Use of "Homeopathic" Ligand-Free Palladium as Catalyst for Aryl-Aryl Coupling Reactions

Asaf Alimardanov,[a,b] Lizette Schmieder-van de Vondervoort,[a] André H. M. de Vries,[a] Johannes G. de Vries[a,*]

[a] DSM Pharma Chemicals, Advanced Synthesis, Catalysis & Development, P. O. Box 18, 6160 MD Geleen, The Netherlands
Fax: (+31)-46-476-7604, e-mail: Hans-JG.Vries-de@dsm.com
[b] Present address: Wyeth Research, 401 N. Middleton Road, Pearl River, NY 10965, USA

Received: July 4, 2004; Accepted: October 22, 2004

Abstract: We have previously shown that the use of ligand-free palladium employing $Pd(OAc)_2$ as catalyst precursor in the Heck reaction of aryl bromides is possible if low catalyst loadings, typically between 0.01–0.1 mol % are used. We have now tested this phenomenon, which we have dubbed "homeopathic" palladium, in biaryl formation using the Suzuki, the Negishi and the Kumada cross-coupling reactions. The Suzuki reaction of aryl bromides, both activated and deactivated, is possible using 0.02–0.05 mol % of $Pd(OAc)_2$. In this reaction turnover frequencies up to 30,000 have been reached with activated substrates. Even aryl chlorides could be reacted if strongly electron-withdrawing substituents were present. The Negishi coupling with a variety of arylzinc halides was possible on aryl bromides containing electron-withdrawing substituents. The Kumada reaction only gave low yields of products under "homeopathic' conditions.

Keywords: biaryls; cross-coupling; ligand-free palladium; nanoclusters; Negishi reaction; Suzuki reaction

Introduction

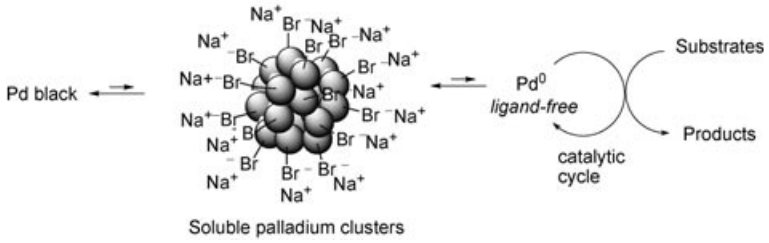
Aromatic substitution reactions are among the most important transition metal-catalysed reactions used for the production of fine chemicals.[1] This steadily growing importance is due to the mild conditions associated with their use, making them compatible with a wide variety of functional groups.[2] Thus, these coupling reactions can be used at an advanced stage in a total synthesis of complex chemicals such as drugs, vitamins, flavours and fragrances, agro-chemicals and performance materials.[3]

The use of 1–5 mol % of a catalyst constituted from a palladium precursor and a phosphine ligand has dominated the field for many years. However, the last 5 years has seen a tremendous advance in the development of new, more active catalyst systems. From the industrial viewpoint the high catalyst loadings and the use of phosphines are detrimental due to the associated high cost and problems of purification. For this reason we have focussed on the use of ligand-free palladium.[4] Although the use of ligand-free palladium in the Heck reaction of aryl iodides has been known for years,[5] we have recently shown that use of ligand-free palladium in the Heck reaction of aryl bromides is possible only when the palladium-substrate ratio is kept low, typically from 0.01–0.1 mol %.[6] This is due to the fact that palladium, once reduced to Pd(0), forms nanoclusters that have a limited stability; eventually these clusters aggregate to form palladium black (Scheme 1).[7] By lowering the palladium concentration, the oxidative addition of the aryl bromide can compete against the cluster formation. These results have recently been confirmed by Schmidt[8] and by Yao.[9] We use the term "homeopathic palladium", originally coined by Beletskaya for these reactions where very low loadings of palladium can be used.[10] Although these reactions are not homeopathic in palladium in the strictest sense, TEM analysis shows that the major part of the palladium is locked up in the inside of the clusters during the reaction, implying that the real active palladium concentration probably is two orders of magnitude smaller than the already low range of 0.1–0.01 mol %.

Interestingly, there is growing evidence that palladacycles and palladium pincer complexes also are rapidly converted to soluble palladium clusters in the Heck reaction.[6,7] On the other hand, little is known about the fate of palladacycles in other C–C bond forming reactions that often take place at much lower temperatures.

