



UNIVERSITY OF AMSTERDAM

UvA-DARE (Digital Academic Repository)

Synthesis and Application of Nano-Structured Metal Catalysts

Durán Páchon, L.

Publication date
2008

[Link to publication](#)

Citation for published version (APA):

Durán Páchon, L. (2008). *Synthesis and Application of Nano-Structured Metal Catalysts*. [Thesis, fully internal, Universiteit van Amsterdam].

General rights

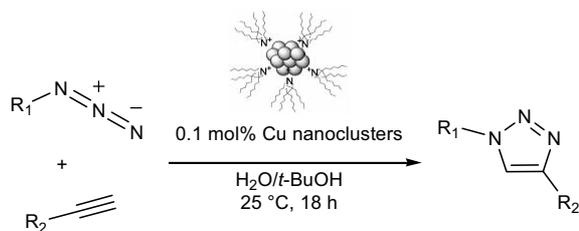
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

*Click Chemistry: Copper nanoclusters
catalyze the cycloaddition of azides
with terminal alkynes*

Chapter 2



Abstract

Air-stable copper nanoclusters are good catalysts in the Cu^I -catalyzed ‘click’ cycloaddition of azides with terminal alkynes to give 1,4-disubstituted 1,2,3-triazoles. No additional base or reducing agent is required. The reaction kinetics using various copper catalyst types and the function of copper particles in this system are studied and discussed.

Part of this work has been published as: ‘Click Chemistry: Copper clusters catalyze the cycloaddition of azides with terminal alkynes’, L. Durán Pachón, J. H. van Maarseveen and G. Rothenberg, *Adv. Synth. Catal.* **2005**, 347, 811.

2.1. Introduction

'Click chemistry', a term introduced by Sharpless and co-workers,¹ denotes a growing family of powerful chemical reactions that are based on 'spring-loaded' energy-intensive substrates that can, under the right conditions, unload their energy to form stable products in high selectivity. This is inspired by the fact that nature also generates substances by joining small modular units.

Ever since their debut in 2001, click reactions are finding more and more applications in drug discovery,^{2,3} organic synthesis,^{4,5} and materials science.^{6,7} Perhaps the most remarkable example is the copper-catalyzed version of the Huisgen 1,3-dipolar cycloaddition of azides to terminal alkynes (**Scheme 2.1, top**).^{8,9} This reaction tolerates a variety of functional groups, is insensitive to water and oxygen, and gives easy access to regiospecific 1,4-disubstituted 1,2,3-triazoles. The 100% atom economy and simple product isolation make this reaction useful in various applications ranging from bio-orthogonal and bio-conjugation,¹⁰⁻¹³ polymer^{14,15} and dendrimer¹⁶ syntheses to the construction of peptide bond surrogates¹⁷ and powerful pharmacophores.²

The reaction is catalyzed by Cu^I species that are either added directly as cuprous salts (with or without ligands),¹⁸ or generated by the reduction of Cu^{II} salts (CuSO₄ with sodium ascorbate),¹⁹ or by the *in situ* oxidation of copper metal turnings to give Cu^I species.⁸ The last option is particularly attractive, as copper metal is inexpensive, and there is no need for a reducing agent as in the case of Cu^{II}. However, reactions are relatively slow and require a significant amount of catalyst. These drawbacks are increasingly important when large-scale production is considered.

The fact that both Cu⁰ and Cu^{II} can be used as catalyst precursors, plus the ubiquitous presence of Cu^I-alkyne intermediates in similar chemical systems,²⁰ such as the Glaser homocoupling²¹ and the Stephens–Castro²² and Sonogashira^{23,24} reactions, led us to think that copper nanoclusters could be efficient catalysts for Huisgen-type cycloadditions. Previous studies in our group showed that Cu clusters are particularly suited to Suzuki,^{25,26} and Sonogashira²⁷ cross-coupling reactions.

particles with a narrow cluster size distribution and no aggregation, with a mean diameter of 4.15 nm (see **Figure 2.1**).

