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New Air-Stable Planar Chiral Ferrocenyl Monophosphine Ligands: Suzuki Cross-Coupling of Aryl Chlorides and Bromides[†]

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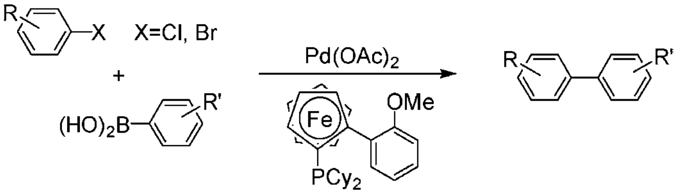
ABSTRACT



A novel class of planar chiral electron-rich monophosphine ligands has been developed. The modular design allows a short and efficient synthesis of an array of aryl-ferrocenyl derivatives carrying the donating bis(dicyclohexyl)phosphino moiety. These new ligands have successfully been applied in the palladium-catalyzed Suzuki cross-coupling of activated as well as nonactivated aryl chlorides at room temperature. The asymmetric coupling of an aryl bromide and an aryl boronic acid was also tested, giving ees up to 54%.

The palladium-catalyzed cross-coupling reaction of main-group organometallic reagents with alkenyl and aryl halides is one of the most versatile synthetic transformations for constructing carbon−carbon bonds.[1] Though much work has been devoted to the development of this particular class of reactions, it was not until recently that low-cost and ready available aryl and alkyl chlorides were successfully included as electrophilic coupling partners. The key to this success was the use of electron-rich and sterically hindered phosphine or carbene ligands.[2] With these ligands, the reluctance of the aryl and alkyl chlorides to undergo oxidative addition to palladium could apparently be overcome.[3] Simple trialkylphosphines as tri-*tert*-butylphosphine (t-Bu$_3$P) and tricyclohexylphosphine (Cy$_3$P) have been shown to be good ligands for many cross-couplings employing aryl chlorides.[4] Furthermore, Buchwald and co-workers have demonstrated that dialkyl biarylphosphines possess unique reactivity in many of these reactions.[5] Driven by these observations, we now report on the synthesis and application of novel members of our aryl-ferrocenyl (pseudo biarylic) family of ligands in the palladium-catalyzed Suzuki cross-coupling of aryl chlorides.[6] These dialkyl arylferrocenylphosphines (aryl-MOPFs) are, in contrast to most electron-rich phosphines, air stable and hence easy to handle.

[†] Part 4 of the series “Synthesis and Application af Aryl-Ferrocenyl (Pseudo-Biarylic) Complexes”. For parts 1−3, see refs 6a−c.

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (b) Farina, V. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol. 12, p 161. (c) Tsuji, J. In *Palladium Reagents and Catalyst*; John Wiley and Sons: Chichester, UK, 1995. (d) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 8, p 799.

(2) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(3) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.

(4) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(5) The biaryl system is a well-established part of many superb ligands. For an illustrative example, see for example: Buchwald, S. L.; Old, D. W.; Wolfe, J. P.; Palucki, M.; Kamikawa, K. US 6307087 B1, October 23, 2001.

(6) (a) Pedersen, H. L.; Johannsen, M. *Chem. Commun.* **1999**, 2517. (b) Pedersen, H. L.; Johannsen, M. *J. Org. Chem.* **2002**, *67*, 7982. (c) Jensen, J. F.; Søtofte, I.; Sørensen, H. O.; Johannsen, M. *J. Org. Chem.* **2003**, *68*, 1258. For other reports on optically pure aryl−ferrocenyl complexes, see: (d) Bringmann, G.; Hinrichs, J.; Peters, K.; Peters, E.-V. *J. Org. Chem.* **2001**, *66*, 629. (e) Lotz, M.; Kramer, G.; Knochel, P. *Chem. Commun.* **2002**, 2546.

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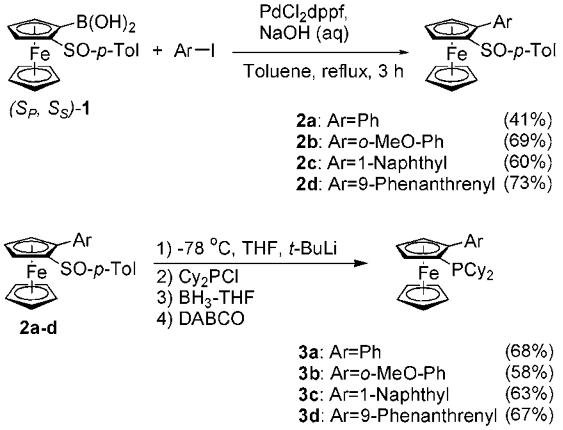
The ligands can be synthesized in two steps from the easily available planar chiral ferrocenyl boronic acid **1** (Scheme 1).[7−8] The Suzuki cross-coupling between **1** and aryl iodide **2a**−**d** affords moderate to good yields of the aryl ferrocenyl sulfoxides **3a**−**d** using previously reported optimized conditions.