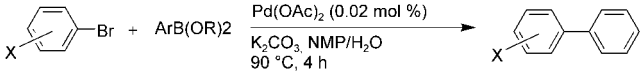
The use of ligand-free palladium (0.5–2 mol %) in the Suzuki coupling of aryl bromides has been reported, but Bu_4NBr was needed for good yields.[11] We have published preliminary high-throughput experimentation results showing that also in this case homeopathic palladi-

  DOI: 10.1002/adsc.200404210



Scheme 1. Nanoclusters as storage of palladium(0) in C–C bond forming reactions.

Table 1. Homeopathic Suzuki reaction of aryl bromides [0.02 mol % $Pd(OAc)_2$].



Entry	Aryl bromide	Boronic acid (ester)	GC yield	Isolated yield
1	4-bromoacetophenone	phenylboronic acid	95%	85%
2	4-bromoacetophenone	4-tolylboronic acid	96%	84%
3	4-bromoacetophenone	2-indenylboronic acid	100%	76%
4	2-bromobenzonitrile	4-tolylboronic acid	100%	90%
5	3-bromopyridine	phenylboronic acid	100%	95% (as HCl salt)
6	2-bromoaniline	phenylboronic acid	89%	80% (as HCl salt)
7	5-bromo-*m*-xylene	phenylboronic acid	34%	
8	4-bromoacetophenone	4-anilineboronic acid pinacol ester	20%	

[a] Toluene as solvent.

um can be used even without tetraalkylammonium salts.[12] Similar results were recently reported by Tao et al. who used $PdCl_2$ in pyridine as solvent with K_2CO_3 as base.[13]

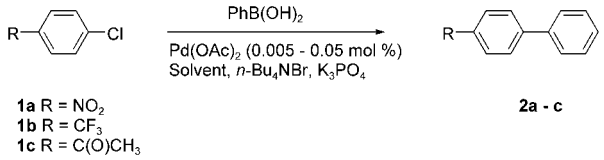
In this paper we report the synthetic details of the use of homeopathic palladium in the Suzuki reaction and the extension of its use to activated aryl chlorides. In addition we report our results on the use of homeopathic palladium in the Negishi and the Kumada reactions.

Results and Discussion

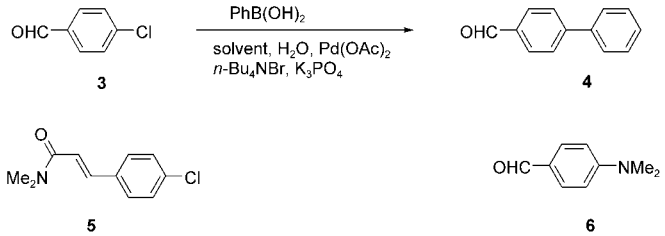
Homeopathic Palladium in the Suzuki Reaction on Aryl Bromides and Chlorides

Biaryl compounds are important intermediates for pharmaceuticals and materials.[1b,2] The Suzuki reaction is one of the methods used in their commercial production.[14] Its application in the production of o-tolylbenzonitrile, an intermediate for several members of the Sartan family of blood-pressure lowering drugs, has been reported.[1b,15] We have used rapid screening in the Chemspeed ASW 2000 to establish the best conditions for the use of homeopathic palladium in the Suzuki reaction on bromobenzene.[12] Initially, we have focussed on aryl bromide conversion as a measure of the reaction rate. From these experiments we have established that NMP/H_2O (19:1) generally is the best solvent, although in some cases toluene could also be used. Out of a range of palladium precursors $Pd(OAc)_2$ emerged as the best one, particularly when toluene was used as solvent. In NMP/H_2O the choice of palladium precursor was less critical and both Pd(II) as well as Pd(0) precursors could be used. Of a number of bases tested, K_2CO_3 gave the best results. Interestingly, in NMP/H_2O 0.5 equivalent of K_2CO_3 is sufficient, although in toluene 1.2 equivalents were necessary. In Table 1 we list the results of a number of 10-mmol scale experiments, which included isolation, performed using 0.02 mol % of catalyst.