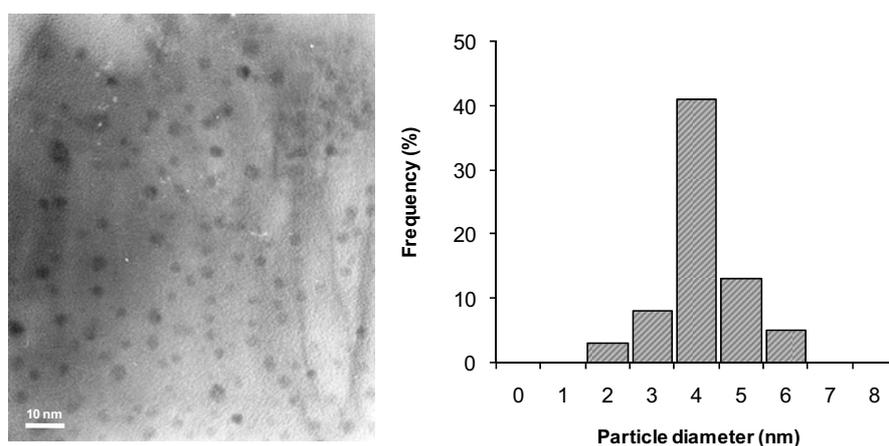


Figure 2.1. Transmission electron micrograph (*left*) and corresponding size distribution (*right*, based on 70 particles counted) of Cu nanoclusters.

2.2.2. Huisgen-type cycloaddition catalysis

In a typical cluster-catalyzed cycloaddition reaction (**Scheme 2.1**, *bottom*), one equivalent of azide **1** was mixed at 25 °C and pressure with two equivalents of alkyne **2** and 0.001 equivalents of copper clusters, in 50 ml of water/*t*-butyl alcohol (2:1). Good conversions and yields were observed for a variety of azide/alkyne combinations (**Table 2.1**). The 1,4-disubstituted 1,2,3-triazoles **3a–f** were easily isolated by filtration, followed by recrystallization, and identified by their melting points and ¹H NMR spectra.

In general, aliphatic alkynes gave higher yields than aromatic ones (typically 85–100% *vs.* ~80%, respectively). The presence of an electron-withdrawing hydroxy group increased the product yield. The phenyl group in the 1-phenylprop-2-yn-1-ol (entries **2** and **5**) was found to slightly impede the reaction, probably because of steric effects, i.e., interfering with the formation of the Cu^I-terminal alkyne species. This effect was observed for both aromatic and aliphatic azides.²

Table 2.1. Huisgen-type cycloadditions catalyzed by copper nanoclusters.^a

Entry	Azide	Alkyne	Product	Yield (%) ^b
1				80
2				85
3				>99 ^c
4				82
5				97
6				>99 ^c

[a] Reaction conditions: 10 mmol azide (1), 20 mmol alkyne (2), 0.1 mmol Cu nanoclusters, 50 ml H₂O/*t*-BuOH (2:1), 25 °C; 18 h.

[b] Yields of isolated products, reported in mol% based on azide starting material.

[c] Yields calculated based on GC values, corrected for the presence of an internal standard.

Sharpless and co-workers reported that the Cu^I-catalyzed synthesis of 1,2,3-triazoles from azides and terminal alkynes could also be catalyzed by Cu⁰ turnings,⁸ as well as by CuSO₄/sodium ascorbate.^{11,12} In both cases, it was suggested that the Cu⁰ and Cu^{II} precursors are oxidized or reduced to give the active Cu^I catalytic species. Such switching between the Cu⁰/Cu^I/Cu^{II} oxidation states was also observed by one of us in the catalytic oxidation of allylic olefins with *t*-butyl hydroperoxide (TBHP), which could also be catalyzed by copper clusters as catalyst precursors.³³

The interesting point about the azide-alkyne cycloadditions, however, is that copper clusters may play a special role here, rather than just ‘reservoirs’ for Cu^I. This is analogous to previous findings in our group on Sonogashira cross-coupling, where copper clusters exhibited very different catalytic properties compared to Cu^I salts.²⁷

2.2.3. Kinetic and mechanistic studies

To gain further insight into the role of the copper clusters in azide-alkyne cycloadditions, we monitored the kinetics of the model reaction between benzyl azide (**1b**) and prop-2-yn-1-ol (**2c**). We compared profiles for four catalytic systems: copper shavings, copper powder, copper nanoclusters, and CuSO₄/ascorbate (**Figure 2.2**). All other reaction conditions were kept constant and blank experiments were performed to exclude systemic effects.

