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Synthesis of Novel Bisphosphine-Containing Polymers and Their Applications as Bidentate Ligands for Nickel(0)-Catalyzed Cross-Coupling Reactions

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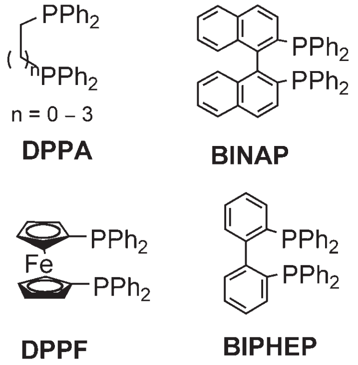
Abstract: The efficient synthesis of two examples of a new type of ferrocene-based bisphosphine-containing polymers and their application as bidentate ligands for Ni(0)-catalyzed cross-coupling reactions of aryl chlorides with arylboronic acids, and aryl fluorides with Grignard reagents are described. Our study may provide a new family of bisphosphine-containing polymers that are readily accessible and potentially useful in transition metal catalysis.

Keywords: aryl chlorides; cross-coupling; immobilization; nickel; phosphane ligands; Suzuki–Miyaura reaction

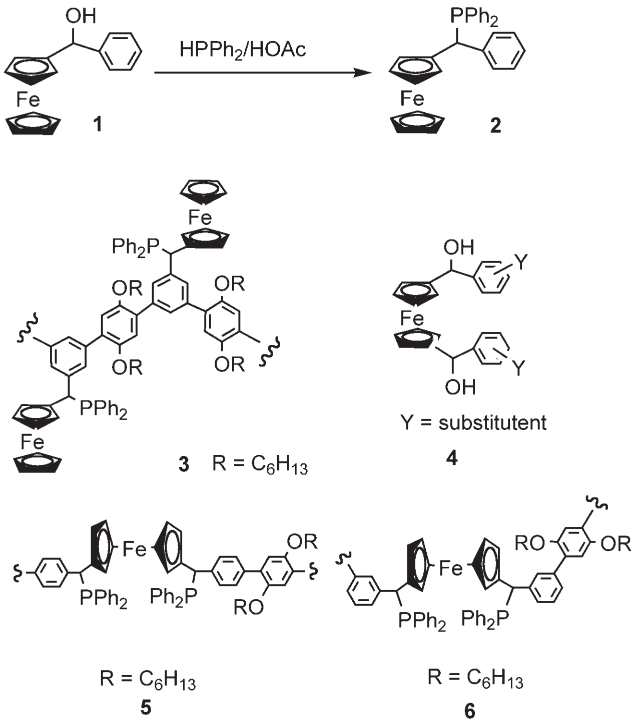


Bisphosphines such as 1,n-diphenylphosphinoalkanes (DPPA) and derivatives, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), 1,1′-bis(diphenylphosphino)-ferrocene (DPPF), and 2,2′-bis(diphenylphosphino)-1,1′-biphenyl (BIPHEP) represent a large group of bidentate ligands in transition metal catalysis.[1,2] They have been demonstrated as very useful ligands in an array of bond-forming reactions including catalytic hydrogenations and transition metal-catalyzed cross-coupling reactions.[1,2] Since the 1970s, studies have been carried out to immobilize bidentate bisphosphines in polymer networks.[3] However, despite the fact that polymer-supported bisphosphines possess advantages such as easy recovery and reuse, and sometimes higher catalytic activities for derived catalysts compared to their monomeric counterparts, only a limited number of polymer-supported bisphosphines has been developed and their applications as ligands in transition metal catalysis have not reached a level that parallels that of their monomeric counterparts.