The reaction generally works well with aryl bromides containing an electron-withdrawing group giving high isolated yields. (Entries 1–4). Catalyst loadings can be lowered even further. For example, 4-bromoacetophenone and phenylboronic acid are coupled almost quantitatively within an hour using 0.0025 mol % of $Pd(OAc)_2$ ($TOF > 30{,}000$ mol/mol·h). Unsubstituted bromides gave excellent yields as well (not shown in this table; results obtained on 1-mmol scale).[12] Heteroaromatic bromides can also be used. Good results were obtained with 3-bromopyridine (Entry 5). Using aryl bromides with electron-donating substituents resulted in mixed results; whereas 2-bromoaniline could be coupled in high yield with phenylboronic acid (Entry 6), 5-bromo-*m*-xylene gave low yields of coupling products under a variety of conditions (Entry 7). The reaction also has a wide scope in boronic acids, although a poor



Scheme 2. Homeopathic Suzuki reaction on aryl chlorides.



Scheme 3.

yield was obtained in the reaction between 4-bromoacetophenone and 4-anilineboronic acid pinacol ester (Entry 8).

We have not made attempts to discover the exact boundaries of the ligand-free palladium catalyst/substrate ratio in the Suzuki reaction. It seems that in this case the working range is less stringent than for the Heck reaction. This is exemplified by 1) the high turnover frequencies we have observed in the ligand-free Suzuki couplings (up to 30,000 mol/mol·h), so very low loadings, e.g., 0.0025 mol % of palladium still result in high yields in acceptable reaction times and 2) by the results reported by Deng et al. They obtained good yields of Suzuki coupling products working at 2 mol % of ligand-free palladium only if Bu_4NBr was added.[11a] Presumably the tetraalkylammonim bromide stabilises the clusters and prevents the deposition of palladium black.[7] Leadbeater obtained poor yields of Suzuki coupling products with 5 mol % of $Pd(OAc)_2$ in water under microwave conditions.[16] Thus, a safe range would be from 0.0025–0.5 mol %.

We next tried to extend the reaction to aryl chlorides.[17] Indeed, activated aryl chlorides can successfully undergo ligand-free Suzuki coupling using $Pd(OAc)_2$ as catalyst precursor.[11b,18] Heterogeneous palladium catalysts have also been used successfully.[19] Cross-coupling of 4-chloronitrobenzene (**1a**) with phenylboronic acid in the presence of 0.05% $Pd(OAc)_2$, 20% *n*-Bu_4NBr, and K_3PO_4 in DMF-H_2O at 130 °C for 17 h afforded 4-nitrobiphenyl (**2a**) in 94% GC yield (Scheme 2). The reaction can be performed in the absence of *n*-Bu_4NBr under otherwise similar conditions to produce the biaryl product in 82% yield, however, 7% of nitrobenzene was also formed in this case. The presence of water (in stoichiometric quantities) is essential, since the reaction is very slow and often does not go to completion under strictly anhydrous conditions.[20] The Suzuki coupling of 4-chloronitrobenzene (**1a**) can be performed with even lower catalyst loading. Thus, cross-coupling in the presence of 0.005% of $Pd(OAc)_2$ under otherwise identical conditions resulted in 83% yield of biaryl **2a**, with 3% of unreacted chloride **1a** remaining. The reaction does not take place in the absence of the catalyst under thermal or microwave irradiation conditions.[21]

The reaction is rather limited in the scope of aryl chlorides. Cross-coupling of 4-chlorobenzonitrile under the similar conditions yielded the corresponding amide as the major product, resulting from the hydrolysis of the nitrile. The amide was the only product observed even when the reaction was performed at ambient temperature over 4 days.

Low catalyst loading Suzuki coupling of 4-chlorobenzaldehyde (**3**) in NMP at 130 °C yielded only 3% of 4-biphenylcarboxaldehyde (**4**) (Scheme 3). Low product yields were also obtained when the reaction was performed in DMF or DMA. Significant amounts of byproducts resulting from the reaction with the solvent (product of condensation with DMA, **5**) or the product of solvent decomposition (reaction with dimethylamine formed as a result of decomposition of DMF to produce amine **6**) were detected in the latter two cases. Only trace amounts of product were formed when toluene was used as a solvent.

