DOI: 10.1002/adsc.200900058

'Click' Dendritic Phosphines: Design, Synthesis, Application in Suzuki Coupling, and Recycling by Nanofiltration

Michèle Janssen,[a] Christian Müller,[a] and Dieter Vogt[a,*]

[a] A Schuit Institute for Catalysis, Eindhoven University of Technology, P.O.Box 513, 5600 MB Eindhoven, The Netherlands
Fax: (+31)-40-245-5054; phone: (+31)-40-247-2483; e-mail: D.Vogt@tue.nl

Received: December 5, 2008; Revised: January 27, 2009; Published online: February 9, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900058.

Abstract: A new synthetic route towards stable molecular-weight enlarged monodentate phosphine ligands *via* 'click' chemistry was developed. These ligands were applied in the Pd-catalyzed Suzuki–Miyaura coupling of aryl halides and phenyl boronic acid. The supported systems show very similar activities compared to the unsupported analogues. Moreover, recycling experiments by means of nanofiltration using ceramic nanofiltration membranes demonstrate that these systems can be recovered and reused efficiently.

Keywords: catalyst recycling; ceramic membranes; cross-coupling; dendrimers; homogeneous catalysis

Homogeneously catalyzed reactions play an increasingly important role in organic synthesis.[1] However, a major drawback of homogeneous catalysts over heterogeneous systems is the difficulty of their recovery and recycling.[2] A range of approaches have been studied over the years, all with their own strengths and weaknesses, leading to the conclusion that one ultimate solution does not exist. This is inherently due to the vast variety of applications, each with its own specific requirements and conditions. Hence, there is a great need for the development of complementary generic methods – a toolbox for practical application. These methods can be roughly divided in biphasic catalysis[3–5] and immobilization on insoluble (heterogenization) and soluble supports (molecular weight enlargement, MWE).[6–8]

MWE catalysts can, in principle, be recovered by means of precipitation, ultracentrifugation or nanofiltration.[9–16] Although there are numerous examples of catalyst recovery, especially *via* precipitation, the field of nanofiltration in homogeneous catalysis is still rather unexploited, because advanced membrane reactor technology is usually needed.[7,17–20] Recently, Rothenberg et al. demonstrated, however, that this is not necessarily required and that a Ru-based transfer hydrogenation catalyst can efficiently be recovered with a relatively simple set-up.[21]

We report here on the synthesis of multiple phosphine ligands attached to a dendritic support *via* 'click' chemistry. Their application in the Pd-catalyzed Suzuki coupling and their facile recovery and reuse by means of nanofiltration has been investigated.

In order to attach a ligand to a soluble support, both ligand and support need to be decorated with an anchoring group. In this respect, we started to focus on 'click' chemistry, since it is an elegant way to attach ligands to a support (Figure 1). The 'click' reaction, officially referred to as Huisgen 1,3-dipolar cycloaddition reaction, has received a lot of attention due to the work by Sharpless and co-workers.[22,23] This reaction between an alkyne and an organic azide exhibits several attractive features, such as high and often quantitative yields as well as a high functional group tolerance. These interesting characteristics have already been widely exploited in polymer and materials science,[24,25] while examples in the field of catalysis are still in their infancy.[26–28]

Figure 1. 'Click' reaction for the attachment of a ligand to a support.

