Synthetic Methods

DOI: 10.1002/anie.200804898

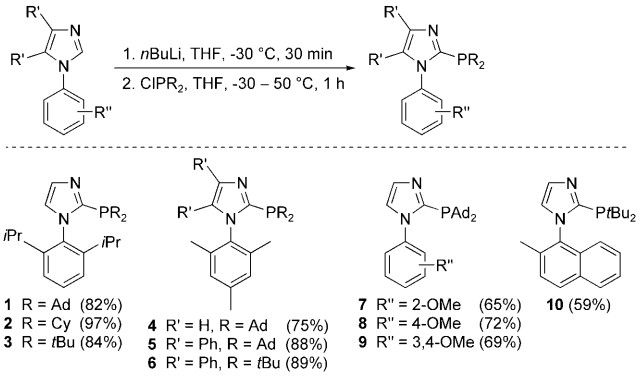
Practical Imidazole-Based Phosphine Ligands for Selective Palladium-Catalyzed Hydroxylation of Aryl Halides**

*Thomas Schulz, Christian Torborg, Benjamin Schäffner, Jun Huang, Alexander Zapf, Renat Kadyrov, Armin Börner, and Matthias Beller**

Phenols are an integral part of numerous pharmaceuticals, polymers, and natural products.[1] In the past the non-oxidative preparation of this class of compounds involved nucleophilic aromatic substitution of activated aryl halides, often under harsh reaction conditions.[2] Smith, Maleczka, and co-workers reported the preparation of non-*ortho*-substituted phenols under milder conditions.[3] However, two steps, CH-activation/borylation and oxidation, were required for the desired transformation. In contrast to well-established palladium-catalyzed aryl ether formations,[4–6] the direct hydroxylation of aryl halides has been a major challenge in coupling chemistry. Buchwald and co-workers achieved this goal for the first time,[7a,b] applying their bulky, monodentate ligands[8] which facilitate C–O reductive elimination. Chen and co-workers[7c] reported the Pd-catalyzed hydroxylation of highly activated aryl bromides in the presence of $P(t\mathrm{Bu})_3$.[9]

Despite these developments, there is a need for easily available ligands which lead to generally applicable, more active catalyst systems for this coupling reaction. Clearly, for selective hydroxylation it is important that the subsequent coupling reaction of the phenol towards diaryl ethers is controlled.

Herein, we describe the synthesis of new, sterically demanding phosphine ligands based on *N*-arylated imidazoles (Scheme 1), and their use in the synthesis of phenols from the corresponding aryl halides. Various dialkyl-2-(*N*-arylimidazolyl)-phosphines (**1**–**10**) were synthesized in one or two reaction steps. Notably, the most active 1-(2,6-diisopropylphenyl)-1*H*-imidazole-based phosphine ligands (**1**–**3**) can be readily prepared on 100 g scale. The corresponding *N*-aryl-1*H*-imidazole unit, which is present in many natural products, including amino acids, nucleic acids, and imidazole-based alkaloids,[10] is easily available by various synthetic strategies and allows high tunability.[11]



Scheme 1. Synthesis of dialkyl-2-(*N*-arylimidazolyl)phosphines.

Ligands **1**–**10** are synthesized using either a copper-catalyzed Ullmann reaction[12] or by a four-component condensation of the corresponding aniline with paraformaldehyde, ammonium acetate, and an α-dicarbonyl component (glyoxal or benzil).[13] The resultant *N*-arylated imidazoles were regioselectively deprotonated with *n*-butyl lithium in THF at −30 °C, and the resulting carbanion subsequently quenched with the corresponding dialkylchlorophosphines to give the desired phosphines in good-to-excellent yields after aqueous work up and single recrystallization from H_2O/EtOH (Scheme 1). Unlike the known *N*-aryl-2-(dialkylphosphino)-(benz)imidazoles,[14,15] the addition of N,N,N′,N′-tetramethylethylenediamine (TMEDA) was not required for selective metalation.[6,16]

The novel phosphine ligands were treated with selenium to give the corresponding phosphine selenides. The magnitude of the coupling constant between the phosphorus and selenium atoms was strongly dependent upon the nature of the organic substituents bound to phosphorus.[17] The values of the coupling constants of **1**–**10** are in the same range as Buchwald's biaryl phosphines **13** and **14** (Table 1), suggesting that the electronic and steric effect of both ligand classes is comparable.

