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Efficient Chemical Synthesis of the Two Anomers of ADP-L-*glycero*- and D-*glycero*-D-*manno*-Heptopyranose Allows the Determination of the Substrate Specificities of Bacterial Heptosyltransferases**

Alla Zamyatina, Sabine Gronow, Clemens Oertelt, Michael Puchberger, Helmut Brade, and Paul Kosma*

Lipopolysaccharides (LPS) of gram-negative bacteria are essential outer membrane components. The lipid moiety and the adjacent first sugar residues, named lipid A and the inner core region, respectively, are of utmost importance for growth and viability.[1, 2] Thus, the development of inhibitors of the early biosynthetic steps in the assembly of LPS are promising alternatives in antibacterial drug design.

Whereas the biosynthesis of the 3-deoxy-D-*manno*-oct-2-ulosonic acid (Kdo) and the lipid A region of LPS is well understood, that of the heptose region containing L-*glycero*- or D-*glycero*-D-*manno*-heptose, or both, is not known in detail. This concerns the biosynthesis of the sugars, their nucleotide derivatives, and the characterization of heptosyltransferases.[3–5] Although it is known that some bacterial heptosyltransferases use ADP-heptose as a substrate, the configuration of the side chain and the anomeric carbon is not known for the physiological sugar nucleotide.[3, 6–8]

For the synthesis of the glycopyranosyl 1-phosphates,[9] L-*glycero*-D-*manno*-heptopyranose (**5**)[10] was subjected to phosphitylation[11] followed by oxidation to give the anomeric phosphate triesters **6** and **7** in approximately 9:1 ratio and in 94% yield (Scheme 1). Alternatively, treatment of **5** with *N*-tetrazolylbisbenzylphosphoramidite increased the formation of the β-anomer **7**.[12] By slow addition of phosphitylating reagent in the presence of an excess of 4-dimethylaminopyridine (DMAP), the thermodynamically and kinetically controlled α- and β-anomeric phosphite triesters, respectively, were obtained. Subsequent in situ oxidation gave **6** (56%) and **7** (34%), respectively. Cleavage of the protecting groups by hydrogenolysis to furnish **8** and **12** followed by deacetylation gave α-and β-heptose 1-phosphates (**9** and **13**, respectively) in near quantitative yields.

Yields reported for chemical syntheses of sugar nucleoside diphosphates through the coupling of a sugar 1-phosphate with nucleoside monophosphoromorpholidate[13] are mostly moderate, not exceeding 25 – 30%, although improvements have been published.[14] Target compound **1** was prepared first

[*] Prof. P. Kosma, Dr. A. Zamyatina, Dr. M. Puchberger
Institute of Chemistry
University of Agricultural Sciences
Muthgasse 18, 1190 Vienna (Austria)
Fax: (+43) 1-36006-6059
E-mail: pkosma@edv2.boku.ac.at
Dr. S. Gronow, Dipl.-Chem. C. Oertelt, Prof. H. Brade
Research Center Borstel
Center for Medicine and Biosciences
Parkallee 22, 23845 Borstel (Germany)

[**] This work was supported by grants from FWF (grant nos. P11449-MOB and P13843-CHE).