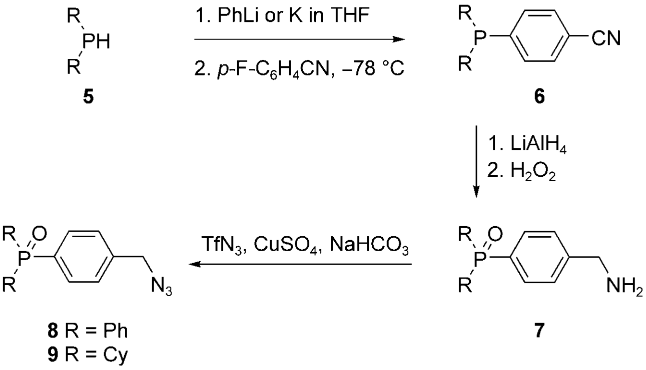
Despite the above-mentioned advantages, a few practical points have to be considered. First, either the support or the ligand has to be decorated with the azide functionality. For safety reasons we chose to functionalize the ligand with an azide anchoring group, avoiding several azide moieties in one molecule. Second, azides and free phosphines would undergo a Staudinger reaction under formation of dinitrogen and an iminophosphorane.[29] For this reason, the phosphine moiety has to be protected as its oxide, sulfide, or BH_3 adduct, until the triazole ring is formed.

For a suitable support we chose tetrakis(4-ethynylphenyl)methane, since this results in a rigid, spherical molecule after ligand attachment. These structures are known to display better retention and less membrane fouling than linear shaped or flat macromolecules.[30]

Based on literature data, triphenylphosphine (**A**), dicyclohexylphenylphosphine (**B**) and 2-dicyclohexylphosphinobiphenyl (**C**) were chosen. These ligands are among the best and most frequently used monodentate phosphines for the Pd-catalyzed Suzuki–Miyaura coupling reaction.[31–33]

Support **4** was prepared according to a literature procedure.[34] Commercially available tetraphenylmethane **1** was selectively brominated in the *para* positions using bromine in the presence of iron filings.[35] The tetra-(4-bromophenyl)-methane **2** was coupled with TMS-protected acetylene in a Sonogashira reaction. After deprotection, support **4** was obtained in 65% overall yield (Scheme 1).

The synthesis of the azide-functionalized ligands started with the deprotonation of diphenyl- or dicyclohexylphosphine with potassium or PhLi, respectively. The obtained phosphide was reacted with 4-fluorobenzonitrile in a nucleophilic aromatic substitution reaction yielding the cyano-functionalized phosphine **6** in high yield.[36]

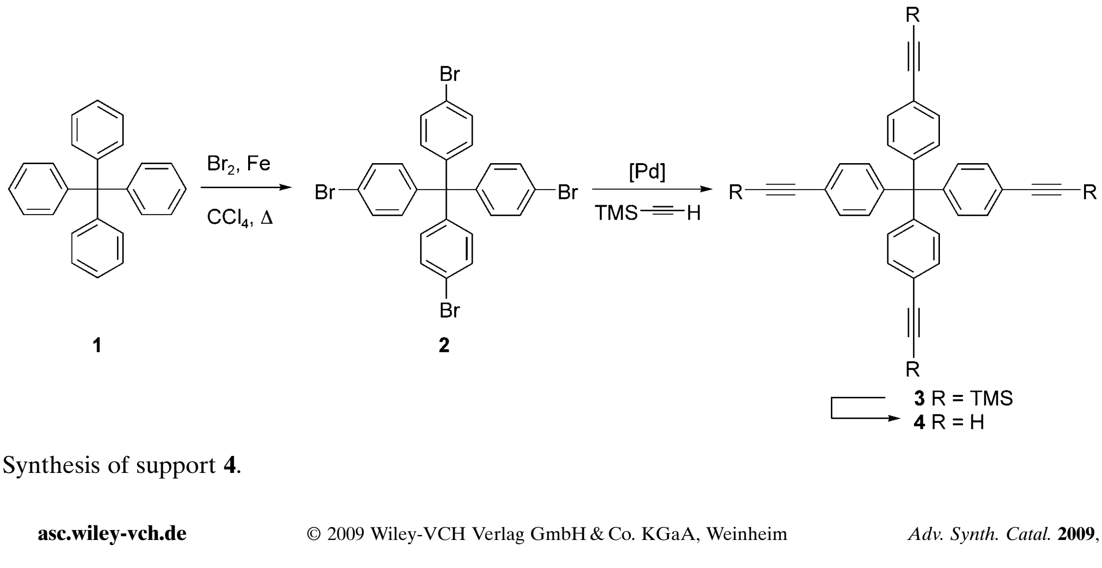


Scheme 2. Synthesis of azide-functionalized phosphine oxides **8** and **9**.