To test the new ligands and their applicability to cross-coupling reactions, the palladium-catalyzed hydroxylation of aryl halides was carried out. Initially, a catalyst derived from $[Pd(dba)_2]$ (dba = dibenzylideneacetone) and ligand **4** showed moderate activity in the hydroxylation of mesityl bromide with sodium hydroxide in a 1:1 mixture of water and 1,4-dioxane at 100 °C (Table 2). The use of potassium hydroxide in place of sodium hydroxide gave slightly improved results, as did NaO*t*Bu and CsOH, whereas triethylamine, K_3PO_4, and inorganic carbonates were ineffective in the reaction. In combination with KOH, 1,4-dioxane was by far the most

[*] T. Schulz, C. Torborg, B. Schäffner, Dr. J. Huang, Dr. A. Zapf, Prof. Dr. A. Börner, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse e.V. an der Universität Rostock
Albert-Einstein-Strasse 29a, 18059 Rostock (Germany)
Fax: (+49) 381-1281-5000
E-mail: matthias.beller@catalysis.de
Dr. R. Kadyrov
Evonik Degussa GmbH—Business Line Catalysis
Rodenbacher Chaussee 4, 63457 Hanau-Wolfgang (Germany)

[**] We thank Dr. W. Baumann, Dr. C. Fischer, A. Koch, S. Buchholz, S. Schareina, A. Kammer, and S. Rossmeisl for excellent analytical support. We gratefully acknowledge Evonik (formerly Degussa) for financial support.

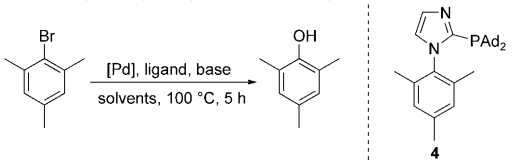
Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200804898.

Table 1: Chemical shifts and $^{31}P{=}^{77}Se$ coupling constants for 2-(*N*-arylimidazolyl)phosphine selenides.[a]

Ligand	δ [ppm]	$^1J_{P=Se}$ [Hz]
1	59.3	718
2	40.3	732
3	62.2	726
4	58.9	712
5	60.0	713
6	63.0	724
7	59.0	715
8	58.9	716
9	59.0	717
10	62.2	726
13	45.2	710
14	71.1	742

[a] The corresponding ligand (0.03 mmol) and selenium (2 equivalents) were dissolved in $CDCl_3$ (0.7 mL) in a NMR tube, heated for a short time at 50 °C and submitted to ^{31}P NMR spectroscopy.

Table 2: Pd-catalyzed hydroxylation of mesityl bromide.



4

Base[a]	Conversion [%]	Yield [%]
NaOH	51	43
KOH	57	55
$CsOH{\cdot}H_2O$	66	50
Na_2CO_3	< 5	< 5
K_2CO_3	5	5
Cs_2CO_3	14	8
K_3PO_4	7	7
NaO*t*Bu	55	46
NEt_3	90	< 1
–	< 5	< 1
Solvent[b]	**Conversion [%]**	**Yield [%]**
1,4-dioxane	57	55
THF	36	36
MeOH	95	14
DMSO	20	20
Toluene	9	9
DMF	43	< 1%
Pd source[c]	**Conversion [%]**	**Yield [%]**
$[Pd(dba)_2]$	57	55
$Pd(OAc)_2$	29	29
$[Pd(CH_3CN)_2Cl_2]$	12	12
$[Pd(PPh_3)_4]$	< 5	< 5