Several interesting things can be observed in **Figure 2.2**. Perhaps, the most significant are the differences between the reaction rates of the various catalyst types. This indicates that the role of Cu particles in the Huisgen 1,3-dipolar cycloadditions is similar to that in the Sonogashira cross-coupling. If the Cu particles were mere ‘reservoirs’ for Cu^I and/or Cu^{II} ions, one would expect similar reaction profiles regardless of the copper source (*cf.* the oxidative Cu/TBHP system where the kinetic profiles for Cu⁰ clusters, Cu^{II} salts and Cu^I salts are indistinguishable³³).

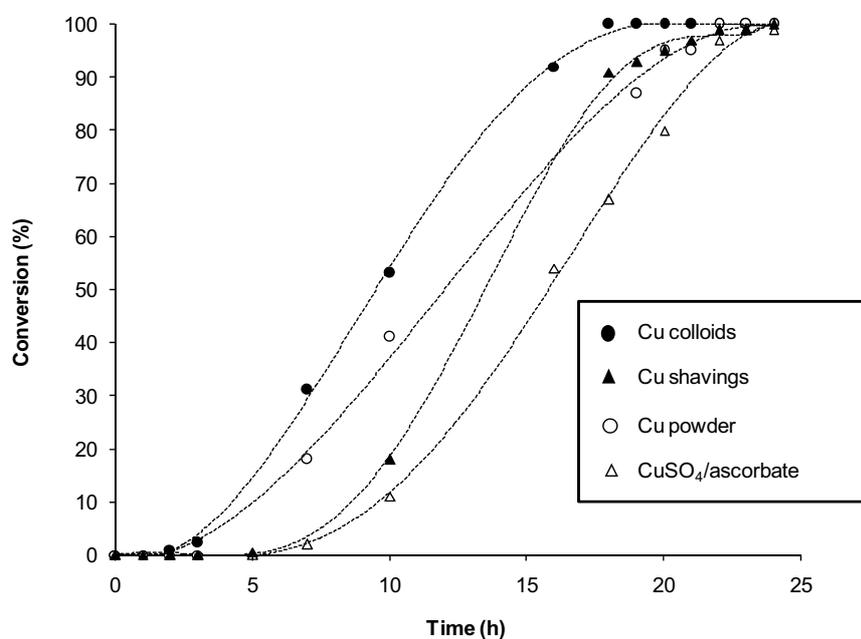


Figure 2.2. Time-resolved reaction profiles observed for the 1,3-cycloaddition of prop-2-yn-1-ol to benzyl azide using various copper catalytic systems. Reaction conditions are as in Table 1. All reactions were performed in duplicate (with error of $\pm 2.3\%$).

Copper nanoclusters displayed the highest activity of the four systems tested, affording 100% conversion after 18 h. The activity trend is Cu^0 clusters > Cu^0 powder > Cu^0 shavings > Cu^{II} /ascorbate. This is in good agreement with the catalyst surface area (in the case of Cu^0). The specific surface area of the clusters and the powder was $168 \text{ m}^2/\text{g}$ and $0.15 \text{ m}^2/\text{g}$, respectively.

One key scientific question is whether the Cu^0 clusters and powder are leaching copper atoms into the solution or not. Indeed, this question stands at the heart of many an argument in heterogeneous catalysis³⁴. To try to answer this question, we performed a separate set of reactions to give **3f** catalyzed by Cu^0 powder. As before, reactions were monitored by gas chromatography (GC). This time, however, we filtered the powder out of the reaction vessel after 7 h, continued to stir, and added the powder back after 20 h. **Figure 2.3** shows the

resulting kinetic profile (‘•’ symbols), together with a control reaction with no filtration (broken curve).

The clear difference between the reaction curves in **Figure 2.3** supports our hypothesis that the reaction occurs on the surface of the copper particles, rather than *via* Cu^0 atoms or $\text{Cu}^{\text{I}}/\text{Cu}^{\text{II}}$ ions that are leached into the reaction mixture. Furthermore, all four profiles in **Figure 2.2** exhibit an induction period, from 1 h in the case of Cu clusters, and up to 5 h in the case of $\text{Cu}^{\text{II}}/\text{ascorbate}$. For the Cu^0 catalysts, the duration of the induction period corresponds to the catalysts surface area. This fact is also in agreement with a reaction that occurs at the catalyst surface. The reaction is probably mediated *via* a Cu^{I} ion on the surface, similar to the mechanism of the Sonogashira coupling.²⁷