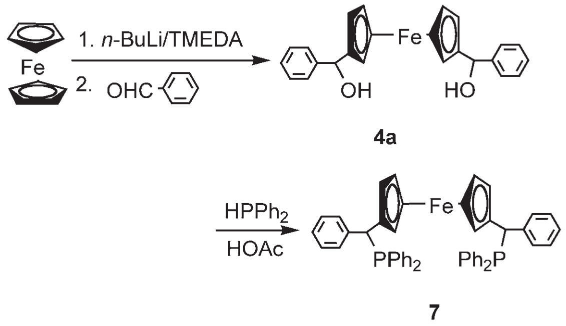
Careful examination suggested that the unbalanced phenomenon of potential advantages bisphosphine-containing polymers could have *vs.* the limited number of bisphosphine-containing polymers developed and studied likely resulted from deficiencies associated with their synthesis and/or catalysis. The synthesis of previously reported bisphosphine-polymers is often characterized by long synthetic steps and/or not readily available starting materials. In addition, the performance of many of the reported bisphosphine-containing polymers is not as good as that of the monomeric counterparts for chosen transformations. It is thus of great interest to develop new types of bisphosphine-containing polymers that meet the following criteria: (a) starting materials are readily available, (b) the synthetic elaboration is short, (c) their electronic and steric properties are tunable, and (d) they should perform equally well as or (e) better than their monomeric counterparts for chosen transformations.

In our laboratory, we are interested in developing new, readily accessible ligands for transition metal catalysis. We have initialized a project to synthesize ferrocenylmethyl-containing ligands from ferrocenylmethyl alcohols based on the following considerations:[4] (a) ferrocenylmethyl alcohols including optically active forms are readily available, and (b) the unique retentive S_N1 reaction at the α-position of ferrocene would allow easy access to a family of ferrocenylmethyl-containing ligands with tunable steric and electronic properties. We have developed a protocol to directly convert ferrocenylmethyl alcohols to monodentate ferrocenylmethylphosphines (Scheme 1),[5] and have also successfully applied it for the preparation of ferrocenylmethylphosphine-containing polymers **3** in very few steps (Scheme 1).[6] Since 1,1′-bis(hydroxymethyl)ferrocenes such as **4** are readily available *via* a one-step reaction from ferrocene and aldehydes and the hydroxy groups of **4** are structurally similar to that of ferrocenylmethyl alcohol **1**, we reasoned that the hydroxy groups in **4** should behave similarly to that of **1** and should also be capable of directly conversion to diphenylphosphosphino moieties. We believed that successfully realizing this could lead us to the development of a new family of ferrocene-based, bisphosphine-containing polymers from readily available starting materials in very few synthetic steps. In this communication, we report the efficient synthesis of two examples of this new type of ferrocenylmethyl-based bisphosphine-containing polymers, **5** and **6**, and their applications as bidentate ligands in Ni(0)-catalyzed cross-couplings of aryl chlorides with arylboronic acids, and aryl fluorides with Grignard reagents.

We began our study by testing the reaction of $HPPh_2$ with diol **4a**, which was readily prepared from ferrocene and benzaldehyde.[4,7,8] We were pleased to find that bisphosphine **7** was indeed formed directly from **4a** under the conditions that are similar to the preparation of **2** (100% conversion, 47% isolated yield) (Scheme 2).



Scheme 1. Direct conversion of ferrocenylmethyl alcohols to ferrocenylmethylphosphines.

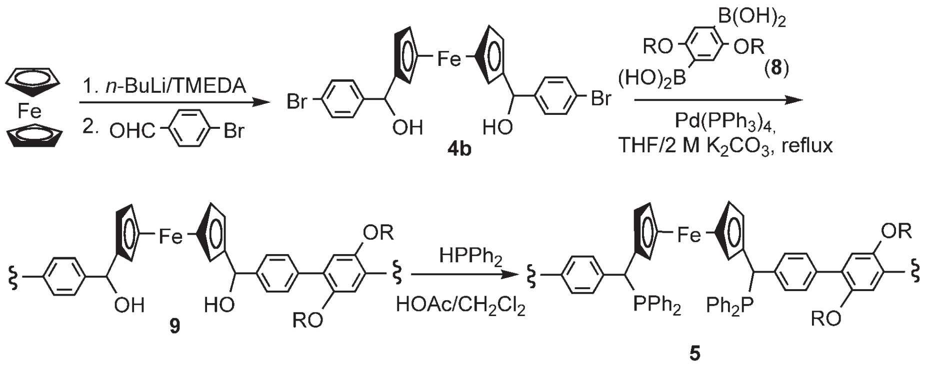


Scheme 2. Direct conversion of 1,1′-bis(1-hydroxy-1-phenylmethyl)ferrocene to bisphosphine **7**.