[a] $[Pd(dba)_2]$ (1 mol%), ligand **4** (4 mol%), base (3 equivalents), H_2O/1,4-dioxane (1:1, 1.2 mL, 0.8 M), 100 °C, 5 h; [b] $[Pd(dba)_2]$ (1 mol%), ligand **4** (4 mol%), KOH (3 equivalents), H_2O/organic solvent (1:1, 1.2 mL, 0.8 M), 100 °C, 5 h; [c] [Pd] (1 mol%), ligand **4** (4 mol%), KOH (3 equivalents), H_2O/1,4-dioxane (1:1, 1.2 mL, 0.8 M), 100 °C, 5 h.

effective organic cosolvent. The other palladium sources investigated were inferior to $[Pd(dba)_2]$.

Next, different ligands were applied to the model hydroxylation reaction, and compared with commercially available ligands (Table 3). In general, the more bulky ligands

Table 3: Ligands for Pd-catalyzed hydroxylation of mesityl bromide.[a]

Entry	Ligand	R	R′	R″	Yield [%]
1	**1**	Ad			77; 72;[b] 88[c]
2	**2**	Cy			0
3	**3**	*t*Bu			49
4	**4**	Ad	H		56
5	**5**	Ad	Ph		75
6	**6**	*t*Bu	Ph		62
7	**7**			2-OMe	0
8	**8**			4-OMe	0
9	**9**			3,4-OMe	0
10	**10**				58
11	**11**				0
12	**12**				0
13	**13**	Cy			1
14	**14**	*t*Bu			8[d]
15	**15**				3
16	**16**				0

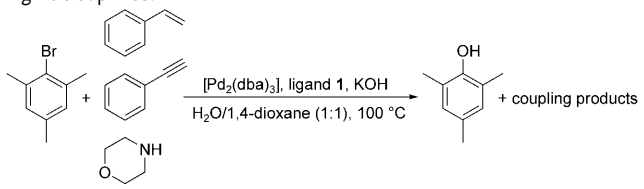
[a] $[Pd_2(dba)_3]$ (1 mol%), ligand (4 mol%), KOH (3 equivalents), H_2O/1,4-dioxane (1:1, 1.2 mL, 0.8 M), 100 °C, 20 h; [b] toluene as organic cosolvent; [c] with $CsOH{\cdot}H_2O$ (3 equivalents) as base, no addition of water; [d] under Buchwald's reaction conditions (mesityl bromide (1 mmol), $[Pd_2(dba)_3]$ (2 mol%), ligand **14** (8 mol%), KOH (3 equivalents), 1,4-dioxane, H_2O, 100 °C, 6 h), a yield of 88% was verified.[7a]

gave better results. For example, adamantyl-substituted ligands proved superior compared to the *tert*-butyl-substituted ligands, whereas cyclohexyl-substituted phosphines led to no reactivity at all (Table 3, entries 1–3). Moreover, for reaction to proceed, substitution at both *ortho*-positions on the aryl ring was necessary (Table 3, entries 7–9). Ligands with a less sterically demanding substitution pattern (mesityl, Table 3, entry 4) were inferior to more bulky ones (2,6-diisopropylphenyl, Table 3, entry 1). Consequently, combining these positive structural features, that is, 1-adamantyl groups attached to phosphorus and isopropyl groups at the 2- and 6-positions of the aryl ring, led to the highest yield in the model reaction (Table 3, entry 1; 77%).

Advantageously, substituents on the imidazole ring could also be altered to improve reactivity (Table 3, entries 5, 6). It is important to note that the commercially available ligands tested led to low or no reactivity (Table 3, entries 11, 12, 15, and 16). Furthermore, only trace amounts of product were detected from the reaction with Buchwald's XPhos ligands under these conditions (Table 3, entries 13, 14).