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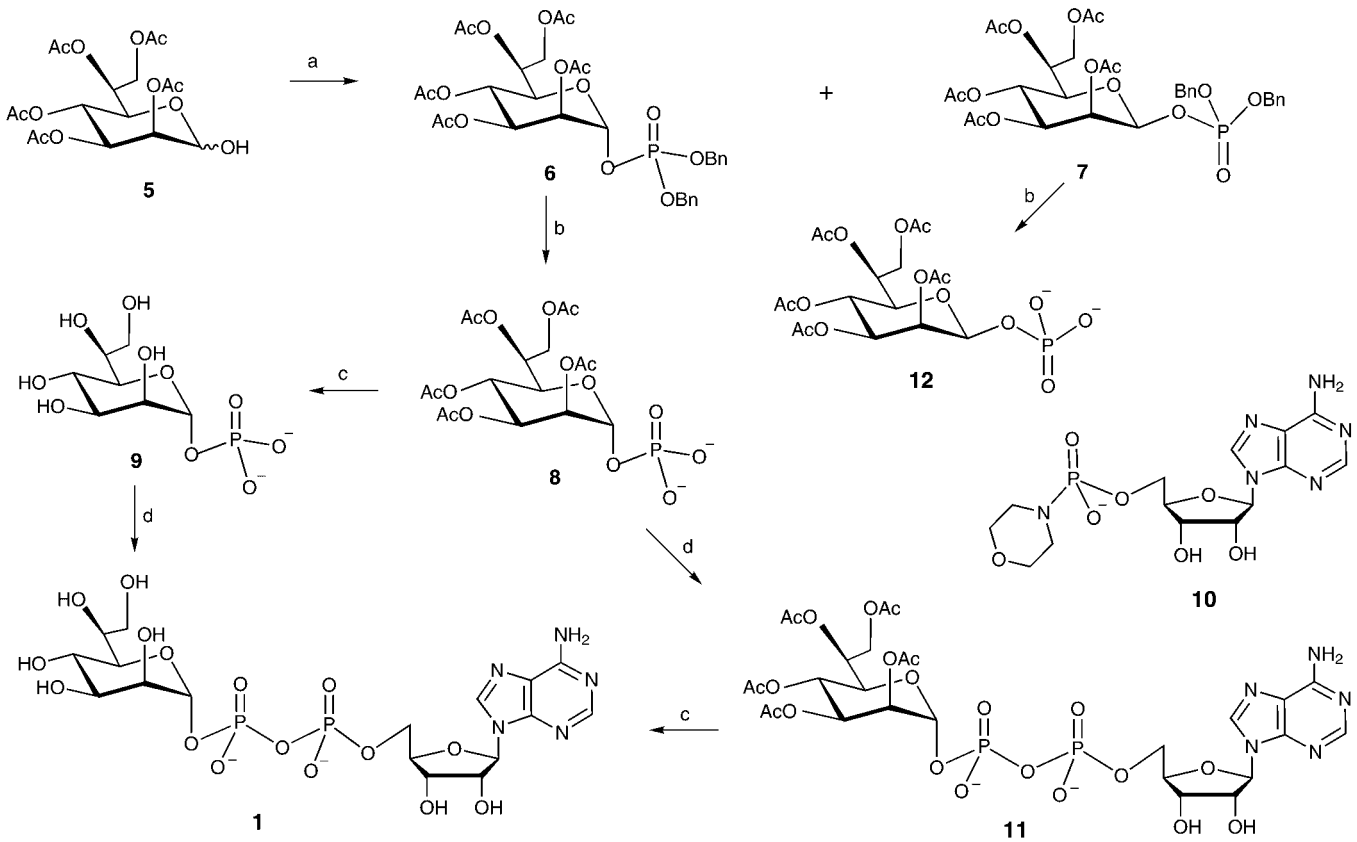
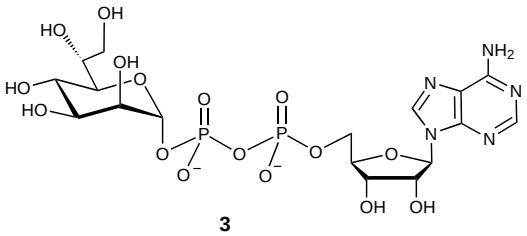


Scheme 1. a) Method A: $(BnO)_2NiPr_2$, 1*H*-tetrazole, CH_2Cl_2, then *t*BuOOH (**6**: 85%; **7**: 9%) or Method B: DMAP, tetrazolyl-NP$(OBn)_2$, CH_2Cl_2/MeCN (1/1), then *t*BuOOH (**6**: 56%; **7**: 34%); b) Pd/C, H_2, MeOH, Et_3N, 99%; c) MeOH/H_2O/Et_3N (3.5/1.5/0.5), RT, 98%; d) 4′-morpholine-*N*,*N*′-dicyclohexylcarboxamidinium salt of **10**, pyridine (**9** → **1**: 15%; **8** → **11**: 90%).

