

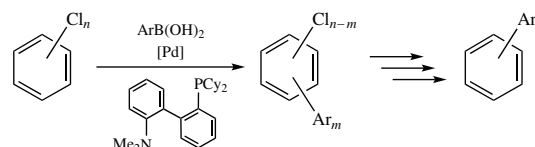
Buchwald ligand-assisted Suzuki cross-coupling of polychlorobenzenes

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Screening of four Buchwald ligands for the cross-coupling of isomeric di-, tri- and tetrachlorobenzenes with arylboronic acids revealed that good yields of exhaustive substitution can be best provided by 2-dicyclohexylphosphino-2'-(dimethylamino)biphenyl (DavePHOS).



Keywords: polychloroarenes, biaryls, cross-coupling, arylboronic acids, Buchwald ligands.

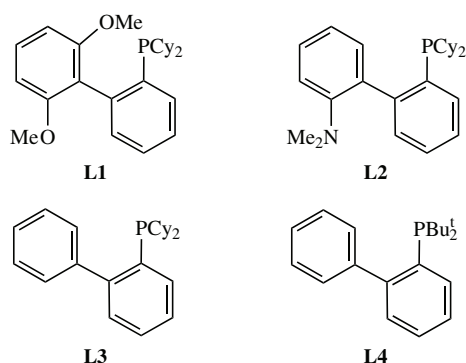
Polychloroarenes (PCAs) are the environmentally hazardous materials. The mostly recognized means for their chemical utilization is catalytic hydrogenolysis of the C–Cl bonds.¹ However, chemical value of thus prepared aromatic hydrocarbons is not great as such compounds are generally accessed by cheaper and simpler ways. On the other hand, PCAs seem prospective starting materials for the preparation of potentially useful substances if the transformations of poorly reactive C–Cl bonds into C–C or C–heteroatom ones become easy to accomplish. The chemical properties of PCAs were systematized in reviews.^{2,3}

The first efforts to attain the cross-coupling diversity for chloroarenes, in particular PCAs, were based on the Kumada reactions involving organomagnesium counterparts while other cases of C–C coupling were scarce (see review³). The product yields were mostly moderate. In the middle of 2000s, PCAs were subjected to the Suzuki coupling with phenylboronic acid in the presence of palladium source, Pd(dba)₂ or Pd(OAc)₂, in combination with PBu₃ as the ligand⁴ or imidazolium salts.⁵ The reactions could be also carried out under ligand-free conditions.^{6,7} In all these studies, good preparative results were rarely achieved due to incomplete conversion, low selectivity and undesired parallel hydrodechlorination.

Within the past decades, the efficient catalytic systems suitable for cross-coupling of non-activated chloroarenes have been suggested. In particular, the Buchwald systems^{8,9} comprising palladium source and special sterically hindered tertiary biphenyl-2-ylphosphines proved very efficient and convenient

for the Suzuki performance. Several reports on the Suzuki coupling of PCAs have emerged.^{10–12} Very promising results with PCAs were delivered using 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **L1** (S-PHOS) as the ligand.¹² However, the authors¹² disclosed no information on catalytic behavior of other Buchwald-type ligands in the PCA coupling reactions. To remove this gap, we decided herein to examine several other available phosphine ligands, in particular, compounds **L2–L4** in such reactions. Previously,¹³ we successfully employed catalytic system Pd(OCOCF₃)₂/**L1** for the Suzuki coupling of some mono- and polychloroarenes in supercritical carbon dioxide.