Suzuki coupling of 4-chlorobenzotrifluoride (**1b**) using 0.005% or 0.05% of $Pd(OAc)_2$ in DMF at 130 °C afforded the desired product **2b** in only 7% yield (Scheme 2). Non-activated aryl chlorides, such as 4-chlorotoluene, yielded only trace amounts of the cross-coupling product under similar conditions [0.01% $Pd(OAc)_2$, DMF, H_2O, K_3PO_4, *n*-Bu_4NBr, 130–150 °C].

Low-Pd loading Suzuki coupling of 4-chloroacetophenone (**1c**) was found to be slow, resulting in only 42% conversion after 7 days at 130 °C in DMA-H_2O (Scheme 2). The reaction is lower-yielding in the absence of *n*-Bu_4NBr or at higher temperatures. Nájera et al. obtained a 67% yield of **2c** using 0.1 mol % of $Pd(OAc)_2$.[18]

For Suzuki reactions of unactivated aryl chlorides the palladium catalysts based on basic phosphines obviously give the best results.[17a] Nájera et al. compared the activity of an oxime-derived palladacycle with that of palladium acetate in Suzuki couplings of *p*-bromo- as well as *p*-chloroacetophenone. In the case of the bromide the rates were identical, which we interpret as a strong indication of a mechanistic similarity based on palladium nanoparticles, but in the case of the chloride the palladacycle gave higher rates than $Pd(OAc)_2$ suggesting mechanistic differences.[22]

Homeopathic Palladium in the Negishi Coupling

In the Negishi coupling the aryl-aryl bond is formed by a transition metal-catalysed coupling between ArZnX and an aryl halide.[23] It is also possible to make the reac-

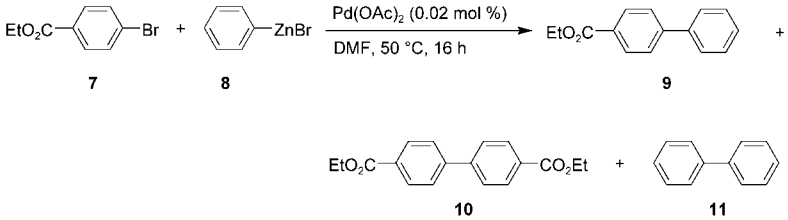
tion catalytic in $ZnCl_2$.[24] This so-called double metal-catalysed Negishi coupling has been used to produce ton amounts of OTBN.[1b–d] Frequently used catalysts are palladium or nickel accompanied by phosphorus-based ligands, such as phosphines, bisphosphines and phosphites.

In initial screening experiments, using 0.02 mol % of $Pd(OAc)_2$ without ligands we found that no reaction occurred between ethyl 4-bromobenzoate (**7**) and PhZnBr (**8**) at room temperature in THF. Raising the temperature to 50 °C and switching the solvent to DMF or NMP eventually led to a 75% yield of the desired biaryl compound (Scheme 4). Lower or substantially higher catalyst loadings led to lower yields. Some homo-coupling is observed in these reactions, both of the aryl bromide as well as of the zinc reagent. The homo-coupling of ArZnBr has been explained by Elsevier et al. as a result of fast exchange of the organo group of the $L_2Pd(Ar)Br$ via pentavalent complexes.[25] Here a different mechanism might be operative. The homo-coupling of ArZnBr may be the result of the coupling taking place via two adjacent palladium atoms on the clusters as the amount of this side product increases with increasing palladium concentration.

We next examined the scope of the homeopathic Negishi reaction (Table 2). The Negishi coupling proceeded well using aryl iodides (Entries 1 and 5) or activated aryl bromides (Entries 2–4) as substrates. Results with bromobenzene under a variety of conditions (Entries 6–11) and with aromatic bromides containing electron-donating groups (Entries 12–15) were less than satisfactory.

Homeopathic Palladium in the Kumada Coupling

The coupling between an arylmagnesium halide and an aryl halide is termed Kumada coupling.[2,20a] In principle this would be the preferred method for cross-coupling as arylZnBr and boronic acid derivatives are often prepared from the corresponding Grignard reagents. However, in view of the higher reactivity of the Grignard reagents the other two methods may be preferred for reasons of selectivity.