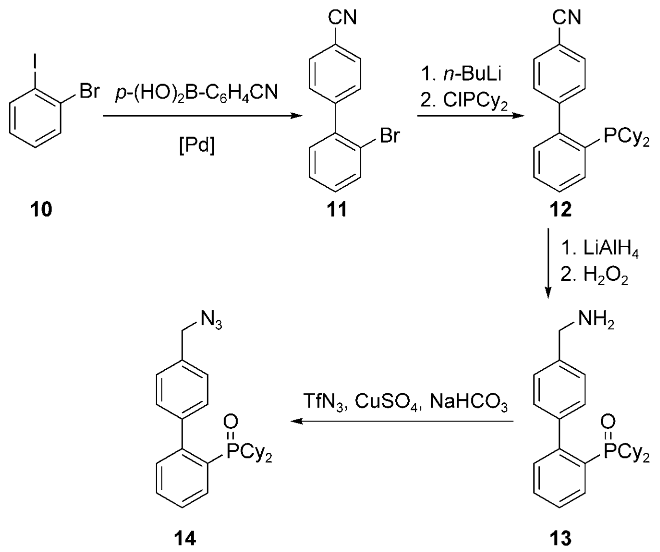
Compound **6** was then reduced to its corresponding benzylamine and protected as its phosphine oxide **7**, necessary to prevent Staudinger reaction once the azide is formed. This was followed by a copper-mediated diazo transfer reaction to obtain the azide-functionalized phosphine oxides **8** and **9** in 64 and 71% overall yield, respectively (Scheme 2).[37]

The synthesis of the azido-functionalized phosphine oxide **14** was achieved by a slightly modified procedure. After a Suzuki coupling between 1-bromo-2-iodobenzene and 4-cyanophenyl boronic acid, **11** was obtained in 80% yield, which was lithiated and subsequently reacted with chlorodicyclohexylphosphine to yield compound **12**.[38,39] Nitrile **12** was reduced to the corresponding benzylamine and protected by reaction with H_2O_2. After the copper-mediated diazo transfer reaction, the azide-functionalized Buchwald phosphine oxide **14** was obtained in 60% overall yield (Scheme 3).

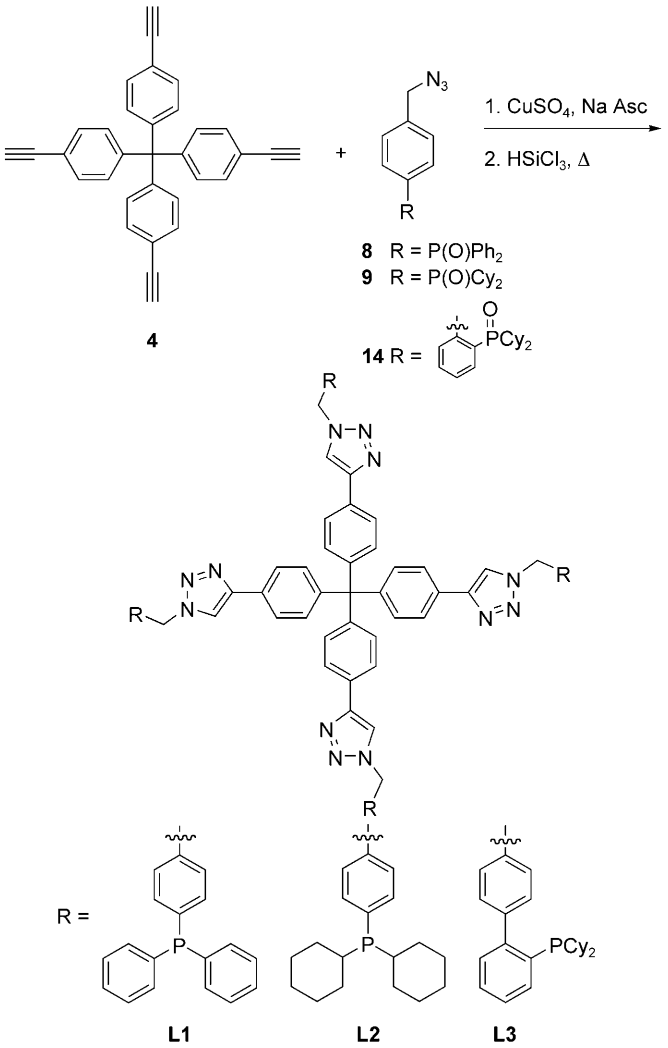
The azide-functionalized phosphine oxides were then attached to support **4** by means of a copper-mediated 1,3-dipolar cycloaddition reaction (‘click’ reaction). After deprotection of the phosphine with excess $HSiCl_3$, the desired molecular-weight enlarged