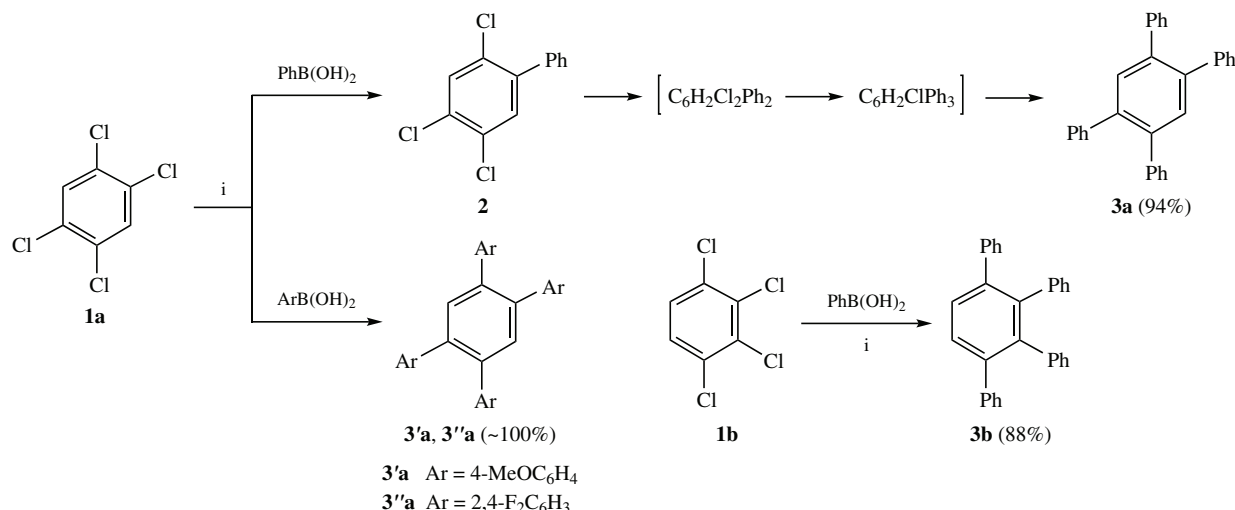
In this work, the most experiments were carried out based on reported conditions of the Buchwald procedure,^{8(a)} namely, Pd(OAc)₂/ligand molar ratio of 1:2, K₃PO₄, toluene, 90 °C, 7–8 h.[†] The ligand tests were performed using 1,2,4,5-tetrachlorobenzene **1a** as the model substrate (Scheme 1, Table 1). In our hands (entry 1), the results with the use of S-PHOS (**L1**) were not as good as documented in the comprehensive study.¹² Under the similar conditions, ligand **L2** [DavePHOS, 2-dicyclohexylphosphino-2'-(dimethylamino)biphenyl] provided the highest conversion of PCA **1a** (see Table 1, entries 1, 2, 6, 8), with the use of 1.1 equiv. PhB(OH)₂ the monosubstitution product **2** having been formed with the good chemoselectivity (entry 2). When potassium phosphate was used as the base, contribution of side hydrodechlorination was regularly insignificant. In case of potassium methoxide possessing reductive properties, the cross-coupling was accompanied by the exhaustive hydrodechlorination



[†] General procedure for the cross-coupling [cf. ref. 8(a)]. A 10 ml Schlenk tube equipped with a stirring bar was charged with Pd(OAc)₂ (7 mg, 0.03 mmol), ligand **L1–L4** (0.06 mmol), PCA (0.5 mmol), PhB(OH)₂ (66 mg, 0.55 mmol) and K₃PO₄ (339 mg, 1.6 mmol), and then capped with a rubber septum. Air was removed by triple evacuation and filling with argon. Deaerated toluene (1 ml) was then injected. The reaction was processed at 85–90 °C for ca. 7 h. A heterogeneous aliquot was mixed with more toluene (~1:10), filtered through a short pad of silica, and the filtrate was analyzed by GC–MS.

For exhaustive arylation of tri- and tetrachlorobenzenes (0.25 mmol), Pd(OAc)₂ (4 mg, 0.018 mmol), ligand **L2** (14 mg, 0.036 mmol), ArB(OH)₂ (1.65 mmol) and K₃PO₄ (492 mg, 2.32 mmol) were applied.

For preparative isolation and product identification, see Online Supplementary Materials.



Scheme 1 Reagents and conditions: i, Pd(OAc)₂, ligand **L2**, K₃PO₄, PhMe, 90 °C, 7–8 h.

Table 1 Optimization of the cross-coupling of 1,2,4,5-tetrachlorobenzene **1a** with PhB(OH)₂ assisted by ligands **L1–L4**.^a

Entry	Ligand	PhB(OH) ₂ (equiv.)	Base	Product composition (GC–MS) (mol%)				
				Coupling products ^b				unreacted 1a
				mono- 2	di-	tri-	tetra- 3a	
1	L1	1.1	K ₃ PO ₄	22 + (1 + 1)	7 + 4 + 7	–	–	55 + (3)
2	L2	1.1	K ₃ PO ₄	97	0.4 + 0.6	–	–	2
3	L2	1.1 ^c	MeOK	(81)	(5 + 5 + 9)	–	–	–
4	L2	2.5	K ₃ PO ₄	20 + (5)	22 + 17 + 34 + (2)	–	–	–
5	L2	6.6 ^d	K ₃ PO ₄	–	–	6	94	–
6	L3	1.1	K ₃ PO ₄	45 + (1 + 1)	4 + 4 + 6	1 + 6	–	31 + (1)
7	L3	6.6 ^d	K ₃ PO ₄	–	2 + 2 + 5	40 + (4)	47	–
8	L4	1.1	K ₃ PO ₄	32 + (1)	1 + 2	–	–	60 + (4)
9	L4	6.6 ^d	K ₃ PO ₄	29 + (2)	4 + 11 + 32	10	10	2