To understand the behavior of the new catalysts, competitive experiments were carried out in the presence of olefins, alkynes and amines (Table 4). One equivalent (with respect to mesityl bromide) of styrene, phenylacetylene, or morpholine was added to the reaction mixture without optimization. Surprisingly, in the presence of styrene, the potential Heck reaction did not occur and the hydroxylated product was formed in 74% yield. Similarly, the coupling reaction in the presence of morpholine is highly chemoselective, albeit with a reduced conversion. Conversely, the alkyne–arene coupling competed with the hydroxylation. Nevertheless, 55% of the desired phenol was obtained, with 22% of the diarylalkyne. These experiments demonstrate for the first time the high specificity of a palladium catalyst system towards hydroxylation reactions.

Table 4: Selectivity of the hydroxylation reaction in presence of competing nucleophiles.[a]

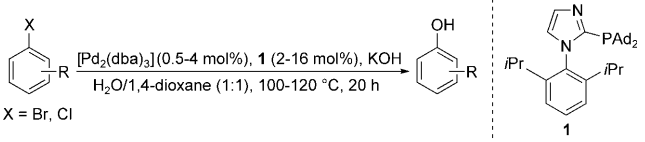


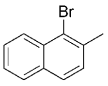
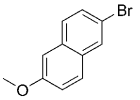
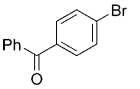
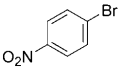
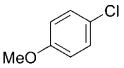
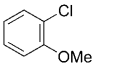
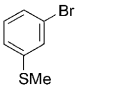
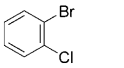
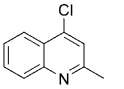
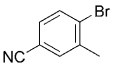
Nucleophile	Yield of phenol [%]	Ratio (phenol/coupling product)
	74	>15:1
	55	2.5:1
	16	>50:1

[a] Mesityl bromide (1 mmol), competing nucleophile (1 mmol), [Pd_2(dba)$_3$] (1 mol%), ligand **1** (4 mol%), KOH (3 equivalents), 1,4-dioxane (0.6 mL), H_2O (0.6 mL), 100°C, 20 h.

Finally, the scope of the catalyst system [Pd_2(dba)$_3$]/ligand **1** was examined by treating various aryl bromides and chlorides with KOH in water/1,4-dioxane (Table 5). Different alkyl-substituted aryl bromides and chlorides were converted into the corresponding phenols in good-to-excellent yields (Table 5, entries 1–6; 73–93%). Both activated substrates, such as 4′-bromobenzophenone (Table 5, entry 8; 91%) and 4-bromonitrobenzene (Table 5, entry 9; 99%), and deactivated arenes, such as anisoles and thioanisoles (Table 5, entries 10–12; 88–94%), were fully converted. For aryl chloride substrates, the use of CsOH as a base led to better results and full conversion. In comparison with 2- and 4-chloroanisole, the hydroxylation of 2-bromo-6-methoxynaphthalene was less selective and afforded the corresponding naphthalene-2-ol in moderate yield (Table 5, entry 7; 50%). On using 1-bromo-2-chlorobenzene as the substrate, as expected when substitution of bromide competes with the substitution of chloride, substitution of bromide occurred preferentially (Table 5, entry 13), and only a small amount (<5%) of the chloride-substituted product could be detected. For full conversion of 4-chloroquinaldine, only 1 mol% of palladium (0.5 mol% of [Pd_2(dba)$_3$]) was required (Table 5, entry 14; 99%). Conversely, complete hydroxylation in the presence of a nitrile group necessitated a higher catalyst loading (Table 5, entry 15; 68%).

Table 5: Palladium-catalyzed synthesis of phenols from aryl halides.[a]



Entry	Substrate	Yield [%]
1		88[b]
2		93
3		90[c]
4		83
5		73
6		80[c]
7		50
8		91
9		99
10		94[b]
11		90[b]
12		88
13		78[d]
14		99[e]
15		68[f]

[a] Substrate (1 mmol), [Pd_2(dba)$_3$] (1 mol%), ligand **1** (4 mol%), KOH (3 equivalents), 1,4-dioxane (0.6 mL), H_2O (0.6 mL), 100°C, 20 h; [b] CsOH·H_2O (3 equivalents) as base with 1,4-dioxane (1.2 mL) and no addition of water, 120°C; [c] [Pd_2(dba)$_3$] (2 mol%), ligand **1** (8 mol%); [d] product = 2-chlorophenol; [e] [Pd_2(dba)$_3$] (0.5 mol%), ligand **1** (2 mol%); [f] [Pd_2(dba)$_3$] (4 mol%), ligand **1** (16 mol%).