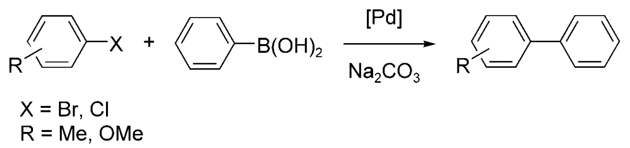
Scheme 1. Synthesis of support **4**.



Scheme 3. Synthesis of azide-functionalized Buchwald phosphine oxide **14**.



Scheme 4. Synthesis of 'click' dendritic ligands **L1**–**L3**.



Scheme 5. Suzuki–Miyaura coupling between aryl halide and phenyl boronic acid.

ligands **L1**–**L3** were obtained in good yields (Scheme 4).[40]

In order to justify immobilization of homogeneous catalysts, they should be easy to prepare and should show high activity as well as high total turnover number (ttn). We chose to investigate the Suzuki reaction, since single monodentate phosphine ligands are frequently applied. Thus, ligands **L1**–**L3** were explored in the Pd-catalyzed coupling of phenylboronic acid and aryl halides (Scheme 5).

First, the activities of the Pd catalysts containing ligands **L1**–**L3** were compared with those of their original unsupported counterparts **A**–**C**. The results are summarized in Table 1. The conversion followed in time is depicted in Figure 2 exemplarily for the catalyst system Pd/**L3** in comparison with Pd/**C**. Both Table 1 and Figure 2 clearly demonstrate that the supported systems show essentially identical activities as the original ones, indicating that the four catalysts on a dendrimer act truly independently. No Pd black formation was observed in any of the catalytic runs. Moreover, NMR studies on the MWE ligands before and after the catalysis experiments showed no degradation of the triazole ring.

Subsequently, the total turnover numbers (ttn) of the three 'click' dendritic systems were determined. The ttn's turned out to be high (~15,000) for all three MWE systems and, moreover, comparable with values reported in the literature.[41]

Since the 'click' dendritic catalysts fulfilled the requirements discussed above, (straightforward synthesis, high ttn and high activity), we applied these sys-

Table 1. Comparison of activities of 'click' dendritic ligands and their unsupported analogues.[a]

Entry	Ligand	Time [h]	Conversion [%]
1	**A**	7	94
2	**L1**	7	96
3	**B**	3	>99
4	**L2**	3	>99
5	**C**	2	>99
6	**L3**	2	>99

[a] *Reaction conditions:* 1.0 mmol 4-bromotoluene, 1.5 mmol phenylboronic acid, 3.0 mmol Na_2CO_3, 0.01 mmol $Pd(OAc)_2$, Pd:P = 1:1, solvent: THF (3 mL)/water (2 mL), $T = 60\,°C$. Yields are GC yields.