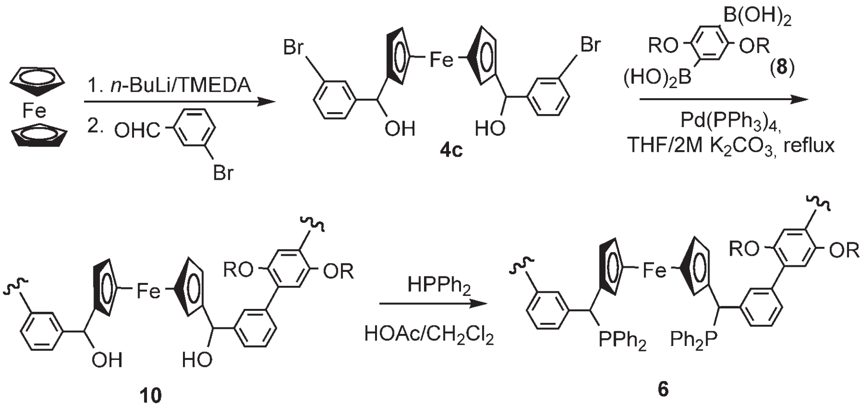
Having established that the feasibility to directly convert 1,1′-bis(hydroxymethyl)ferrocenes to 1,1′-bis(diphenylphosphosphinomethyl)ferrocenes, we were settled to extend this protocol for the preparation of ferrocene-based bisphosphine-containing polymers. As shown in Scheme 3, starting from inexpensive ferrocene, reaction with *n*-BuLi and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) followed by treatment with 4-bromobenzaldehyde generated dibromide **4b** in 75% yield.[7] Pd(0)-catalyzed Suzuki cross-coupling polymerization with diboronic acid **8** generated polymer **9** in 96% yield.[9] By following the procedure described above, we were pleased to find that treatment of polymer **9** with $HPPh_2$ smoothly generated polymer **5**. Polymer **5** is soluble in common organic solvents such as THF, toluene, dichloromethane and can be precipitated out from methanol. GPC (polystyrene standards, THF) analysis shows its molecular weight is $M_w = 4{,}300$, $M_n = 3{,}100$ (PDI = 1.41). The complete conversion of $-OH$ to $-PPh_2$ was confirmed by ^1H NMR.

Polymer **6** was prepared in a similar manner by starting from ferrocene and 3-bromobenzaldehyde (Scheme 4). Polymer **6** is also soluble in common organic solvents such as THF, toluene, dichloromethane. The complete conversion of $-OH$ to $-PPh_2$ was also confirmed by ^1H NMR.

Transition metal-catalyzed Suzuki coupling of deactivated aryl chlorides with arylboronic acids has only been realized recently and represents a notable advance in transition metal-catalyzed chemistry.[10–12] Although a number of ligands can now achieve this objective, truly recoverable and reusable ligands are rare.[13] We have employed **5** as a ligand for Ni(0)-catalyzed Suzuki coupling reactions of aryl chlorides and arylboronic acids. As shown in Table 1, $Ni(COD)_2$/**5** complexes (3 mol %/9 mol%) smoothly catalyzed the coupling reaction between aryl chlorides, including electron-rich ones, and arylboronic acids. The polymer ligands exhibited similar catalytic efficiency as bisphosphine **7** (Table 1, entries 15, 16), and can be readily recovered and reused (Table 1, entries 2, 8, 11).



Scheme 3. Preparation of bisphosphine-containing polymer **5**.



Scheme 4. Preparation of bisphosphine-containing polymer **6**.