In summary, we synthesized a series of novel imidazole-based phosphine ligands. These phosphines were readily generated in high yields and purities from the corresponding imidazole precursors, by a convenient lithiation–phosphorylation method. Notably, the preparations could be easily scaled up to afford the phosphines on 100 g scale for potential applications. The ligands are remarkably stable towards air and were successfully applied as ligands in the palladium-catalyzed selective hydroxylation of aryl halides with low palladium loadings in the majority of cases. The hydroxylation procedure was uncomplicated and did not require special reagents.[3] Further applications of these ligands are currently under investigation in our laboratories.

Received: October 7, 2008
Published online: December 22, 2008

Keywords: chemoselectivity · homogeneous catalysis · hydroxylation · palladium · phosphines

[1] a) J. H. P. Tyman, *Synthetic and Natural Phenols*, Elsevier, New York, **1996**; b) Z. Rappoport, *The Chemistry of Phenols*, Wiley-VCH, Weinheim, **2003**; c) J. F. Hartwig in *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-I. Negishi), Wiley-Interscience, New York, **2002**.

[2] a) C. A. Fyfe in *The Chemistry of the Hydroxyl Group*, *Vol. 1* (Ed.: S. Patai), Wiley-Interscience, New York, **1971**, pp. 83–127; b) C. Hoarau, T. R. R. Pettus, *Synlett* **2003**, 127; c) P. Hanson, J. R. Jones, A. B. Taylor, P. H. Walton, A. W. Timms, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1135; d) T. George, R. Mabon, G. Sweeney, J. B. Sweeney, A. J. Tavassoli, *Chem. Soc. Perkin Trans. 1* **2000**, 2529, and references therein.

[3] R. E. Maleczka, F. Shi, D. Holmes, M. R. Smith III, *J. Am. Chem. Soc.* **2003**, *125*, 7792.

[4] a) A. V. Vorogushin, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 8146; b) K. E. Torraca, X. Huang, C. A. Parrish, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 10770; c) C. H. Burgos, T. E. Barder, X. Huang, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 4427; *Angew. Chem. Int. Ed.* **2006**, *45*, 4321; d) A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 4369; e) K. E. Torraca, S.-I. Kuwabe, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12907; f) C. A. Parrish, S. L. Buchwald, *J. Org. Chem.* **2001**, *66*, 2498.

[5] a) N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553; b) Q. Shelby, N. Kataoka, G. Mann, J. F. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 10718.

[6] a) S. Harkal, K. Kumar, D. Michalik, A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, M. Beller, *Tetrahedron Lett.* **2005**, *46*, 3237; b) N. Schwarz, A. Pews-Davtyan, K. Alex, A. Tillack, M. Beller, *Synthesis* **2007**, *23*, 3722.

[7] a) K. W. Anderson, T. Ikawa, R. E. Tundel, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 10694; b) M. C. Willis, *Angew. Chem.* **2007**, *119*, 3470; *Angew. Chem. Int. Ed.* **2007**, *46*, 3402; c) G. Chen, A. S. C. Chan, F. Y. Kwong, *Tetrahedron Lett.* **2007**, *48*, 473.

[8] For further applications of Buchwald's biarylphosphine ligands in C–C and C–N bond formation see: a) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; b) J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360; c) J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1158; d) H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11818; e) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653; f) D. Gelman, S. L. Buchwald, *Angew. Chem.* **2003**, *115*, 6175; *Angew. Chem. Int. Ed.* **2003**, *42*, 5993; g) D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722.