Scheme 1. Ligand Synthesis

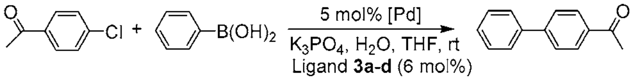


Standard sulfoxide cleavage with *t*-BuLi generates the optically pure ferrocenyl anions, which were trapped with chlorodicyclohexylphosphine to give aryl-MOPFs **3a**−**d**. The phosphines were borane protected to prevent oxidation during aqueous workup. Concomitant DABCO deprotection afforded the free phosphine ligands in 58−68% yield (cf. Scheme 1). In contrast to tricyclohexylphosphine and tri-*tert*-butylphosphine, these phosphines turned out to be air stable and could be stored for month without any precautions taken.

Initially, the performances of the aryl-MOPFs (**3a**−**d**) were tested in the Suzuki cross-coupling of commercially available 4-chloro-acetophenone and phenyl boronic acid. Applying $Pd(OAc)_2$ as a palladium source and a Pd:ligand ratio of 1:1.2 afforded smooth cross-couplings at room temperature, affording the corresponding biaryl compound in good to excellent yield, as outlined in Table 1.

A variety of different bases and solvents were tested, but the superior combination turned out to be K_3PO_4 in THF. Notably, Pd_2dba_3 and aryl-MOPFs **3a**−**d** did not catalyze the reaction (entry 5, Table 1). As already mentioned, ligands **3a**−**d** were effective under the exact same reaction conditions, yet the highest yield (91%) was obtained when the palladium complex of **3b** was employed. This indicated that ligand **3b** could function as a model for other substrate couplings (vide infra).

Table 1. Room-Temperature Suzuki Cross-Coupling of 4-Chloro-acetophenone and Phenyl Boronic Acid

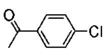
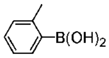
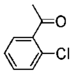
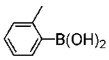
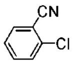
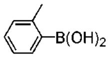
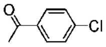
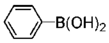


entry[a]	ligand **3**	[Pd]	conv. [%][b,c]	yield [%]
1	**3a**	$Pd(OAc)_2$	99 (98)	84
2	**3b**	$Pd(OAc)_2$	>99 (>99)	91
3	**3c**	$Pd(OAc)_2$	96 (92)	73
4	**3d**	$Pd(OAc)_2$	>99 (>99)	85
5	**3a**,**b**,**c**, or **d**	Pd_2dba_3	<1	

[a] Conditions: 1.0 equiv of aryl chloride (0.07 M in THF), 2.0 equiv of aryl boronic acid, 5 mol % [Pd], 6 mol % ligand **3**, 3.0 equiv of K_3PO_4, 8 equiv of H_2O, 24 h. [b] Measured by GC to an internal standard. [c] Conversion after 1 h in parenthesis.

At the outset, the catalytic performance of $Pd(OAc)_2$:**3b** was tested in the cross-coupling of various activated aryl chlorides and aryl boronic acids, as summarized in Table 2.[9−10] The yield of the coupling products were good to very good but highly dependent on the Pd:ligand ratio. This was reflected in the outcome from entry 4, where the Pd:ligand ratio was 1:2.5 and the conversion only was 3%. The strong

Table 2. Suzuki Cross-Coupling of Activated Aryl Chlorides Using Ligand **3b** and $Pd(OAc)_2$

entry[a]	aryl chloride	aryl boronic acid	Pd:P	conv. [%][b]	yield [%][c]
1			1:1.2	>99	89
2			1:1.2	94	90
3			1:1.2	77	75
4			1:2.5	<3	nd.

[a] Conditions: 1.0 equiv of aryl chloride (0.07 M in THF), 2.0 equiv of aryl boronic acid, 5 mol % $Pd(OAc)_2$, 6 mol % ligand **3b**, 3.0 equiv of K_3PO_4, 8 equiv of H_2O. Reaction time: 24 h at room temperature. Reaction time not optimized. [b] Measured by GC to an internal standard. [c] Isolated yield.

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(7) For the synthesis of optically pure (*S*p,*S*s)-**1**, see also ref 6c.

