^{13}C NMR (75.47 MHz, D_2O, pD 5): $\delta = 156.50$ (C-6^{Ade}), 153.64 (C-2^{Ade}), 150.15 (C-4^{Ade}), 140.92 (C-8^{Ade}), 119.71 (C-5^{Ade}), 97.62 (C-1^{Hep}, ^2J(C-1,P) = 6.0 Hz), 87.92 (C-1^{Rib}), 84.95 (C-4^{Rib}, ^3J(C-4,P) = 9.0 Hz), 75.36 (C-2^{Rib}), 73.09 (C-5^{Hep}), 71.43 (C-3^{Rib}), 71.35 (C-3^{Hep}), 71.19 (C-2^{Hep}), 69.63 (C-6^{Hep}), 66.97 (C-4^{Hep}), 66.25 (C-5^{Rib}, ^2J(C-5,P) = 5.0 Hz), 63.49 (C-7^{Hep}), ^1J(C-1,H-1) = 174.0 Hz; ^{31}P NMR: $\delta = -10.7$ (d, P^{Rib}, ^2J(P,P) = 21.1 Hz), -13.1 (d, P^{Hep}); negative ion MALDI-TOF MS: m/z: found 618.31, calcd 618.36 (for $C_{17}H_{27}N_5O_{16}P_2$ $[M-H]^-$); elemental analysis: calcd for $C_{17}H_{27}N_5O_{16}P_2 \cdot N(C_2H_5)_3 \cdot 0.5\,H_2O$ (756.605): C 37.87, H 5.99, N 11.52; found: C 38.08, H 6.13, N 11.07.

Compound **2** (Et_3NH salt): $[\alpha]_D^{20} = -31$ ($c = 0.3$ in H_2O); ^{1}H NMR (300 MHz, D_2O, pD 4.7): $\delta = 8.60$ (s, 1H; H-8^{Ade}), 8.37 (s, 1H; H-2^{Ade}), 6.18 (d, ^3J(1,2) = 5.8 Hz, 1H; H-1^{Rib}), 5.23 (dd, ^3J(1,2) = 1.0, ^3J(1,P) = 8.5 Hz, 1H; H-1^{Hep}), 4.75 (m, 1H; H-2^{Rib}), 4.50 (dd, ^3J(2,3) = 4.9, ^3J(3,4) = 3.8 Hz, 1H; H-3^{Rib}), 4.42 (m, 1H; H-4^{Rib}), 4.25 (m, 2H; H-5a,5b^{Rib}), 4.07 (dd, ^3J(2,3) = 3.2 Hz, 1H; H-2^{Hep}), 3.95 (m, 1H; H-6^{Hep}), 3.82 (dd, ^3J(3,4) = ^3J(4,5) = 9.7 Hz, 1H; H-4^{Hep}), 3.87–3.67 (m, 2H; H-7a,7b^{Hep}), 3.67 (dd, 1H; H-3^{Hep}), 3.37 (dd, ^3J(5,6) = 1.7 Hz, 1H; H-5^{Hep}), 3.20 (m, 6H; CH_2N), 1.28 (t, 9H; Me); ^{13}C NMR (75.47 MHz, D_2O, pD 5): $\delta = 156.75$ (C-6^{Ade}), 153.99 (C-2^{Ade}), 150.23 (C-4^{Ade}), 140.89 (C-8^{Ade}), 119.80 (C-5^{Ade}), 96.89 (C-1^{Hep}, ^2J(C-1,P) = 4.8 Hz), 87.84 (C-1^{Rib}), 84.88 (C-4^{Rib}, ^3J(C-4,P) = 8.7 Hz), 76.04 (C-5^{Hep}), 75.34 (C-2^{Rib}), 73.72 (C-3^{Hep}), 71.73 (C-2^{Hep}), 71.49 (C-3^{Rib}), 69.71 (C-6^{Hep}), 66.66 (C-4^{Hep}), 66.35 (C-5^{Rib}, ^2J(C-5,P) = 5.8 Hz), 63.40 (C-7^{Hep}); ^1J(C-1,H-1) = 163.3 Hz; ^{31}P NMR: $\delta = -10.8$ (d, P^{Rib}, ^2J(P,P) = 20.8 Hz), -12.8 (d, P^{Hep}); negative ion MALDI-TOF MS: m/z: found 618.63, calcd 618.36 (for $C_{17}H_{27}N_5O_{16}P_2$ $[M-H]^-$).

Enzymatic in vitro assays to test the transfer of the α- and β-configured ADP-heptoses **1**–**4** by heptosyltransferase I of *E. coli* were basically performed as described in refs. [6a, 21].