Notwithstanding this evidence, three more points should be considered: First, it may be that after the copper powder is filtered off, some Cu^{I} and/or Cu^{II} may still remain in solution, but as there is no more reducing agent, it will rapidly convert all Cu^{II} (in **Figure 2.3** we see that after 7 h, when the copper powder is filtered off, the reaction slows down considerably, but does not stop). Second, the surface of copper metal is usually coated by a monolayer of Cu^{I} oxide, a dark red powder when in bulk, but virtually unnoticeable when on the metal, which may serve as the source of Cu^{I} . This may explain why the reaction slows down and eventually stops, but does not stop immediately, after copper metal is removed. Third, studies on the mechanism of the homogeneously-catalyzed reaction show that Cu^{I} acetylide is almost certainly an intermediate in the catalytic cycle.³⁵ If this is the case, it means that Cu^0 by itself cannot catalyze the reaction – one way or another, Cu^{I} has to form.

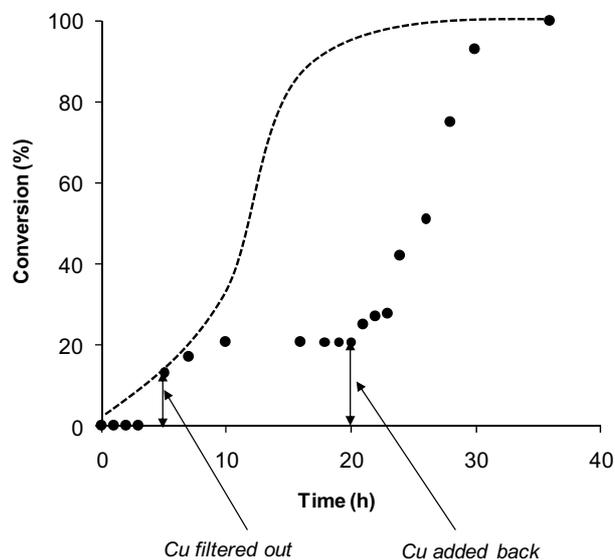


Figure 2.3. Time-resolved reaction profile observed for the 1,3- cycloaddition of prop-2-yn-1-ol and benzyl azide using copper powder as catalyst. Reaction conditions are as in Table 1. ‘•’ symbols represent the kinetic profile of the experiment filtering and adding back Cu powder. The broken line shows a control experiment without filtering of the copper catalyst.

2.3. Conclusion

Cu nanoclusters are efficient catalysts for 1,3-cycloadditions of azides to terminal alkynes. Reaction conditions are improved in comparison with previous catalytic systems. There is evidence that the catalysis occurs on the particles’ surface, but the mechanism is complex, and more work is needed to ascertain the specific role of the clusters. It is possible that a Cu^{I} -alkyne intermediate is involved, similar to the case with Sonogashira reactions.

2.4. Experimental section

2.4.1. Materials and instrumentation

^1H NMR was measured on a Varian Mercury vx300NMR spectrometer at 25 °C. Chemical shifts of spectra are referenced to Me_4Si and internal solvent resonances. TEM images for nanoparticles characterization were obtained with a JEOL-TEM 1200 EXII instrument, operated at an accelerating voltage of 120 kV. Samples for TEM were prepared by placing 150 μl of cluster suspension on carbon-coated copper grids. These were then placed in vacuum oven at 50 °C at 250 mm of Hg to evaporate the solvent. GC analysis was performed on a GC-8000 gas chromatograph with a 100% dimethylpolysiloxane capillary column (DB-1, 30 m \times 0.325 mm). All products were identified by their GC retention times and their ^1H NMR spectra. Samples for GC were diluted with 1 ml dimethylformamide (DMF) and filtered through an alumina plug prior to injection. GC conditions: isotherm at 110 °C (2 min); ramp at 30 °C/min to 280 °C; isotherm at 280 °C (15 min). A Coulter Multisizer Isoton II particle counter was used to measure. Unless noted otherwise, chemicals were purchased from commercial firms and were used as received. Tetra-*n*-octylammonium formate (TOAF) was prepared as published previously.²⁵ Azides were synthesized following literature procedures.^{36,37}

2.4.2. Synthesis of copper nanoclusters

A Schlenk-type vessel equipped with a magnetic stirrer was evacuated and refilled with N_2 . The vessel was charged with CuCl solutions in DMF (10 ml, 10 mM) using a syringe. 10 ml of a 0.2 M TOAF solution in DMF was added in one portion to the solution at 80 °C, and the mixture was stirred for 24 h under inert atmosphere. The color of the mixture changed from reddish to very dark brown. The resulting suspension was stored under N_2 and used as a catalyst stock solution in the Huisgen-type cycloadditions.