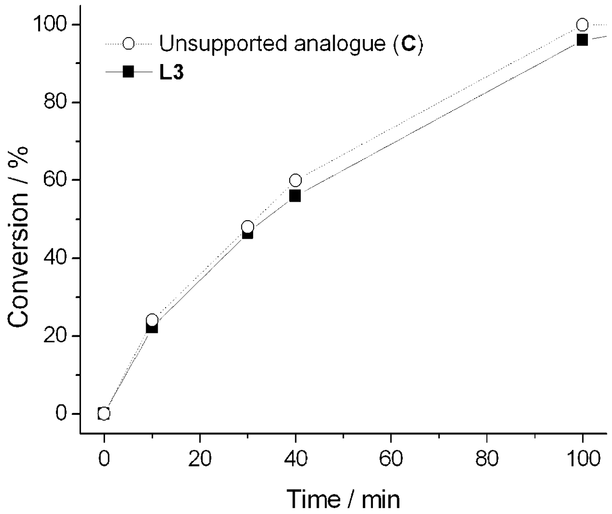


Figure 2. Comparison of activities of Pd/**L3** and its unsupported analogue **C**.

tems in a nanofiltration set-up. This in-house made set-up consists of a commercially available ceramic membrane tube,[42] which is capped with Teflon discs and fixed in a stainless steel holder (Figure 3). The molecular weight cut-off of the applied membrane is 450 Da. Since the molecular weight of our 'click' dendritic ligands is higher than 1600 Da, the membrane should in principle be able to retain the corresponding catalysts.

Prior to use, the membrane tube was thoroughly evacuated, filled with N_2 and soaked in THF. Subsequently, the 'click' dendritic Pd catalyst solution was injected into the membrane tube. The stainless steel holder was placed in a 50 mL Schlenk tube and a solution of aryl halide, phenylboronic acid and Na_2CO_3 in 25 mL of THF and 15 mL of water was added. The Schlenk tube was then placed in a thermostatic shake bath at 60 °C and the reaction was allowed to proceed for 16 h. At the end of the reaction, the complete reaction mixture was collected by syringe and replaced by a fresh substrate solution. Between these recycling runs no additional Pd was added. The results obtained with the systems Pd/**L1**–**L3** are shown in Table 2.

In case of Pd/**L1** and Pd/**L2**, the recycling runs were performed with a substrate to Pd ratio of 125:1. In both cases a clear drop in activity was observed after the third run. This could be due to either Pd leaching or catalyst deactivation, although the ttn of the catalysts was not yet reached. ICP-AES analysis of the product solutions revealed a Pd leaching of 0.8% per run for Pd/**L1** and 0.4% per run for Pd/**L2**, which

Table 2. Recovery and reuse of Pd/**L1**–**L3** catalysts.[a]

Run	Ligand	Pd added [mol%]	Yield [%]
1	**L1**	0.8	>99
2	**L1**	0	96
3	**L1**	0	97
4	**L1**	0	90
5	**L1**	0	55
1	**L2**	0.8	>99
2	**L2**	0	>99
3	**L2**	0	>99
4	**L2**	0	76
5	**L2**	0	66
1	**L3**	0.1	>99
2	**L3**	0	82
3	**L3**	0	78
4	**L3**	0	64
5	**L3**	0	72

[a] *Reaction conditions:* 1.0 equiv. 4-bromotoluene, 1.5 equiv. phenylboronic acid, 3.0 equiv. Na_2CO_3, Pd:click dendrimer = 4:1, Pd precursor = $Pd(OAc)_2$, solvent: THF (30 mL) + H_2O (20 mL), $T = 60$ °C, time = 16 h. Yields are GC yields.