Received: April 12, 2000 [Z14981]

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A New Highly Efficient Catalyst System for the Coupling of Nonactivated and Deactivated Aryl Chlorides with Arylboronic Acids**

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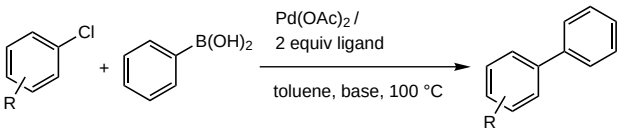
Dedicated to Professor Othmar Stelzer on the occasion of his 60th birthday

Substituted biphenyls are central components of fine chemicals for a diverse range of applications. In particular pharmaceuticals[1] and herbicides[2] with biaryl substructures are of general interest. In addition, biaryls are applied as chiral ligands in catalysis,[3] as liquid crystals,[4] or organic conductors.[5] The most common method used for linking the central aryl–aryl bond is the palladium- or nickel-catalyzed coupling of aryl halides or aryl pseudohalides with arylboronic acids [Suzuki reaction, Eq. (1)].[6] This method has



(1)

the advantage over other alternatives in that stoichiometric amounts of heavy metals are not required (unlike the Ullmann and Stille couplings that use copper and tin, respectively). From an industrial viewpoint the chemically

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[**] Palladium-Catalyzed Reactions for Fine Chemical Synthesis, Part 17. The authors thank C. Fuhrmann for the excellent support in the laboratory, Dipl.-Chem. W. Mägerlein for ligand samples of 2-(dicyclohexylphosphanyl)toluene and -anisole as well as DMC^2 for generous donations of palladium compounds. Part 16: F. Vollmüller, W. Mägerlein, S. Klein, J. Krause, M. Beller, *Adv. Synth. Catal.*, in press.

inert, but cheap and readily accessible aryl chlorides are particularly important as starting materials for transition metal catalyzed C–C and C–X coupling.[7] Therefore it is not surprising that activation of chloroarenes has developed into one of the most intensely studied areas of homogeneous catalysis in the last decade.[7] In Suzuki reactions of non-activated and deactivated chloroarenes[8] in the last three years Indolese[9] and Miyaura et al.[10] have achieved significant success with nickel catalysts, and the groups of Fu,[11] Buchwald,[3b, 12] Guram,[13] Nolan,[14] Herrmann,[15] as well as ourselves[16] have achieved similar success with palladium catalysts.

Despite the good yields obtained in many Suzuki reactions of chloroarenes, generally, comparatively large amounts of catalyst are required (1–3 mol %).[17] The application of such amounts of homogeneous catalysts make industrial applications almost impossible. Given the current price of palladium, this leads to catalyst costs of >100 € per kg product;[18] that is, the availability and the price advantage of chloroarenes over other haloarenes as substrates no longer plays a role!

We describe herein a new catalyst system, with which we have achieved the coupling of nonactivated and deactivated aryl chlorides highly efficiently in good yields with generally only 0.005 mol % palladium and thus under industrially viable conditions.

As a starting point for the development of new more efficient catalyst systems, we chose the synthesis of diadamantylphosphanes. Adamantylphosphanes, which are sterically demanding, basic ligands, have hitherto been little examined in catalysis.[19] Among a variety of diadamantylalkylphosphanes tested in initial experiments with chloroarenes, the diadamantyl-*n*-butylphosphane ($BuPAd_2$) proved to be extremely reactive. In order to compare the new ligands with the best catalyst systems known to date for the Suzuki reaction, we chose the reaction of 4-chlorotoluene with phenylboronic acid. In all cases the reaction conditions optimized by Buchwald et al.[12b] for Suzuki reactions were employed (palladium source: palladium(II) acetate; P:Pd = 2:1; solvent: toluene; base: potassium phosphate; 100 °C). As Table 1 shows, simple triphenylphosphane did not lead to an active catalyst (<5% yield; Table 1, entry 1). With Buchwald's 2-(dicyclohexylphosphanyl)biphenyl the reaction proceeds very well (93%) in the presence of at least 0.05 mol % palladium (Table 1, entry 5);[12b] however, it reaches its limits at 0.01 mol % palladium (47%; Table 1, entry 6) and gives the desired product in only 16% yield in the presence of 0.005 mol % catalyst. The comparison with the electronically similar, but sterically significantly less demanding ligands dicyclohexylphenylphosphane as well as 2-(dicyclohexylphosphanyl)toluene and -anisole (Table 1, entries 2, 3, and 4, respectively)[7q] illustrates the importance of the right Tolman angle. Even the steric demand of the standard ligand tricyclohexylphosphane is not sufficient for this reaction (Table 1, entry 7). On the other hand, tri-*tert*-butylphosphane, introduced by Fu et al.[11] for the Suzuki reaction, is a simple, but efficient ligand for the coupling of 4-chlorotoluene (92% at 0.01 mol % Pd; 41% at 0.005 mol % Pd; Table 1, entries 8 and 9, respectively). With diadamantyl-*n*-butylphosphane, we obtained even significantly improved turnover numbers (Table 1, entries 10 and 11). Thus, our catalyst system represents the most productive catalyst system described to date for the arylation of chloroarenes (87% yield at 0.005 mol % Pd; TON = 17400). The reaction with the new ligand system is already complete after a few hours; to allow a better comparison it was left to run for 20 hours. Already after four hours 4-methylbiphenyl is obtained in 74% yield, which corresponds to a turnover frequency of 3700 per hour; thus also the activity of the new system is unparalleled.