2.4.3. Procedure for 1,3-dipolar cycloaddition of azides with terminal alkynes

Example (1): 1,4-diphenyl-1*H*-1,2,3-triazole (3a). A solution of phenyl azide (**1a**; 10 mmol, 1.33 g) and phenylacetylene (**2a**; 20 mmol, 2.04 g) in 50 ml of $\text{H}_2\text{O}/t\text{-BuOH}$ (2:1) was

stirred in a round-bottomed flask equipped with a magnetic stirring bar. A *pre*-prepared suspension of copper nanoclusters (0.1 ml, 10 mM, equivalent to 0.1 mol% of copper relative to **1a**) was then added in one portion and the reaction mixture was stirred at 25 °C for 18 h. Reaction progress was monitored by GC. The product precipitated in the reaction mixture and was collected by filtration, washed (2×20 ml H_2O), and dried under vacuum to obtain colorless needles of the product; yield: 1.77 g (80% yield based on **1a**); mp: 176 – 179 °C (lit., 181 – 183 °C); ^1H NMR (Me_4Si): $\delta = 7.26 - 7.58$ (m, 7H, Ph), 7.79 – 7.95 (m, 3H, Ph), 8.27 (s, 1H, CH). Good agreement was found with literature values.³⁸

Example (2): (1-benzyl-1H-1,2,3-triazol-4-yl)(phenyl)methanol (3e). Reaction and work-up were performed as described above, but using benzyl azide (**1b**; 10 mmol, 1.19 g) and 1-phenyl-2-propyn-1-ol (**2b**; 20 mmol, 2.64 g) as reagents, to give the product as a white solid; yield: 2.21 g (97%); mp: 120 – 123 °C; ^1H NMR (Me_4Si): $\delta = 2.24$ (1H, OH), 5.46 (s, 2H, CH_2), 6.01 (s, 1H, CH), 6.91 – 7.93 (m, 10H, Ph).

2.4.4. Reaction profiles and kinetic analysis

The reaction profiles were obtained for the model reaction between benzyl azide (**1b**) and prop-2-yn-1-ol (**2c**) for four different catalytic systems: copper shavings, copper powder, copper nanoclusters, and $\text{CuSO}_4/\text{ascorbate}$ (see **Figure 2.1**). All other reaction conditions were kept constant and appropriate blank experiments were performed to exclude systemic effects.

In this analysis, the correlation coefficient, R^2 , gives a measure of the amount of variability in the data that is accounted for by a given model (in this case, a 2nd-order rate equation). The R^2 values and the second-order rate constants (k) were as follows: Cu colloids: $R^2 = 0.886$, $k = 8.3 \times 10^{-3}$ (four observations); Cu powder: $R^2 = 0.912$, $k = 6.7 \times 10^{-3}$ (four observations); Cu shavings: $R^2 = 0.921$, $k = 3.1 \times 10^{-3}$ (five observations); Cu sulfate/ sodium ascorbate: $R^2 = 0.908$, $k = 0.9 \times 10^{-3}$ (six observations).

2.4.5. Surface analysis and calculation procedures

The surface area of copper powder was calculated assuming spherical particles (4.483 μm of diameter measured in a size particle counter and 8.92 g/ml of density) obtaining 0.15 m^2/g . The same procedure was used to calculate the surface area of copper nanoclusters (assuming spherical particles of 4 nm of diameter and 8.92 g/ml of density) giving 168 m^2/g .