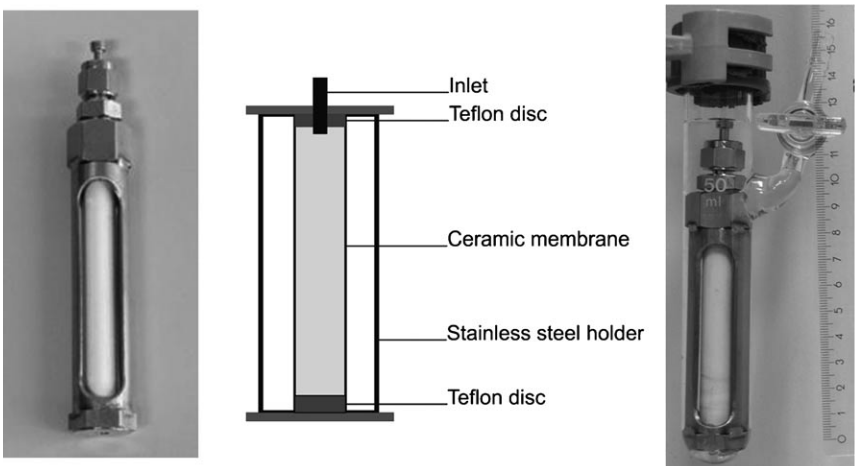


Figure 3. Ceramic nanofiltration membrane set-up.

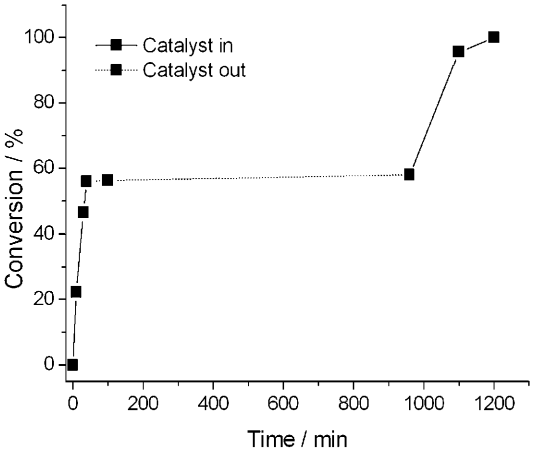


Figure 4. Reaction profile for the formation of 4-methylbiphenyl.

seems too small to account for the large drop in activity.

The recycling runs for Pd/**L3** were performed with a Pd loading of only 0.1 mol%. The first run revealed a higher activity of the catalyst systems compared to remaining ones, but the yield of 4-methylbiphenyl was essentially constant in the last four runs. ICP-AES analysis of the product solutions showed a Pd leaching of 0.8% per run. To reject the hypothesis that the leached Pd accounts for the observed activity, we performed an experiment in which the substrate solution was completely removed from the membrane tube containing the Pd/**L3** catalyst after 40 min. At this time the conversion had reached 56%. 16 h later, no significant further increase in conversion (58%) was observed. The substrate solution was transferred back into the Schlenk tube containing the membrane tube. Interestingly, full conversion was reached after 2 h (Figure 4). From this experiment we can conclude that the catalytic reaction takes place inside the membrane tube and that the leached Pd accounts only for a very small amount of conversion (~2% in 16 h). Moreover, the membrane tube can be stored for 16 h under argon without significant catalyst deactivation.

In conclusion, a new synthetic route towards stable dendritic monodentate phosphine ligands via 'click' chemistry was developed. These ligands were applied in the Pd-catalyzed Suzuki–Miyaura coupling of aryl halides and phenylboronic acid. The supported systems show very similar activities as their original unsupported analogues. Recycling experiments by means of nanofiltration using ceramic nanofiltration membranes demonstrate that these systems can be recovered and reused efficiently.

Experimental Section

General Procedure for the Suzuki–Miyaura Coupling of Aryl Halides

An oven-dried Schlenk tube was charged with a Teflon coated stirring bar, aryl halide (1.0 mmol), phenylboronic acid (183 mg, 1.5 mmol) and Na_2CO_3 (318 mg, 3.0 mmol) and evacuated and backfilled with argon for 3 times. Then, 3 mL of THF and 2 mL of water were added. When the substrates and the base had dissolved, the catalyst solution consisting of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and the ligand (0.01 mmol of P) in 1 mL of THF, was added and the mixture was put in a pre-heated oil bath at 60 °C.