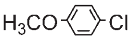
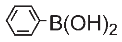
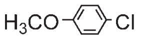
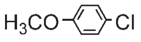
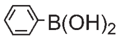
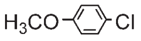
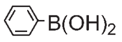
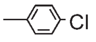
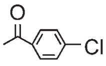
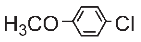
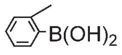
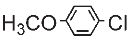
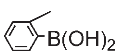
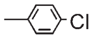
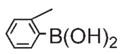
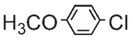
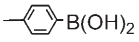
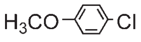
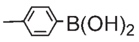
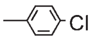
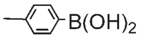
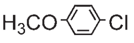
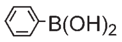
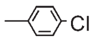
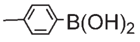
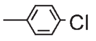
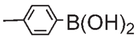
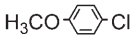
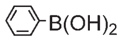
To establish the coordination nature of the new type of bisphosphine-containing polymers in Ni(0)-catalyzed cross-couplings of aryl chlorides with arylboronic acids, we have compared the catalytic behavior of different ligands using the cross-coupling reaction of *p*-chloroanisole with phenylboronic acid as the model reaction. We found that monodentate ferrocenylmethylphosphine **2**, as well as its polymeric form **3**, was an efficient ligand for room temperature Ni(0)-catalyzed cross-coupling of aryl chlorides with arylboronic acids (Table 2, entries 1, 2). On the other hand, the same reactions only take place at elevated temperature when bidentate DPPF and 1,2-bis(diphenylphosphino)ethane (DPPE) are used as ligands (Table 2, entries 3–5).[12] We found that the catalytic property of polymer **5** was very similar to that of DPPF and DPPE (Table 2, entries 6–9). These results suggested that the phosphine moieties in polymers **5** and **6** most likely functioned as bidentate ligands rather than monodentate ones.

We also briefly examined another type of challenging cross-coupling reaction that involves bidentate ligands such as DPPP/DPPE as ligands: the cross-coupling of fluoroarenes with Grignard reagents.[14,15] We found that polymer **5** behaved similarly as DPPE and its monomeric counterpart **7** (Table 3). Polymer **5** has also been demonstrated to be recoverable and reusable.

In summary, the synthesis of two examples of a new type of ferrocene-based bisphosphine-containing polymers and their application as bidentate ligands for Ni(0)-catalyzed cross-coupling reactions are described. Our study showed that (a) this new family of ferrocene-based bisphosphine-containing polymers could be readily accessible in very few steps from readily available starting materials, (b) the catalytic properties of the new ferrocene-based bisphosphine polymers exhibited in Ni(0)-catalyzed cross-coupling reactions of aryl chlorides with arylboronic acids, and aryl fluorides with Grignard reagents were comparable to those of their monomeric counterparts, and (c) the polymer could be recovered and reused. Our future work will be focused on the preparation of other related polymers including optically active ones and exploration of their applications for other Pd(0)- and Ni(0)-catalyzed cross-coupling reactions.

Table 1. Ni(0)-catalyzed cross-coupling reactions of aryl chlorides with arylboronic acids.[a]

$$\text{Ar-Cl} + \text{B(OH)}_2\text{-Ar'} \xrightarrow[\text{K}_3\text{PO}_4\text{, THF, reflux, 20-24 h}]{\text{3 mol \%Ni(COD)}_2\text{ /9\% ligand}} \text{Ar -Ar'}$$

Entry	Ar-Cl	Ar'-B(OH)$_2$	Ligand	Yield [%][b]
1			**5**	84
2			**5**	82[c]
3			No ligand	17
4			**9**	18
5			**5**	60
6			**5**	70
7			**5**	60
8			**5**	69[c]
9			**5**	67
10			**5**	78
11			**5**	84[c]
12			**5**	99
13			**6**	89
14			**6**	93
15			**7**	95[d}
16			**7**	82[d]

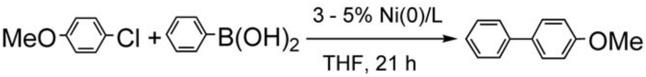
[a] *Reaction conditions* (not optimized): aryl chlorides (1.0 mmol.), arylboronic acids (1.5 equivs.), K_3PO_4 (3 equivs.), 3 mol % Ni(COD)$_2$, ligand (9 mol % based on repeat unit), THF (2 mL).

