	BPmPm	77
4	K_3PO_4	TtBP	72
5	K_3PO_4	*rac*-binap	47
6	K_3PO_4	bdpp	31

We have thus demonstrated that combinatorial libraries with efficient catalyst systems can be developed for scientifically and industrially important reactions[19] by using simple synthetic strategies from organometallic chemistry. A broad application of the P-functionalized ligand class may be expected since many homogeneous catalysts with late transition metals contain pyridine and/or phosphane ligands.[20] The time-saving and simple preparation of the ligands is especially advantageous.

Experimental Section

All reagents are commercially available and were used without further purification. Air- and water-sensitive materials were handled with the exclusion of air and moisture in Schlenk flasks or in a glove box (Braun, Labmaster 130). Solvents (Aldrich and Cambridge Isotope Laboratories) were dried with sodium tetraethylaluminate or molecular sieve (CH_2Cl_2, CD_2Cl_2).

1: Under argon, *n*BuLi (2.5 M, 1.6 mL, 4 mmol) in hexane was added to di(2-pyridyl)amine (0.68 g, 4 mmol) in diethyl ether (10 mL) at $-77\,^{\circ}C$. After 1 h chlorodiphenylphosphane (0.72 mL, 0.882 g, 4 mmol) in diethyl ether (4 mL) was added dropwise. During the addition the reaction mixture became brilliant yellow. After stirring for 48 h at room temperature the solution was transferred into another Schlenk flask by filtration and evaporated to dryness, the residue extracted twice each time with a mixture of diethyl ether (10 mL) and THF (10 mL). The solvents were distilled off in vacuum into a flask cooled with dry ice and the residue was dried at 1 mbar and room temperature. Yield: 1.42 g (quantitative). Elemental analysis (%) calcd for $C_{22}H_{18}N_3P$: C 74.35, H 5.11, N 11.82; found: C 74.50, H 5.31, N 11.68; ^1H NMR (C_6D_6): $\delta = 8.16$ (m, 2H), 7.73 (m, 4H), 6.97 (m, 6H), 6.57 (d, 2H), 6.33 (ddd, 2H); ^{13}C NMR (C_6D_6): $\delta = 158.35$, 158.29, 148.81, 138.74, 138.54, 136.97, 136.07, 136.06, 133.76, 133.55, 132.04, 128.77, 128.53, 128.11, 118.37, 118.26; ^{31}P NMR (C_6D_6): $\delta = 69.37$.

2: Under argon, dichloromethane (4 ml) was added to $[PdCl_2(cod)]$ (0.071 g, 0.25 mmol) and **1** (0.089 g) in a Schlenk flask. After layering with diethyl ether (6 mL) pale yellow crystals were obtained after about 1 week. These were collected by filtration, washed with diethyl ether (4 mL), and dried in vacuum. Yield: 0.10 g (75%). Elemental analysis (%) calcd for $C_{22}H_{18}Cl_2N_3PPd$: C 49.60, H 3.41, N 7.89; found: C 49.29, H 3.51, N 7.81; ^1H NMR (CD_2Cl_2): $\delta = 9.43$ (m, 1H), 8.24 (m, 1H), 7.88 (m, 5H), 7.66 (m, 1H), 7.50 (m, 4H), 7.37 (m, 5H), 7.08 (m, 1H), 7.02 (m, 1H), 6.70 (m, 1H), 6.54 (m, 1H); ^{13}C NMR (CD_2Cl_2): $\delta = 150.4$, 150.1, 149.1, 140.2, 138.5, 133.4, 133.3, 132.2, 127.8, 127.7, 125.9, 125.3, 122.8, 121.7, 121.7, 120.8, 118.0; ^{31}P NMR (CD_2Cl_2): $\delta = 99.2$.

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[7] A search in the CSD data bank for P,N-ligand dichloropalladium complexes with a five-membered ring gave the following bond lengths [Å] and angles [°] (mean values): Pd-N 2.074(12), Pd-P 2.206(5), Pd-Cl 2.33(1); N-Pd-P 84.7(5).

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[11] Conditions: all reactions were carried out in the parallel apparatus (see ref. [8]) under argon. In the case of the diphenyl- and dicyclohexyl-substituted phosphanyl residues the ligands were prepared in parallel by the metalation of the amines with *n*BuLi at -77 °C and the addition of an equivalent of chlorodiphenylphosphane or chlorodicyclohexylphosphane. The preparation of the catalyst systems with di(*tert*-butyl)phosphane substituents was carried out in situ when one equivalent of each of amine, chlorodi(*tert*-butyl)phosphane, and the catalyst precursor were heated together with the base (K_3PO_4, K_2CO_3, Na_2CO_3, or NaO*t*Bu) in a Schlenk flask for 1 h at 60 °C. The substrates were then added at room temperature. The screening reactions were carried out as follows: the base was dried in vacuum at 130 °C for 24 h and transferred into the flask in a vacuum box. The stock solutions of the substrates (haloarenes and phenylboronic acid, concentration $c = 1$ mol L^{-1}, 1 mL, or 1.2 mL) and reagents (ligands and catalyst precursors, $c = 0.025$ mol L^{-1}) were then added and the stirred mixture heated to the reaction temperature. The evaluation of the reaction products was carried out by gas chromatography at the end of the reaction. 1st Library: THF, 1.2 mmol base, 1 mmol 4-chlorobenzonitrile, 1.2 mmol phenylboronic acid, 1 % catalyst precursor, 1 equiv ligand, 60 °C, 24 h; 2nd library: THF, 1.2 mmol base, 1 mmol 4-chloroanisole, 1.2 mmol phenylboronic acid, 1 % catalyst precursor, 1 equiv ligand, 60 °C, 24 h; 3rd library: 1,4-dioxan, 1.2 mmol base, 1 mmol 3-chloropyridine, 1.2 mmol phenylboronic acid, 1 % catalyst precursor, 1 equiv ligand, 60 °C, 24 h; 4th library: 1,4-dioxan, 1.2 mmol base, 1 mmol 2-chloro-4,6-dimethoxytriazine, 1.2 mmol phenylboronic acid, 1 % catalyst precursor, 1 equiv ligand, 60 °C, 24 h. A full description of the experiments can be found in the Supporting Information.

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[18] The increased activity of nickel catalysts compared to palladium catalysts could be explained by the action of the free heteroaryl residue as a "secondary base": the protons released in the cleavage step could be more rapidly abstracted and transferred to the auxiliary base (e.g. K_3PO_4) outside of the actual reaction sphere. Further experiments on this are planned.

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