General Procedure for the Recycling Runs

The ceramic membrane was oven-dried and evacuated for 16 h in the antechamber of a nitrogen-filled glovebox in order to remove air. Then, the ceramic membrane was placed in a stainless steel holder inside the glovebox. The membrane tube was soaked in THF/water and then filled with catalyst solution: $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and ligand (0.01 mmol) in 1 mL of THF. The membrane tube was closed and the holder was placed in a 50 mL Schlenk tube and a solution of 10 mmol aryl bromide and 15 mmol phenylboronic acid in 30 mL of THF and 30 mmol Na_2CO_3 in 20 mL of water was added. This Schlenk tube was placed in a thermostatic shake bath at 60 °C. The reaction was allowed to proceed for 16 h.

Acknowledgements

We thank A. Elemans-Mehring, W. van Herpen and A. Staring for technical assistance. This research was funded by the Netherlands Research School Combination on Catalysis (NRSC-C). C.M. thanks the Netherlands Organization for Scientific Research (NWO) for financial support.

References

[1] B. Cornils, W. A. Herrmann, *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Three Volumes*, Wiley-VCH, Weinheim, **2002**.
[2] J. A. Gladysz, (Guest Editor), *Recoverable Catalysts and Reagents*, in: *Chem. Rev.* **2002**, 102, 3215–3892.
[3] B. Hamers, P. S. Bäuerlein, C. Müller, D. Vogt, *Adv. Synth. Catal.* **2008**, *350*, 332–342.
[4] K. Kunna, C. Müller, J. Loos, D. Vogt, *Angew. Chem.* **2006**, *118*, 7447–7450; *Angew. Chem. Int. Ed.* **2006**, *45*, 7289–7292.
[5] B. Cornils, W. A. Herrmann, I. T. Horvath, W. Leitner, S. Mecking, H. Olivier-Bourbigou, D. Vogt, *Multiphase Homogeneous Catalysis*, Volumes 1 and 2, Wiley-VCH, Weinheim, **2005**.
[6] D. J. Cole-Hamilton, *Science* **2003**, *299*, 1702–1706.
[7] C. Müller, M. G. Nijkamp, D. Vogt, *Eur. J. Inorg. Chem.* **2005**, *20*, 4011–4021.