In the presence of alternative bases that are even more suitable for an industrial reaction, for example potassium carbonate, 4-methylbiphenyl was obtained in a respectable yield of 74% in the presence of 0.01 mol % $Pd(OAc)_2$ and 0.02 mol % $BuPAd_2$ (TON = 7400) .

Other chloroarenes led to results similar to those for 4-chlorotoluene, essentially independent of their steric and electronic properties (Table 2). *ortho*-substituents are tolerated, and even the strongly sterically hindered 2,6-dimethyl-substituted chlorobenzene was coupled to approximately 70% yield (TON = 13600; Table 2, entry 4). Only strongly electron-donating groups (e.g. methoxy groups) led to a drop in the yield to about 60% (Table 2, entries 8 and 9). Heteroaryl chlorides, such as 3-chloropyridine, are likewise converted highly efficiently to the corresponding biaryls (99%; Table 2, entry 12).

A further reduction of the amount of catalyst by a factor of 5 to 10 ppm Pd (based on the chloroarene), was tested, for

Table 1. Influence of the ligand on the coupling of 4-chlorotoluene and phenylboronic acid.

Entry	PR_3	Pd [mol %]	Yield [%]	TON
1	PPh_3	0.1	5	50
2	$PhPCy_2$	0.1	23	230
3[a]	(*o*-tol)PCy_2	0.1	49	490
4[a]	(*o*-anisyl)PCy_2	0.1	42	420
5[12b]	(*o*-biph)PCy_2	0.05	93	1860
6	(*o*-biph)PCy_2	0.01	47	4700
7	PCy_3	0.1	23	230
8	$PtBu_3$	0.01	92	9200
9	$PtBu_3$	0.005	41	8200
10	$BuPAd_2$	0.01	94	9400
11	$BuPAd_2$	0.005	87	17400

[a] P/Pd = 4:1.

Table 2. Suzuki coupling of different aryl chlorides with phenylboronic acid in the presence of $Pd(OAc)_2$/2 $BuPAd_2$.

Entry	R	Pd [mol %]	Yield [%]	TON
1	4-Me	0.005	87	17400
2[a]	4-Me	0.005	74	14800
3	2-Me	0.005	85	17000
4	2,6-Me_2	0.005	68	13600
5	H	0.005	80	16000
6	2-F	0.005	96	19200
7	2-F	0.001[b]	55	55000
8	4-MeO	0.005	64	12800
9	3-MeO	0.005	58	11600
10	2-CN	0.005	100	20000
11	2-CN	0.001[b]	69	69000
12	"3-N"[c]	0.005	99	19800

[a] 4 instead of 20 h. [b] Pd:P = 1:4. [c] 3-chloropyridine.

  1433-7851/00/3922-4154 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2000**, *39*, No. 22

example, for the reactions of 4-chlorotoluene, 2-fluorochlorobenzene, and 2-chlorobenzonitrile. The new catalyst system reached its limits for such low palladium concentrations. Nevertheless 2-fluorobiphenyl and 2-cyanobiphenyl were obtained in satisfactory yields of 55 and 69%, respectively (with corresponding TONs of 55000 and 69000, respectively; Table 2, entries 7 and 11, respectively).

Diadamantyl-*n*-butylphosphane/palladium(II) acetate represents the as yet most efficient catalyst system for the coupling of chloroarenes with arylboronic acids. It is significantly better in terms of the productivity and activity than the hitherto best known catalyst systems. Even with deactivated aryl chlorides turnover numbers of 10000–20000 are achieved for good to excellent yields. The described catalyst system as well as similar systems are currently being tested in other catalytic C–C and C–X coupling reactions.

Experimental Section

Procedure for 4-methylbiphenyl: In an ACE pressure tube 4-chlorotoluene (3.0 mmol), phenylboronic acid (4.5 mmol), tripotassium phosphate (6.0 mmol), hexadecane (100 μL; as internal GC standard), the ligand, and palladium(II) acetate were suspended in dry toluene (6 mL) in an argon atmosphere. The pressure tube was sealed and suspended in a preheated oil bath at 100 °C. After 20 h the mixture was allowed to cool to room temperature and the solids were dissolved by addition of dichloromethane (10 mL) and dilute sodium hydroxide (10 mL). The organic phase was analyzed by gas chromatography. To isolate the product, the organic phase was washed with water and saturated brine, and dried. The solvent was removed by distillation and the residue was purified by chromatography with hexane/ethyl acetate (9:1; v/v) over silica gel 60. ^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): $\delta = 7.63$ (m, 2H), 7.54 (m, 2H), 7.47 (m, 2H), 7.36 (m, 1H), 7.29 (m, 2H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, 21 °C): $\delta =$ 141.1, 138.3, 137.0, 129.5, 128.7, 127.0, 126.9, 126.9, 21.1; MS (70 eV, EI): *m*/*z* (%): 168 (100) [M^+], 152 (15) [$M^+ - CH_3$].

Received June 5, 2000 [Z15216]

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