[b] Yields of isolated products.

[c] Recovered polymer was used.

[d] Conversion based on ^{1}H NMR.

Table 2. Ni(0)-catalyzed Suzuki cross-coupling of *p*-chloroanisole with phenylboronic acid.[a]



Entry	Ligand	Temperature	Yield [%][b]
1	**2**	Room Temp.	89
2	**3**	Room Temp.	33
3	DPPF or DPPE	Room Temp.	<10
4	DPPF	80 °C	86[c]
5	DPPE	80 °C	84[d]
6	**5**	Room Temp.	0
7	**7**	Room Temp.	0
8	**5**	70 °C	84
9	**7**	70 °C	82

[a] *Reaction conditions: p*-chloroanisole (1.0 equiv.), phenylboronic acid (1.5 equivs.), K_3PO_4 (3 equivs.), THF (2 mL).

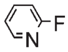
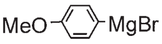
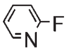
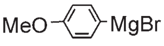
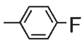
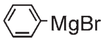
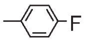
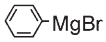
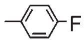
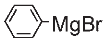
[b] Yield of isolated products.

[c] Ref.[12a]

[d] Ref.[12c]

Table 3. Ni(0)-catalyzed cross-coupling reactions of aryl fluorides with Grignard reagents.[a]

$$\text{Ar-F} + \text{BrMg-Ar} \xrightarrow[\text{THF, r. t., 18 - 24 h}]{\text{Ni(acac)}_2\text{/ligand (1:1)}} \text{Ar-Ar'}$$

Entry	Ar-F	BrMg-Ar	Ni(acac)$_2$	Ligand	Yield [%][b]
1			5 mol %	**5**	53
2			5 mol %	**7**	68
3			5 mol %	**5**	76[c]
4			5 mol %	**7**	77[c]
5			10 mol %	**5**	78[c,d]

[a] *Reaction conditions* (not optimized): fluoride (1.0 mmol), Grignard reagent (1.5–2.0 equivs.), 1:1 ratio of Ni-(acac)$_2$/ligand (based on repeat unit), THF (2 mL).

[b] Yield of isolated products.

[c] Based on ^{1}H NMR.

[d] Recovered polymer was used.

Experimental Section

Preparation of Polymer 5

To a solution of polymer **9** (0.67 g, 1 mmol based on repeating unit) in CH_2Cl_2 (5 mL), HOAc (2 ml) was added under N_2. $HPPh_2$ (1.64 mL, 10 wt % in hexanes) was syringed into the flask. The mixture was stirred overnight at room temperature. The solvents were evaporated under vacuum. The residue was dissolved in a small amount of degassed CH_2Cl_2 and precipitated from degassed MeOH. The process was repeated four more times. The precipitate was obtained by syringing out the solvent. After drying under vacuum, **5** was obtained as a yellow solid; yield: 0.534 g (53%).

General Procedure for Ni(COD)$_2$/Polymer Ligand-Catalyzed Suzuki Cross-Coupling Reactions of Aryl Chlorides with Arylboronic Acids

To a vial containing **5** or **6** (45 mg, 0.0045 mmol), Ni(COD)$_2$ (4.12 mg, 0.0015 mmol), arylboronic acid (91 mg, 0.75 mmol), K_3PO_4 (318 mg, 1.5 mmol) was added THF (2.0 mL). After the mixture was stirred at room temperature for *ca.* 5 min, aryl chloride (0.5 mmol) was added by a syringe. The reaction mixture was allowed to reflux for 24 h. The reaction was quenched by water and extracted with diethyl ether. The organic layer was washed with brine. Evaporation of solvents and purification of the residue by column chromatography on silica gel with ethyl acetate/hexane as eluent afforded the biphenyl products.

For detailed procedures and characterization data, see Supporting Information.

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References and Notes

[1] a) M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*, Wiley-VCH, Weinheim, **1998**; b) P. J. Stang, *Transition Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, New York, **1998**; c) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, **1995**; c) J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, **1987**.