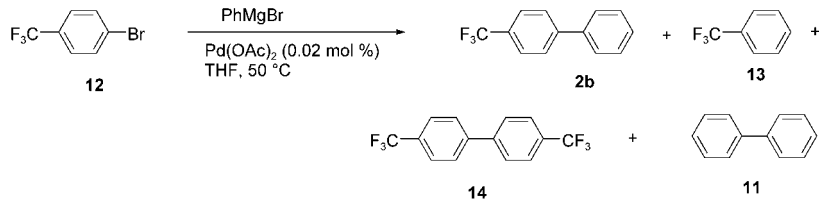


Scheme 4.

Table 2. Scope of homeopathic ligand-free Negishi coupling ($ArX + Ar'ZnX \rightarrow Ar{-}Ar'$).

Entry	ArX	Ar′ZnX	Solvent	Temp. [°C]	Yield of Ar–Ar′ [%][a, b]	Unreacted ArX [%]	Ar–Ar [%]	Ar′–Ar′ [%]
1	$EtO_2CC_6H_4I$	PhZnBr	DMF	50	81	0	1	11
2	$EtO_2CC_6H_4Br$	PhZnBr	DMF	50	75	0	5	18
3	NCC_6H_4Br	PhZnBr	DMF	50	65	0	5	20
4	$F_3CC_6H_4Br$	PhZnBr	DMF	50	76	2	9	15
5	PhI	4-MeC_6H_4ZnI	DMF	50	74	0	6	9
6	PhBr	4-MeC_6H_4ZnI	DMF	50	10	85	<1	4
7	”	”	DMF	100	16	83	<1	7
8	”	”	DMA	50	34	52	<1	6
9	”	”	DMA	100	34	53	<1	6
10	”	”	NMP	50	48	37	<1	6
11	”	”	NMP	100	41	50	<1	5
12	$CH_3C_6H_4Br$	PhZnBr	THF-DMF	55	15[c]	42	<1	4
13	”	”	DMF	50	5	89	0	5
14	”	”	DMF	25	12[d]	79	0	5
15	$MeOC_6H_4Br$	PhZnBr	DMF	25	2[d]	45	0	3

[a] The reactions were typically performed with 0.02 mol % $Pd(OAc)_2$ for 16 h.
[b] GC yields using experimentally determined or calculated response factors.
[c] 0.01 mol % $Pd(OAc)_2$ used.
[d] Reaction time: 3 days.



Scheme 5.

Unlike the case of the arylzinc derivatives, the choice of solvents suitable for Kumada coupling is limited due to the higher reactivity of the Grignard reagents. Polar aprotic solvents like DMF or NMP cannot be used in this case. Cross-coupling of 4-bromobenzotrifluoride (**12**) with phenylmagnesium chloride in THF in the presence of 0.02 mol % of $Pd(OAc)_2$ at 50 °C for 16 h did result in the formation of the biaryl product **2b**, but in only 27% yield, with 28% of unreacted **12** and 4% of 4,4′-bis-(trifluoromethyl)biphenyl (**14**) present (Scheme 5). Significant amounts of the Grignard homo-coupling product **11** (54%), and aryl bromide reduction product trifluorotoluene (**13**) (27%) were formed. Lower reaction temperatures resulted in much slower reaction (4% cross-coupling product, 83% aryl bromide, 17% biphenyl, 4% trifluorotoluene). Very low conversion (1%) was observed in the case of 4-bromotoluene, with significant amounts of **11** formed.

Conclusion

We have shown that use of low ("homeopathic") loadings of $Pd(OAc)_2$ can be used to advantage in the Suzuki reaction of a variety of arylboronic acids (and esters) on aryl bromides and highly activated aryl chlorides. Also in the Negishi reaction on activated aryl bromides the homeopathic palladium concept can be used. However, the method failed in the Kumada reaction, where the desired cross-coupling products could only be obtained in low yields.

Experimental Section

Suzuki Reaction on Aryl Bromides

The aryl halide (10 mmol), boronic acid or ester (12–13 mmol) and K_2CO_3 (5–10 mmol) were put in a 100-mL, three-neck, round-bottom flask equipped with an egg-shaped magnetic stirring bar, a condenser with N_2 inlet on top and a thermometer. After the solvent (NMP/H_2O, 19:1, 50 mL) was added and the reaction mixture was heated at 90 °C the $Pd(OAc)_2$ solution (0.02 mol % in 0.5–1.0 mL of solvent) was added. The conversion of the aryl halide was determined by GC analysis (CP sil 5CB or CP sil 8CB column; temperature gradient from 80–300 °C) using hexyl ether as internal standard. After the reaction had gone to completion the mixture was allowed to cool to ambient temperature. When toluene was used as the solvent only water was added. When NMP/water was used more water and an organic solvent were added. These mixtures were filtered using dicalite speed plus filter aid in order to remove Pd black. The two layers that were obtained were separated and the organic phase was washed with water, dried on Na_2SO_4, and concentrated. The reaction products that contain an amine function were purified as HCl salts. The other products were purified by recrystallisation from hot IPA. All products were known compounds and had NMR and mass spectra in agreement with their structures.