(8) The ferrocene sulfoxide chemistry was originally developed by Kagan et al.: (a) Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan, H. B. *J. Org. Chem.* **1997**, *62*, 6733. (b) Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1998**, *63*, 3511. See also: (c) Hua, D. H.; Lagneau, N. M.; Chen, Y.; Robben, P. M.; Clapham, G.; Robinson, P. D. *J. Org. Chem.* **1996**, *61*, 4508. For the azaferrocenyl series, see: (d) Hansen, J. G.; Søtofte, I.; Johannsen, M. *Org. Lett.* **2001**, *3*, 499. (e) Hansen. J. G.; Johannsen, M. *J. Org. Chem.* **2002**, *68*, 1266.

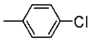
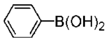
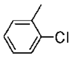
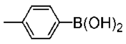
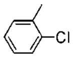
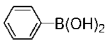
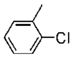
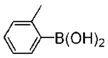
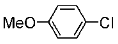
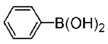
(9) For ferrocene based monophosphine ligands in Suzuki cross-coupling of aryl chlorides, see: (a) Pickett, T. E.; Richards, C. J. *Tetrahedron Lett.* **2001**, *42*, 3767. (b) Liu, S. Y.; Choi, M. J.; Fu, G. C. *Chem. Commun.* **2001**, 2408. (c) Kataoka, N.; Shelby, Q.; Stambuli, J. P. Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553. (d) Pickett, T. E.; Roca, F. X.; Richards, C. J. *J. Org. Chem.* **2003**, *68*, 2592.

(10) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363. (c) Wolfe, J. P.; Buchwald, S. P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (d) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153. (e) Andreu, M. G.; Zapf, A.; Beller, M. *Chem. Commun.* **2000**, 2475. (f) Botella, L.; Nájera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179.

relation between the Pd:ligand ratio and the activity of the catalyst was further verified in a series of experiments. The results consistently showed that >99% conversion could be maintained if the ratio was kept around or below 1.5 but that the activity of the catalyst was clearly highest at ratios between 0.9 and 1.2.

The novel catalytic species generated from Pd and aryl-MOPF **3b** proved to be equally efficient in the coupling of deactivated aryl chlorides. Conducting the reactions at a slightly elevated temperature (60 °C) afforded the products in excellent yields within 24 h (Table 3). Importantly, 2.5 equiv of the ligand per palladium is required to preserve the activity of the catalyst under these reaction conditions.

Table 3. Suzuki Cross-Coupling of Unactivated Aryl Chlorides

entry[a]	aryl chloride	aryl boronic acid	conv. [%][b]	yield [%][c]
1			94	89
2			>99	96
3			95	90
4			85	83
5			79	77

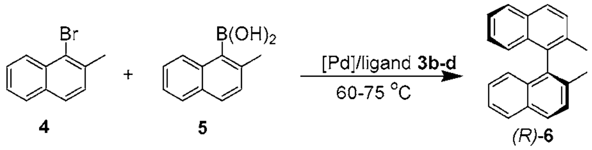
[a] Conditions: 1.0 equiv of aryl chloride (0.07 M in THF), 2.0 equiv of aryl boronic acid, 2 mol % Pd(OAc)$_2$, 5 mol % ligand **3b**, 3.0 equiv of K$_3$PO$_4$, 8 equiv of H$_2$O. Reaction time: 24 h at 60 °C. Reaction time not optimized. [b] Measured by GC to an internal standard. [c] Isolated yield.

The reactions could also be performed at room temperature and with the former Pd:ligand ratio (1:1.2), although the turnover frequency was slightly lower (63% yield in 24 h for the reaction depicted in entry 1, Table 3).

Several observations confirm that the activity of a given palladium−phosphine catalyst depends significantly on the molar ratio between palladium and the ligand. Recently, we reported a dramatic rate enhancement attained in the palladium-catalyzed hydrosilylation of styrene using a diphenyl 1-naphthyl-MOPF ligand. Decreasing the Pd:ligand ratio from 1:2 to 1:1.2 increases the TOF from 67 to 180 000 h^{-1}.[6b] We propose that this effect results primarily from a high activity of the monophosphine palladium complex. The paramount activity of the MOPF ligands compared to, e.g., triphenylphosphine, might be due to a unique aryl−palladium interaction stabilizing and activating palladium (0) intermediates in the catalytic cycle. Reported X-ray structures of related biaryl compounds confirm the existence of such interactions.[11] At present we do not have any experimental data to validate the catalytic active species in the present Suzuki reactions. Notably, however, the cross-coupling reactions proceeding at room temperature are inhibited when the ligand concentration exceeds 2 equiv of ligand per palladium. This indicates that the rate-limiting process involves a palladium complex coordinating only one ligand. Contrasting this hypothesis, the coupling at a slightly raised temperature benefits from a 2.5:1 ratio between the ligand and palladium. However, the catalyst is slightly prone to thermal decomposition and an excess of the ligand is necessary to prevent precipitation of palladium black. Supporting this, traces of dephosphorylated aryl−ferrocene were detected in these latter reactions. Moreover, due to the bulkiness of the MOPF ligands, palladium di-MOPF complexes are presumably relatively labile. Hence, dissociation of a ligand to provide an active monophosphino catalyst should be attainable, especially at elevated temperatures.[12]