by coupling AMP-morpholidate (**10**) to the tributyl- or trioctylammonium salt of α-heptosyl 1-phosphate (**9**) as described for the synthesis of GDP-fucose.[15] The salts of **9** were only partially soluble in pyridine and homogeneous reaction conditions could not be achieved. ADP-L-*glycero*-α-D-*manno*-heptopyranose (**1**) was isolated in only 15% yield with recovery of **9** in 60% yield. On the other hand, coupling of the soluble monotriethylammonium salt of the *O*-acetylated heptosyl phosphate **8** with **10** afforded ADP-per-*O*-acetyl-L-*glycero*-α-D-*manno*-heptopyranose (**11**) in 90% yield after purification by anion-exchange chromatography. Subsequent deacetylation of **11** with MeOH/H_2O/Et_3N directly gave ADP-heptose **1** in 99% yield after lyophilization. The overall yield for the preparation of **1**, from **5**, was 76%.

The β-configured ADP-heptose **2** was prepared in a similar way (Scheme 2). Coupling of the β-heptosyl 1-phosphate **12** to AMP-morpholidate (**10**) gave a high yield (90%) of the protected ADP-heptose **14**. Attempts to cleave the acetate groups from **14** with aqueous NH_3 or with MeOH/H_2O/Et_3N at pH 12–13, however, led to the formation of the 1,2-cyclic phosphate **15** with release of AMP. The structure of **15** was determined from the ^{31}P NMR ($\delta = 17.8$) and ^{13}C NMR signals ($\delta = 79.5$) assigned to C-2, and from subsequent treatment of **15** with 1M NaOH, which gave an approximately 1:1 mixture of heptose 2-phosphate (**16**) and β-heptose 1-phosphate (**13**). Deacetylation of **14** with MeOH/0.1M aq. $Et_3NH^+HCO_3^-$/Et_3N (pH 10–11) at $-30\,^\circ C$ gave **2** as the major component (80%). Anion-exchange chromatography of the crude material on a Bio-Rad High Q resin led to the separation of **15**, and residual AMP was removed by gel chromatography on a Superdex peptide column. Diphosphate **2** slowly decomposed at room temperature at pH 5 (30% decomposition after 10 days).

The ADP-heptoses **3** and **4** with D-*glycero*-D-*manno*-configuration were synthesized by phosphitylation with tetrazolyl-NP$(OBn)_2$ in good overall yields (50% for **3** and 24% for **4**, based on the initial quantity of penta-*O*-acetyl-D-*glycero*-D-*manno*-heptose[16]).



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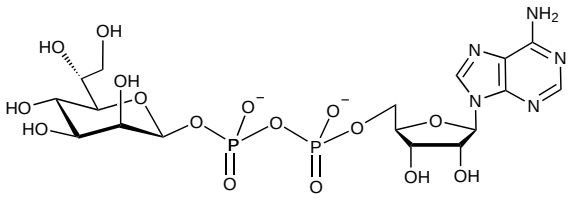