4-Nitro-1,1′-biphenyl from 4-Chloronitrobenzene

4-Chloronitrobenzene (1 g, 6.28 mmol, 99% pure), phenylboronic acid (1.16 g, 1.5 equivs., 9.42 mmol), K_3PO_4 (2.69 g, 2 equivs., 12.56 mmol), *n*-Bu_4NBr (0.409 g, 0.2 equivs., 1.26 mmol), DMF (15 mL), and H_2O (0.23 mL, 2 equivs., 12.56 mmol) were placed in a 50-mL Schlenk tube. $Pd(OAc)_2$ [0.005 mol %; 0.0003 mmol; 0.14 mL of the solution of 10 mg of $Pd(OAc)_2$ in 20 mL of DMF] was added. The solution was deoxygenated by purging with Ar for 5 min. The reaction mixture was stirred in a sealed Schlenk tube at 130 °C for 4 h. GC analysis using tridecane as an internal standard indicated the formation of 4-nitro-1,1′-biphenyl in 85% yield.

Negishi Coupling

Arylzinc halide (3 mmol, 6 mL of 0.5 M THF solution) was placed in a 25-mL, round-bottom flask. The solvent was evacuated in vacuum at room temperature. Anhydrous DMF (4 mL) was added, followed by aryl halide (1 mmol) and $Pd(OAc)_2$ [0.02 mol %, 0.1 mL of the solution of 9 mg of $Pd(OAc)_2$ in 20 mL of DMF]. The reaction mixture was stirred at 50 °C for 16 h. The yield was determined by CG using tridecane as an internal standard.

Acknowledgements

We thank Joe Miller for stimulating discussions. We thank the Dutch Ministry of Economic affairs for a subsidy under the EET Scheme (EETK99104).

References and Notes

[1] a) H.-U. Blaser, A. Indolese, F. Naud, U. Nettekoven, A. Schnyder, *Adv. Synth. Catal.* **2004**, *346*, 1583–1598; b) J. G. de Vries, in: *Encyclopedia of Catalysis*, (Ed.: I. T. Horvath), John Wiley & Sons, New York, **2003**, Vol. 3, p. 295; b) J. G. de Vries, *Can. J. Chem.* **2001**, *79*, 1086; c) J. G. de Vries, A. H. M. de Vries, C. E. Tucker, J. A. Miller, *Innovations Pharm. Tech.* **2001**, *1*, 125; d) C. E. Tucker, J. G. de Vries, *Topics in Catalysis*, **2002**, *19*, 111; e) M. Beller, A. Zapf, in: *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Eds.: E. Negishi, A. de Meijere), John Wiley & Sons, Inc., Hoboken, N. J., **2002**, Vol. 1, p. 1209; f) A. Zapf, M. Beller, *Topics in Catalysis* **2002**, *19*, 101.

[2] a) *Metal-Catalyzed Cross-coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**; *Metal-Catalyzed Cross-coupling Reactions,* 2nd edn., (Eds.: F. Diederich, A. de Meijere), Wiley-VCH, Weinheim, **2004**, Vols. 1 and 2.

[3] *Transition Metals for Organic Synthesis; Building Blocks and Fine Chemicals* (Eds.: M. Beller, C. Bolm), Wiley-VCH, **1998**, Vols. 1 and 2; b) *Transition Metals for Organic Synthesis; Building Blocks and Fine Chemicals,* 2nd edn. (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, Vols. 1 and 2.

[4] a) M. S. Stephan, A. J. J. M. Teunissen, G. K. M. Verzijl, J. G. de Vries, *Angew. Chem. Int. Ed. Eng.* **1998**, *37*, 662; b) M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van - Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586; c) A. H. M. de Vries, F. J. Parlevliet, L. Schmieder-van de Vondervoort, J. H. M. Mommers, H. J. W. Henderickx, M. A. N. Walet, J. G. de Vries, *Adv. Synth. Catal.* **2002**, *344*, 996.