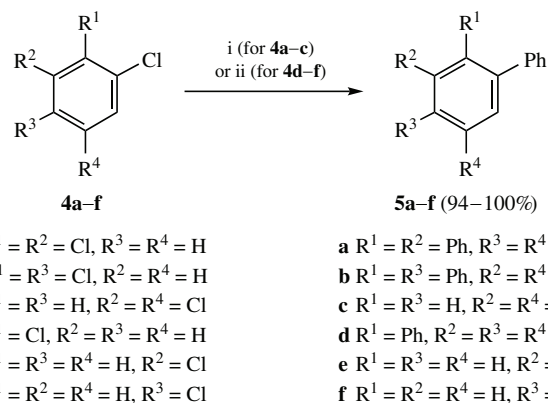
^a Conditions: 6 mol% of Pd(OAc)₂, 12 mol% of **L1–L4**, K₃PO₄ (1.5–3 equiv. to PhB(OH)₂), PhMe, 90 °C, 7–8 h. ^b Parentheses relate to hydrodechlorinated analogues. ^c In dioxane. ^d 7.2 mol% of Pd(OAc)₂, 14.4 mol% of the ligand.

(entry 3). Raising the amount of the cross-counterpart to 2.5 equiv. provided the growth for the fraction of disubstitution products (entry 4). When this parameter reached value of 6.6 equiv., 1,2,4,5-tetraphenylbenzene **3a** was formed in the analytical yield of 94% (entry 5). Under these conditions, relative 1,2,4,5-tetraarylbenzenes **3'a** and **3''a** were obtained in good yields (see Scheme 1). Isomeric 1,2,3,4-tetraphenylbenzene **3b** was also synthesized from the corresponding precursor **1b** in a yield of 88% (the rest 12% were the isomeric Ph₃C₆H₂Cl). However, two other tested ligands **L3** and **L4** appeared much less efficient promoters for the cross-coupling between 1,2,4,5-tetrachlorobenzene **1a** and PhB(OH)₂ under optimal conditions [7.2 mol% Pd(OAc)₂, 14.4 mol% of a ligand, K₃PO₄] than ligand **L2** affording regioisomeric mixtures of products of incomplete conversion (see Table 1, entries 6–9).

The proposed **L2**-based catalytic system proved to be very efficient in arylation reactions of isomeric trichlorobenzenes **4a–c** with phenylboronic acid (5 equiv.) to produce the corresponding triphenylbenzenes **5a–c** in nearly quantitative yields (Scheme 2). Less active dichlorobenzenes **4d–f** in reaction with excess PhB(OH)₂ (3 equiv.) gave mixtures of mono- and disubstitution products. Luckily, their full conversion into terphenyls **5d–f** was achieved on replacement of potassium phosphate with more basic hydroxide.

The Pd(OAc)₂/**L2** catalyzed reaction of hexachlorobenzene with excess (8.6 equiv.) PhB(OH)₂ afforded a mixture of tri-, tetra- and pentaphenylated benzene derivatives in a 10:70:20

ratio, each group was comprised of regioisomers and some hydrodechlorination by-products. Hexaphenylbenzene was never detected in these experiments. These results do not contradict those of the study¹² where C₆Cl₆ was transformed into C₆Ph₆ in moderate yield with the use of catalytic system PdCl₂(MeCN)₂/**L1** and with the very prolonged processing (the preparative yields of C₆Ph₆ were achieved on moving to more active hexabromo-benzene).



Scheme 2 Reagents and conditions: i, PhB(OH)₂ (5 equiv.), Pd(OAc)₂, ligand **L2**, K₃PO₄, PhMe, 90 °C, 7–8 h; ii, PhB(OH)₂ (3 equiv.), Pd(OAc)₂, ligand **L2**, KOH, PhMe, 90 °C, 7–8 h.

In conclusion, we have compared several Buchwald ligands **L1–L4** in the Suzuki cross-coupling of non-activated polychloroarenes with arylboronic acids. Among the ligands tested, 2-dicyclohexylphosphino-2'-(dimethylamino)biphenyl (DavePHOS) provided the best results, quantitatively converting di-, tri- and tetrachlorobenzenes into the corresponding polyarylbenzenes. Some recent catalytic systems and reactants¹⁴ may also represent good challenge for employing toward PCAs.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.05.039.

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