Dendritic Oxidation Catalysts

DOI: 10.1002/anie.201206003

Dendritic Fluoroalcohols as Catalysts for Alkene Epoxidation with Hydrogen Peroxide**

Albrecht Berkessel, Jan Krämer, Florian Mummy, Jörg-M. Neudörfl, and Rainer Haag*

Dedicated to Professor Waldemar Adam on the occasion of his 75th birthday

Fluorinated alcohols such as 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) are known to

enhance the rate and selectivity of various reactions involving positively or partially positively charged transition states.[1] High ionizing power, strong hydrogen-bond donor ability, and low nucleophilicity account for the observed effects.[2] Quite remarkable accelerations (up to ca. 10^5) have been achieved by using TFE—and in particular HFIP—as the solvent in the epoxidation of olefins with aqueous hydrogen peroxide used as the terminal oxidant.[3] The same holds for certain Baeyer–Villiger-type oxidations of ketones with aqueous H_2O_2, which proceed by cationic rearrangements of peroxidic ketone–H_2O_2 adducts.[4] In the oxidation of thioethers with aqueous H_2O_2, fluoroalcohol solvents provide remarkable selectivities for sulfoxide formation, with basically no overoxidation to sulfones.[5]

Overall, the preparative scope of aqueous hydrogen peroxide—probably, besides O_2, the most "clean" and readily available oxidant to date—is greatly enhanced when used in fluoroalcohols as solvents. The necessity of applying a fluoroalcohol as the solvent poses limitations, as these materials are, for example, prohibitively expensive for large-scale applications.

One solution to the problem is to switch from a fluoroalcohol solvent to a fluoroalcohol catalyst, which can be used in conventional solvent systems. Our previous studies on the mechanism of HFIP-catalyzed epoxidation by H_2O_2—ultimately aiming at the development of such catalysts—identified multiple hydrogen-bonding interactions between the solvent and the oxidant as the crucial factor.[3] Figure 1 illustrates how the oxidant is electrophilically activated by multiple hydrogen bonds from a total of two or even three HFIP molecules. Most importantly, cyclic hydrogen-bond networks are established, which allow (almost) barrier-free proton transfer from the proximal O atom (the one to become the epoxide O atom) of H_2O_2 to the distal one. Clearly, high local concentration of the fluoroalcohol—as in a solvent—is

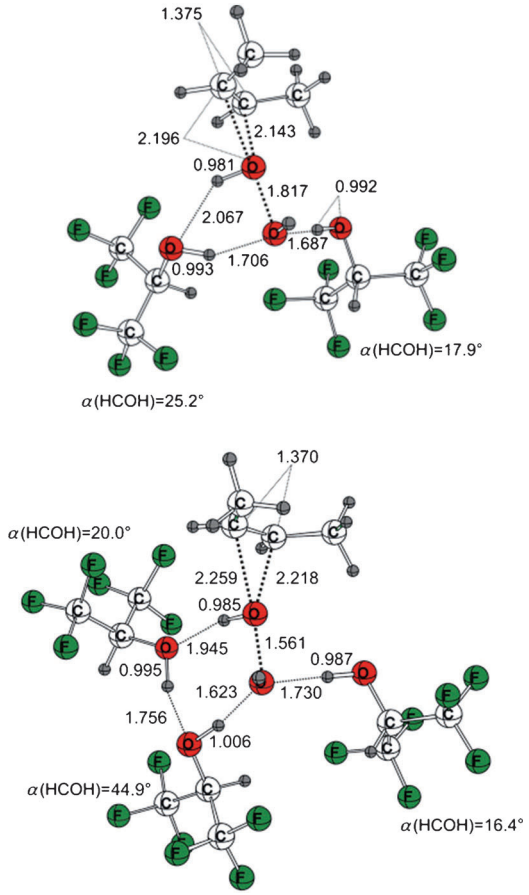


Figure 1. Catalysis of (*Z*)-2-butene epoxidation, effected by two (top) and three (bottom) molecules of HFIP, through hydrogen-bonding networks (from Ref. [3b]).

[*] Prof. Dr. A. Berkessel, J. Krämer,[+] Dr. J.-M. Neudörfl
Department of Chemistry, University of Cologne
Greinstrasse 4, 50939 Cologne (Germany)
E-mail: berkessel@uni-koeln.de
Homepage: http://www.berkessel.de
Dr. F. Mummy,[+] Prof. Dr. R. Haag
Department of Chemistry and Biochemistry
Freie Universität Berlin
Takustrasse 3, 14195 Berlin (Germany)
[+] These authors contributed equally to this work.