[5] a) T. Jeffery, *J. Chem. Soc. Chem. Commun.* **1984**, 1287–1289; b) T. Jeffery, in: *Advances in Metal-Organic Chemistry*, (Ed.: L. S. Liebeskind), JAI Press, Inc., Greenwich, CT, USA, **1996**, Vol. 5, p. 153; c) T. Jeffery, *Tetrahedron* **1996**, *30,* 10113.

[6] A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx, J. G. de Vries, *Org. Lett.* **2003**, *5*, 3285.

[7] M. T. Reetz, J. G. de Vries, *Chem. Commun.* **2004**, 1559–1563.

[8] A. F. Schmidt, V. V. Smirnov, *J. Mol. Catal. A: Chem.* **2003**, *203*, 75.

[9] Q. Yao, E. P. Kinney, Z. Yang, *J. Org. Chem.* **2003**, *68*, 7528.

[10] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009.

[11] a) Y. Deng, L. Gong, A. Mi, H. Liu, Y. Jiang, *Synthesis* **2003**, 337; b) D. Zim, A. L. Monteiro, J. Dupont, *Tetrahedron Lett.* **2000**, *41*, 8199.

[12] J. G. de Vries, A. H. M. de Vries, *Eur. J. Org. Chem.* **2003**, 799.

[13] X. Tao, Y. Zhao, D. Sheng, *Synlett* **2004**, 359.

[14] For reviews, see: a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) A. Suzuki, *J. Organomet. Chem*. **1999**, *576*, 147; c) A. Suzuki, in: *Metal-Catalyzed Cross-coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, p. 49.

[15] H. Geissler, in: *Transition Metals for Organic Synthesis; Building Blocks and Fine Chemicals*, (Eds.: M. Beller, C. Bolm), Wiley-VCH, **1998**, Vol. 1, p. 158.

[16] N. E. Leadbeater, M. Marco, *Org. Lett.* **2002**, *4*, 2973.

[17] For some reviews and leading references on Pd/phosphine catalysts and palladacycles as catalyst for the Suzuki reaction on aryl chlorides, see: a) A. F. Littke, G. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176; b) R. B. Bedford, *Chem. Commun.* **2003**, 1787; c) M. Miura, *Angew. Chem. Int. Ed.* **2004**, *43*, 2201; d) L. Botella, C. Nájera, *Angew. Chem. Int. Ed.* **2002**, *41*, 179.

[18] For a single example of the use of 0.1 mol % $Pd(OAc)_2$ as catalyst in the Suzuki reaction on aryl chlorides, see: D. A. Alonso, C. Nájera, M. C. Pacheco, *J. Org. Chem.* **2002**, *67*, 5588.

[19] a) C. R. LeBlond, A. T. Andrews, Y. Sun, J. R. Sowa Jr., *Org. Lett.* **2001**, *3*, 1555; b) B. M. Choudary, S. Madhi, N. S. Chowdari, M. L. Kantam, B. Sreedhar, *J. Am. Chem. Soc.* **2002**, *124*, 14127.

[20] The presence of large excess of water leads to the formation of unidentified high-boiling point impurities, especially after prolonged reaction times.

[21] For an example of microwave-assisted transition metal-free Suzuki-type coupling of aryl bromides, see: N. E. Leadbeater, M. Marco, *J. Org. Chem.* **2003**, *68*, 5660.

[22] L. Botella, C. Nájera, *J. Organomet. Chem.* **2002**, *663*, 46.

[23] a) *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Eds.: E. Negishi, A. de Meijere), John Wiley & Sons, Inc., Hoboken, N. J., **2002**, Vols. 1 and 2; b) E. Negishi, F. Liu, in: *Metal-Catalyzed Cross-coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, p. 12; c) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2001**, *58*, 417.

[24] a) J. A. Miller, R. P. Farrell, *Tetrahedron Lett.* **1998**, *39*, 6441; b) J. A. Miller, R. P. Farrell, *Tetrahedron Lett.* **1998**, *39*, 7275.

[25] R. van Asselt, C. J. Elsevier, *Organometallics* **1994**, *13*, 1972.