[2] a) B. M. Trost, I. Fleming, *Comprehensive Organic Synthesis*, Vols. 1 and 2, Pergamon, Oxford, **1991**; b) E. N. Jacobsen, A. Pfaltz, Y. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*, Springer, Heidelberg, Berlin, **1999**; c) I. Ojima, *Catalytic Asymmetric Synthesis*; VCH, Weinheim, **1993**.

[3] For recent comprehensive reviews: a) J. Gladysz (Guest Editor), *Chem. Rev.* **2002**, *102*, 3215–3810; also see: b) S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, I. Storer, S. J. Taylor, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3815–4195.

[4] For reviews of ferrocenes: a) A. Togni, T. Hayashi, *Ferrocene. Homogeneous Catalysis. Organic Synthesis. Materials Sciences*, VCH, Weinheim, **1995**; b) C. J. Richards, A. J. Locke, *Tetrahedron: Asymmetry* **1998**, *9*, 2377–2407.

[5] Z.-Y. Tang, Y. Lu, Q.-S. Hu, *Org. Lett.* **2003**, 5; 297–300.

[6] Q.-S. Hu, Z.-Y. Tang, Y. Lu, H.-B. Yu, *J. Am. Chem. Soc.* **2003**, 125, 2856–2857.

[7] T. Sammakia, H. A. Latham, *J. Org. Chem.* **1996**, *61*, 1629–1635.

[8] a) L. Schwink, P. Knochel, *Chem. Eur. J.* **1998**, *4*, 950–968; b) J. J. A. Perea, M. Lotz, P. Knochel, *Tetrahedron: Asymmetry* **1999**, *10*, 375–384; c) L. Schwink, T. Ireland, K. Puntener, P. Knochel, *Tetrahedron: Asymmetry* **1998**, *9*, 1143–1163.

[9] Q.-S. Hu, in: *Synthetic Methods for Step-Growth Polymers*, (Eds.: M. Rogers, T. Long), Wiley, Chichester, **2003**, Chapter 9, 467–526.

[10] For a recent review on Pd(0)-catalyzed cross-couplings of aryl chlorides, see: A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211.

[11] For recent reviews on nickel-catalyzed Suzuki cross-couplings of aryl chlorides, see: a) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470; b) B. H. Lipshutz, *Adv. Synth. Catal.* **2001**, *343*, 313–326.

[12] a) V. Percec, G. M. Golding, J. Smidrkal, O. Weichold, *J. Org. Chem.* **2004**, *69*, 3447–3452; b) K. Inada, N. Miyaura, *Tetrahedron* **2000**, *56*, 8657–8660; c) S. Saito, S. Oh-tani, N. Miyaura, *J. Org. Chem.* **1997**, *62*, 8024–8030; d) A. F. Indolese, *Tetrahedron Lett.* **1997**, *38*, 3513–3516; e) S. Saito, M. Sakai, Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 2993–2996.

[13] Ligand-containing polymers for aryl chlorides cross-couplings, see: a) A. Datta, K. Ebert, H. Plenio, *Organometallics* **2003**, *22*, 4685–4691; b) C. A. Parrish, S. L. Buchwald, *J. Org. Chem.* **2001**, *66*, 3820–3827.

[14] F. Mongin, L. Mojovic, B. Guillamet, F. Trecourt, G. Queguiner, *J. Org. Chem.* **2002**, *67*, 8991–8994.

[15] For other ligand-catalyzed cross-coupling reaction of aryl fluorides with Grignard reagents: a) N. Yoshikai, H. Mashima, E. Nakamura, *J. Am. Chem. Soc.* **2005**, *127*, 17978–17979; b) J. W. Dankwardt, *J. Organometallic Chem.* **2005**, *690*, 932–938; c) K. Lamm, M. Stollenz, M. Meier, H. Görls, D. Walther, *J. Organometallic Chem.* **2003**, *681*, 24–36; d) V. P. W. Böhm, C. W. K. Gstöttmayr, T. Weskamp, W. A. Herrmann, *Angew. Chem. Int. Ed.* **2001**, *40*, 3387–3389.