References

1. Kolb, H. C.; Finn, M. G.; Sharpless, K. B., *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
2. Kolb, H. C.; Sharpless, K. B., *Drug Discov. Today*, **2003**, *8*, 1128.
3. Roper, S.; Kolb, H. C., *Met. Princip. Med. Chem.* **2006**, *34*, 313.
4. Wang, Q.; Chittaboina, S.; Barnhill, H. N., *Lett. Org. Chem.* **2005**, *2*, 293.
5. Sharpless, K. B.; Manetsch, R., *Exp. Opin. Drug Discov.* **2006**, *1*, 525.
6. Binder, W. H.; Sachsenhofer, R., *Macromol. Rapid Commun.* **2007**, *28*, 15.
7. Lutz, J.-F., *Angew. Chem. Int. Ed.* **2007**, *46*, 1018.
8. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B., *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.
9. Tornøe, C. W.; Christensen, C.; Meldal, M., *J. Org. Chem.* **2002**, *67*, 3057.
10. Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G., *J. Am. Chem. Soc.* **2003**, *125*, 3192.
11. Link, A. J.; Vink, M. K. S.; Tirrell, D. A., *J. Am. Chem. Soc.* **2004**, *126*, 10598.
12. Speers, A. E.; Cravatt, B. F., *Chem. Biol.* **2004**, *11*, 535.
13. Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V., *Org. Lett.* **2004**, *6*, 2853.
14. Diaz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G., *J. Polym. Sci. Pol. Chem.* **2004**, *42*, 4392.
15. Scheel, A. J. K., H.; Voit, B. I., *Macro. mol. Rap. Comm.* **2004**, *25*, 1175.
16. Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V., *Angew. Chem. Int. Ed.* **2004**, *43*, 3928.
17. Horne, W. S. Y., M. K.; Stout, C. D.; Ghadiri, M. R., *J. Am. Chem. Soc.* **2004**, *126*, 15366.
18. Lewis, W. G.; Magallon, F. G.; Fokin, V. V.; Finn, M. G., *J. Am. Chem. Soc.* **2004**, *126*, 9152.
19. Meng, J.-C.; Averbuj, C.; Lewis, W. G.; Siuzdak, G.; Finn, M. G., *Angew. Chem. Int. Ed.* **2004**, *43*, 1255.
20. For a review on acetylenic coupling see: Siemsen, P.; Livingston, R. C.; Diederich, F., *Angew. Chem. Int. Ed.* **2000**, *39*, 2633.
21. Shen, W.; Thomas, S. A., *Org. Lett.* **2000**, *2*, 2857.
22. Vasilevsky, S. F.; Klyatskaya, S. V.; Korovnikova, O. L.; Stass, D. V.; Amitina, S. A.; Grigir'ev, I. A.; Elguero, J., *Tetrahedron Lett.* **2004**, *45*, 7741.

23. Sonogashira, K. *Metal-catalyzed cross-coupling reactions*; 1st ed.; Wiley-VCH: Weinheim, 1975.
24. Sonogashira, K.; Tohda, Y.; Hagihara, N., *Tetrahedron Lett.* **1975**, 4467.
25. Thathagar, M. B.; Beckers, J.; Rothenberg, G., *J. Am. Chem. Soc.* **2002**, *124*, 11858.
26. Thathagar, M. B.; Beckers, J.; Rothenberg, G., *Adv. Synth. Catal.* **2003**, *345*, 979.
27. Thathagar, M. B.; Beckers, J.; Rothenberg, G., *Green Chem.* **2004**, *6*, 215.
28. Moreno-Mañas, M.; Pleixats, R., *Acc. Chem. Res.* **2003**, *36*, 638.
29. Reetz, M. T.; Breinbauer, R.; Wanniger, K., *Tetrahedron Lett.* **1996**, *37*, 4499.
30. Reetz, M. T.; Lohmer, G., *Chem. Commun.* **1996**, 1921.
31. Beller, M.; Fischer, H.; Kühlein, K.; Reisinger, C. P.; Hermann, W. A., *J. Organomet. Chem.* **1996**, *520*, 527.
32. Narayanan, R.; El-Sayed, M. A., *J. Am. Chem. Soc.* **2003**, *125*, 8340.
33. Rothenberg, G.; Feldberg, L.; Wiener, H.; Sasson, Y., *J. Chem. Soc., Perkin Trans. 2* **1998**, 2429.
34. Arends, I. W. C. E. S., R. A., *App. Catal. A: Gen.* **2001**, *212*, 175.
35. Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Fokin, V. V.; Noodleman, L.; Sharpless, K. B., *J. Am. Chem. Soc.* **2005**, *127*, 211.
36. Kurumi, M.; Sasaki, K.; Takata, H.; Nakayama, T., *Heterocycles* **2000**, *12*, 2809.
37. Alvarez, S. G.; Alvarez, M. T., *Synth.* **1997**, *4*, 413.
38. Wang, Z. X.; Qin, H. L., *Chem. Commun.* **2003**, 2450.