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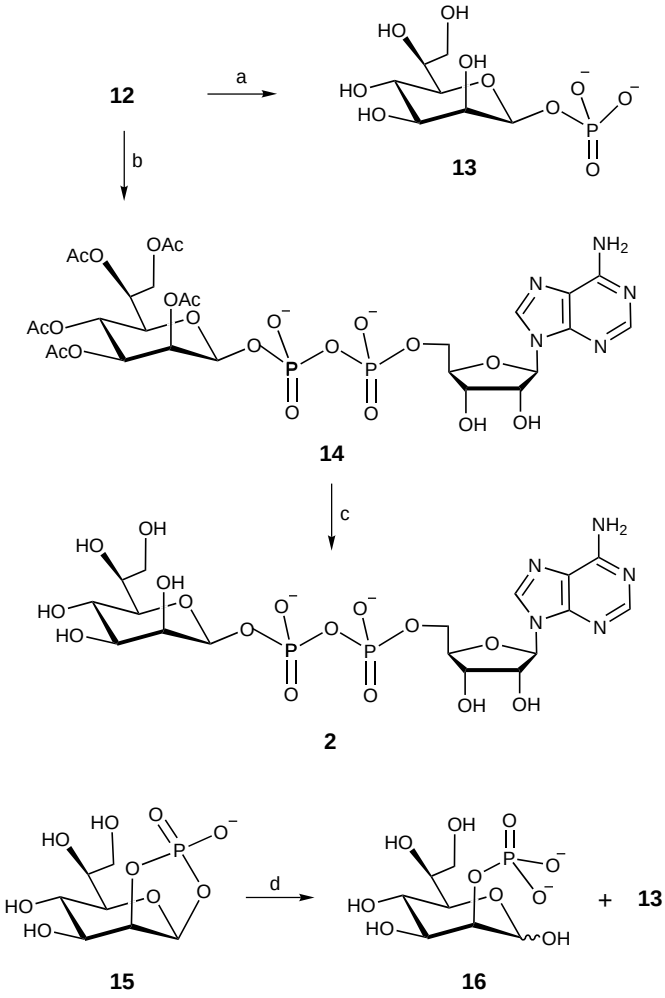
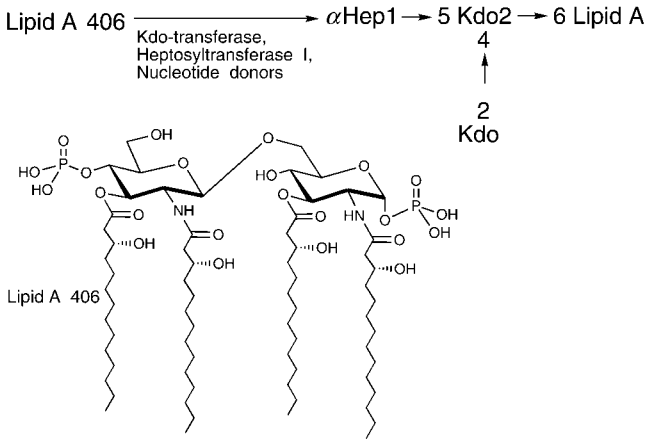


Scheme 2. a) Pd/C, H_2, MeOH, Et_3N, 98%; b) 4′-morpholine-*N*,*N*′-dicyclohexylcarboxamidinium salt of **10**, pyridine, 90%; c) MeOH/0.1M $Et_3NH^+HCO_3^-$/Et_3N (3/4/0.15), −30 °C, 80%; d) 1M NaOH.

Compounds **1**–**4** were subjected to a coupled in vitro reaction, in which two Kdo residues and one heptose were transferred sequentially by Kdo transferase and heptosyltransferase I of *E. coli*, respectively, using synthetic lipid A 406[17] as an acceptor (Scheme 3). Both enzymes were used as recombinant proteins expressed in a gram-positive host devoid of LPS-biosynthesis genes. Reaction products were detected after separation by thin-layer chromatography and blotting with monoclonal antibody S36-20, which recognizes Rd_2-type LPS.[18] Since this antibody does not bind to LPS without heptose nor to LPS with two heptose residues, the data show that a single heptosyl residue had been transferred. Similar results were obtained with a natural donor from a bacterial extract[19] (Figure 1, lane 1) and with synthetic ADP-L-*glycero*-*β*-D-*manno*-heptose (**2**; lane 2). Incubation of the reaction mixture with ADP-D-*glycero*-*β*-D-*manno*-heptose (**4**) also led to product formation, however, at least tenfold higher concentrations were needed in comparison with **2** (lane 3). Neither ADP-L-*glycero*-*α*-D-*manno*-heptose (**1**) nor ADP-D-*glycero*-*α*-D-*manno*-heptose (**3**) were substrates for heptosyltransferase I (lanes 4 and 5). Heptosyltransferase II exhibited the same sugar nucleotide specificity (data not shown).



Scheme 3. In vitro assay with synthetic lipid A 406, recombinant Kdo transferase, and recombinant heptosyltransferase I from *E. coli*.