With the previous results, in hand we anticipated that the MOPF could also be used in the asymmetric coupling reaction between aryl halides and aryl boronates. Three MOPF ligands (**3b**−**d**) were tested in the asymmetric Suzuki cross-coupling of naphthyl bromide **4** and naphthyl boronic acid **5** as shown in Table 4. The reactions proceeded at an elevated temperature (70 °C) and with toluene, Pd$_2$dba$_3$, and K$_3$PO$_4$ as the best reaction parameters. The reaction conditions, which were applied in the cross-coupling of activated aryl chlorides and arylboronic acids, gave no conversions. Especially for the combination of Pd$_2$dba$_3$ and ligand **3d**, the reaction had to be conducted in THF and not toluene (entries 5 and 6, Table 4).

Table 4. Asymmetric Synthesis of 2,2′-Dimethyl Binaphthalene **6** via the Suzuki Reaction



entry[a]	ligand	base	solvent	yield [%]	ee [%]
1	**3b**	K$_3$PO$_4$	toluene	62	43 (*R*)
2	**3b**	CsF	DME	28	46 (*R*)
3	**3b**	Ba(OH)$_2$	DME	30	46 (*R*)
4	**3c**	K$_3$PO$_4$	toluene	65	54 (*R*)
5	**3d**	K$_3$PO$_4$	toluene	<1	nd
6	**3d**	K$_3$PO$_4$	THF	32	45 (*R*)

[a] Conditions: 1.0 equiv of naphthyl bromide **4**, 1.5 equiv of naphthyl boronic acid **5**, 2 mol % [Pd], 5 mol % ligand **3**, 2−3 equiv of [Pd]:ligand = 1:2.5, K$_3$PO$_4$, 8 equiv of H$_2$O. Reaction time: 4−24 h, and not optimized. Temp = 60−75 °C. [b] Isolated yield of **6**. [c] Ee of **6** measured by HPLC on a OD-H column (100% hexane).

Overall, the yield of the reaction can still be improved, and fortunately the ee value seems to be unaffected by the

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(11) (a) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162. (b) See also: Kočovsky, P.; Vyskočil, Š.; Císařová, I.; Sejbal, J.; Tišlerová, I.; Smrčina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714 and references therein.

(12) For the synthesis and charaterization of a Pd complex with a bulky monophosphine ligand, see: Stambuli, J. P.; Bühl, M.; Hartwig, J. *J. Am. Chem. Soc.* **2002**, *124*, 9346.

solvent, palladium source, and base employed, which simplifies ligand screening. The highest ee value (54%) from this ligand series cannot compete with the best reported;[13] however, the large potential for structural variation and the straightforward synthesis of these make them currently an interesting structure for catalyst development in this field.

In conclusion, a new modular class of air-stable planar chiral ferrocene ligands has been introduced. These novel electron-rich phosphine ligands were successfully applied in the palladium-catalyzed Suzuki cross-coupling of a range of activated aryl chlorides. Notable were the mild reaction conditions employed, i.e., low temperatures and a relatively weak base. Electron-rich aryl chlorides also were efficiently coupled with different aryl boronic acids at room temperature or under slightly elevated temperatures. Due to the planar chirality of the ferrocene parent structure, all members of the ligand family are inherently chiral and the first test result showed promise for the use of the ligands in this field also. Future studies will be directed toward the synthesis and testing of more members of the MOPF family.[14]

Supporting Information Available: Experimental procedures and characterization of the MOPF ligands (**3**) and ^{1}H and ^{13}C NMR spectra of compounds **3a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] (a) Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 1723. For other examples, see: (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.

[14] After the completion of this manuscript, a paper appeared describing the synthesis of compound **3b** by a similar strategy: Herrbach, A.; Marinetti, A.; Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2003**, *68*, 4897.