[8] D. Cole-Hamilton, R. Tooze, *Catalyst Separation, Recovery and Recycling: Chemistry and Process Design*, Springer, Berlin, Heidelberg, **2006**.
[9] D. Astruc, F. Chardac, *Chem. Rev.* **2001**, *101*, 2991–3023.
[10] D. de Groot, B. F. M. de Waal, J. N. H. Reek, A. P. H. J. Schenning, P. C. J. Kamer, E. W. Meijer, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2001**, *123*, 8453–8458.
[11] R. J. M. Klein Gebbink, C. A. Kruithof, G. P. M. van Klink, G. van Koten, *Rev. Mol. Biotechnol.* **2002**, *90*, 183–193.
[12] C. Müller, L. J. Ackerman, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2004**, *126*, 14960–14963.
[13] G. E. Oosterom, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Angew. Chem.* **2001**, *113*, 1878–1901; *Angew. Chem. Int. Ed.* **2001**, *40*, 1828–1849.
[14] J. N. H. Reek, D. de Groot, G. E. Oosterom, P. C. J. Kamer, P. W. N. M. van Leeuwen, *C. R. Chim.* **2003**, *6*, 1061–1077.
[15] G. P. M. van Klink, H. P. Dijkstra, G. van Koten, *C. R. Chim.* **2003**, *6*, 1079–1085.
[16] R. van Heerbeek, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Rev.* **2002**, *102*, 3717–3756.
[17] H. P. Dijkstra, N. Ronde, G. P. M. van Klink, D. Vogt, G. van Koten, *Adv. Synth. Catal.* **2003**, *345*, 364–369.
[18] E. B. Eggeling, N. J. Hovestad, J. T. B. H. Jastrzebski, D. Vogt, G. van Koten, *J. Org. Chem.* **2000**, *65*, 8857–8865.
[19] N. J. Hovestad, E. B. Eggeling, H. J. Heidbuchel, J. T. B. H. Jastrzebski, U. Kragl, W. Keim, D. Vogt, G. van Koten, *Angew. Chem.* **1999**, *111*, 1763–1765; *Angew. Chem. Int. Ed.* **1999**, *38*, 1655–1658.
[20] R. Sablong, U. Schlotterbeck, D. Vogt, S. Mecking, *Adv. Synth. Catal.* **2003**, *345*, 333–336.
[21] A. V. Gaikwad, V. Boffa, J. E. ten Elshof, G. Rothenberg, *Angew. Chem.* **2008**, *120*, 5487–5490; *Angew. Chem. Int. Ed.* **2008**, *47*, 5407–5410.
[22] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056–2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.
[23] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708–2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599.
[24] W. H. Binder, R. Sachsenhofer, *Macromol. Rapid Commun.* **2007**, *28*, 15–54.
[25] M. Malkoch, R. J. Thibault, E. Drockenmüller, M. Messerschmidt, B. Voit, T. P. Russell, C. J. Hawker, *J. Am. Chem. Soc.* **2005**, *127*, 14942–14949.
[26] R. J. Detz, S. Arévalo Heras, R. de Gelder, P. W. N. M. van Leeuwen, H. Hiemstra, J. N. H. Reek, J. H. van Maarseveen, *Org. Lett.* **2008**, *10*, 1323.
[27] D. Liu, W. Gao, Q. Dai, X. Zhang, *Org. Lett.* **2005**, *7*, 4907–4910.
[28] a) E. M. Schuster, M. Botoshansky, M. Gandelman, *Angew. Chem.* **2008**, *120*, 4631–4634; *Angew. Chem. Int. Ed.* **2008**, *47*, 4555–4558; b) M. Meise, R. Haag, *ChemSusChem* **2008**, *1*, 637–642.
[29] H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635–646.
[30] R. W. Baker, *Membrane Technology and Applications*, Wiley, New York, **2000**.
[31] U. Christmann, R. Vilar, *Angew. Chem.* **2005**, *117*, 370–378; *Angew. Chem. Int. Ed.* **2005**, *44*, 366–374.
[32] J. P. Wolfe, S. L. Buchwald, *Angew. Chem.* **1999**, *111*, 2570–2573; *Angew. Chem. Int. Ed.* **1999**, *38*, 2413–2416.
[33] J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
[34] E. Galoppini, R. Gilardi, *Chem. Commun.* **1999**, 173–174.
[35] L. M. Wilson, A. C. Griffin, *J. Mater. Chem.* **1993**, *3*, 991–994.
[36] M. Hingst, M. Tepper, O. Stelzer, *Eur. J. Inorg. Chem.* **1998**, 73–82.
[37] A. Titz, Z. Radic, O. Schwardt, B. Ernst, *Tetrahedron Lett.* **2006**, *47*, 2383–2385.
[38] K. Glegola, E. Framery, K. M. Pietrusiewicz, D. Sinou, *Adv. Synth. Catal.* **2006**, *348*, 1728–1733.
[39] M. Nishimura, M. Ueda, N. Miyaura, *Tetrahedron* **2002**, *58*, 5779–5787.
[40] H. Fritzsche, U. Hasserodt, F. Korte, G. Friese, K. Adrian, *Chem. Ber.* **1965**, *98*, 171–174.
[41] J. Lemo, K. Heuzé, D. Astruc, *Chem. Commun.* **2007**, 4351–4353.
[42] http://www.inopor.com.