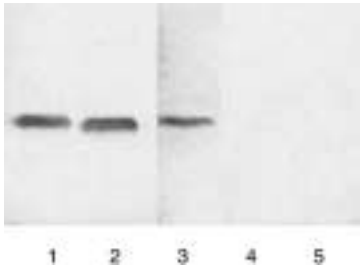


Figure 1. Immunoblot of reaction products of heptosyltransferase I of *E. coli* with ADP-L-*glycero*-D-*manno*-heptose of unknown anomeric configuration from a natural extract[19] (lane 1), ADP-L-*glycero*-*β*-D-*manno*-heptose (**2**; 0.1 mM; lane 2), ADP-D-*glycero*-*β*-D-*manno*-heptose (**4**; 1 mM; lane 3), ADP-L-*glycero*-*α*-D-*manno*-heptose (**1**; 1 mM; lane 4) or ADP-D-*glycero*-*α*-D-*manno*-heptose (**3**; 1 mM; lane 5) as sugar nucleotide donors. Reaction products were separated by thin-layer chromatography, blotted, and visualized with a monoclonal antibody which recognizes Rd_2-type LPS.[18]

The data show unequivocally that ADP-L-*glycero*-*β*-D-*manno*-heptose represents the physiological sugar nucleotide donor for heptosyltransferases from *E. coli*. ADP-D-*glycero*-*β*-D-*manno*-heptose also serves as a substrate, which is in accordance with the finding that mutants of ADP-L-*glycero*-D-*manno*-heptose-6-epimerase (gmhD) incorporate D-*glycero*-D-*manno*-heptose.[20] The synthetic approach using partially acetylated sugar phosphates for the coupling step gives excellent yields, allows efficient purification and might be applicable in the synthesis of other sugar nucleoside diphosphates as well. This should facilitate studies of glycosyltransferases in general, and in particular biosynthetic studies of LPS which contain L-*glycero*- and D-*glycero*-D-*manno*-heptoses.

Experimental Section

Compound **1** (Et_3NH salt): $[\alpha]_D^{20} = +4.5$ ($c = 1$ in H_2O); ^1H NMR (300 MHz, D_2O, pD 5): $\delta = 8.51$ (s, 1H; H-8^{Ade}), 8.26 (s, 1H; H-2^{Ade}), 6.14 (d, $^3J(1,2) = 6.0$ Hz, 1H; H-1^{Rib}), 5.51 (dd, $^3J(1,2) = 1.9$, $^3J(1,P) = 7.4$ Hz, 1H; H-1^{Hep}), 4.75 (m, 1H; H-2^{Rib}), 4.52 (dd, $^3J(2,3) = 5.1$, $^3J(3,4) = 3.5$ Hz, 1H; H-3^{Rib}), 4.39 (m, 1H; H-4^{Rib}), 4.22 (m, 2H; H-5a,5b^{Rib}), 4.02 (dd, $^3J(2,3) =$ 3.2 Hz, 1H; H-2^{Hep}), 3.99 (m, 1H; H-6^{Hep}), 3.94–3.80 (m, 3H; H-3, H-4, H-5^{Hep}), 3.73 (dd, $^2J(7a,7b) = 11.6$, $^3J(6,7a) = 6.2$ Hz, 1H; H-7a^{Hep}), 3.64 (dd, $^3J(6,7b) = 7.1$ Hz, 1H; H-7b^{Hep}), 3.19 (q, 6H; CH_2N), 1.26 (t, 9H; Me);

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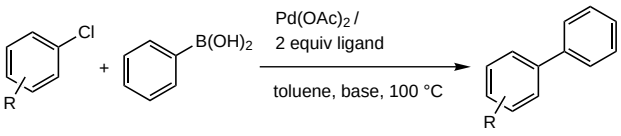
A New Highly Efficient Catalyst System for the Coupling of Nonactivated and Deactivated Aryl Chlorides with Arylboronic Acids**

Alexander Zapf, Andreas Ehrentraut, and Matthias Beller*

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

[*] Prof. Dr. M. Beller, Dr. A. Zapf, Dipl.-Chem. A. Ehrentraut
Institut für Organische Katalyseforschung an der Universität Rostock e. V. (IfOK)
Buchbinderstrasse 5–6, 18055 Rostock (Germany)
Fax: (+49) 381-466-9324
E-mail: matthias.beller@ifok.uni-rostock.de

[**] 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.