[9] For further examples of $P(t\mathrm{Bu})_3$ as a monodentate ligand, see: a) A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176; b) A. F. Littke, L. Schwarz, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 6343; c) A. F. Littke, G. C. Fu, *Angew. Chem.* **1998**, *110*, 3586; *Angew. Chem. Int. Ed.* **1998**, *37*, 3387; d) A. F. Littke, G. C. Fu, *Angew. Chem.* **1999**, *111*, 2568; *Angew. Chem. Int. Ed.* **1999**, *38*, 2411; e) C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 2719; f) M. R. Netherton, G. C. Fu, *Org. Lett.* **2001**, *3*, 4295; g) T. Hama, J. F. Hartwig, *Org. Lett.* **2008**, *10*, 1545; h) T. Hama, J. F. Hartwig, *Org. Lett.* **2008**, *10*, 1549; i) W. Su, S. Raders, J. G. Verkade, X. Liao, J. F. Hartwig, *Angew. Chem.* **2006**, *118*, 5984; *Angew. Chem. Int. Ed.* **2006**, *45*, 5852; j) T. Hama, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 4976; k) X. Liu, J. F. Hartwig, *J. Am. Chem. Soc.* **2004**, *126*, 5182; l) T. Hama, X. Liu, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 11176; m) M. Jørgensen, S. Lee, X. Liu, J. P. Wolkowski, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 12557; n) N. A. Beare, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 541; o) M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 1473; p) S. Shekhar, J. F. Hartwig, *Organometallics* **2007**, *26*, 340; q) M. W. Hooper, M. Utsunomiya, J. F. Hartwig, *J. Org. Chem.* **2003**, *68*, 2861; r) R. Kuwano, M. Utsunomiya, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 6479; s) S. Lee, M. Jørgensen, J. F. Hartwig, *Org. Lett.* **2001**, *3*, 2729; t) J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, L. M. Alcazar-Roman, *J. Org. Chem.* **1999**, *64*, 5575; u) J. F. Hartwig, *Synlett* **2006**, 1283, and references therein.

[10] a) M. R. Grimmet in *Comprehensive Heterocyclic Chemistry*, *Vol. 4* (Ed.: K. T. Potts), Pergamon, Oxford, **1984**, pp. 345–498; b) M. R. Grimmet in *Comprehensive Heterocyclic Chemistry II*, *Vol. 3* (Ed.: I. Shinka), Pergamon, Oxford, **1996**, pp. 77–220.

[11] K. Ebel in *Houben-Weyl: Methoden der organischen Chemie: Hetarene III, 1H-Imidazole* (Ed.: E. Schaumann), Thieme, Stuttgart, **1994**, pp. 1–215.

[12] a) H. Zhang, Q. Cai, D. Ma, *J. Org. Chem.* **2005**, *70*, 5164; b) E. Alcalde, I. Dinarès, S. Rodríguez, C. G. de Miguel, *Eur. J. Org. Chem.* **2005**, 1637.

[13] a) B. E. Ketz, A. P. Cole, R. M. Waymouth, *Organometallics* **2004**, *23*, 2835; b) M. G. Gardiner, W. A. Herrmann, C.-P. Reisinger, J. Schwarz, M. Spiegler, *J. Organomet. Chem.* **1999**, *572*, 239.

[14] M. Beller, S. Harkal, F. Rataboul, A. Zapf, C. Fuhrmann, T. Riermeier, A. Monsees, *Adv. Synth. Catal.* **2004**, *346*, 1742.

[15] F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, U. Dingerdissen, M. Beller, *Chem. Eur. J.* **2004**, *10*, 2983.

[16] For catalytic applications of the cata*CX*ium P ligands see: a) A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, C. Fuhrmann, N. Shaikh, U. Dingerdissen, M. Beller, *Chem. Commun.* **2004**, 38; b) A. Zapf, M. Beller, *Chem. Commun.* **2005**, 431; c) M. Beller, A. Zapf, T. Riermeier, *Spec. Chem. Mag.* **2004**, *24*, 22.

[17] D. W. Allen, B. F. Taylor, *J. Chem. Soc. Dalton Trans.* **1982**, 51.