[**] Financial support by the Fonds der Chemischen Industrie is gratefully acknowledged. J.K. thanks Henkel KGaA, Düsseldorf, for a doctoral fellowship. A.B. acknowledges COST Membership (CM0905, Organocatalysis). R.H. would like to acknowledge the financial support from the Cluster of Excellence "Unifying Concepts in Catalysis".

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201206003.

the prerequisite for the effective formation of such multiply hydrogen-bonded supramolecular aggregates. We therefore envisaged the attachment of fluoroalcohol head groups to relatively polar dendritic polymers for the catalyst design. By doing so, a high local concentration of the fluoroalcohol is assured, together with compatibility of the catalyst with both the highly polar aqueous H_2O_2 and olefin/solvent mixtures. As the dendritic scaffold, we chose hyperbranched polyglycerol (hPG, **1**). Herein, we present the synthesis of hPG-supported HFIP analogues (Figure 2), together with their application as catalysts for the metal-free epoxidation of alkenes with hydrogen peroxide.

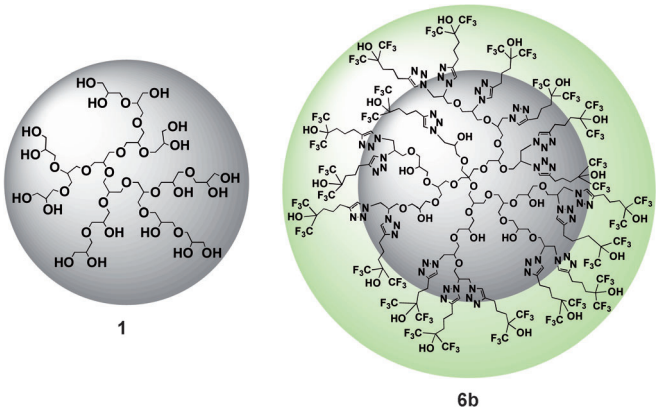
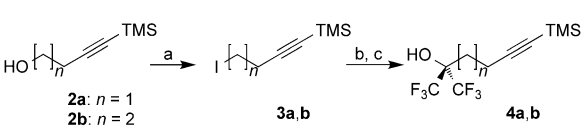


Figure 2. Epoxidation catalyst **6b** based on hyperbranched polyglycerol **1** as a polymeric support for HFIP analogues.

We recently presented the hyperbranched polyglycerol **1** (hPG, Figure 2) as a soluble high-loading support for applications in the field of organic synthesis[6,7] and catalysis.[8,9] This polyether can be easily synthesized on a kilogram scale by anionic ring-opening polymerization of glycidol,[10] and benefits from the highly branched, dendritic structure containing primary and secondary hydroxy functional groups. The latter can be converted into other functional groups such as azides and amines. The high local concentration of functional groups (13.5 mmol g^{-1}, ca. 100 per PG molecule), good solubility in a wide range of organic solvents (depending on the functional group), chemical stability (inert ether bonds), and noncoordinating behavior make these dendritic polymers attractive supports for a wide range of catalysts.

For the synthesis of the polymeric epoxidation catalysts shown schematically in Figure 2 we used the alkynyl fluoroalcohols **4a** and **4b** as HFIP analogues. Compounds **4a**,**b** were synthesized from commercially available 3-butynol (for **4a**) and 4-pentynol (for **4b**), respectively, in three steps (Scheme 1). First, the alkyne function was quantitatively silylated with *n*-butyllithium and trimethylsilyl chloride (not shown in Scheme 1).[11] The resulting TMS-protected alkynols **2a**,**b** were converted into the corresponding iodo compounds **3a**,**b** by treatment with triphenylphosphine, imidazole, and iodine.[11,12] In the last step, the iodides **3a**,**b** were first transformed to the organozinc compounds by treatment with zinc, 1,2-dibromoethane, and trimethlysilyl chloride. The organozinc compound was then added to hexafluoroacetone (HFA) in the presence of a copper(I) catalyst to afford the corresponding fluoroalcohols **4a** and **4b** in good yields (Scheme 1).[13]



Scheme 1. Synthesis of the bis(trifluoromethyl)alkynols **4a** and **4b**. Reagents and conditions: a) imidazole, PPh_3, I_2, Et_2O/CH_3CN, 0 °C; **3a** 85 %, **3b** 90 %; b) Zn, $C_2H_4Br_2$, TMS-Cl, DMF, RT; c) HFA, CuBr·Me_2S, DMF, −40 °C; **4a** 72 %, **4b** 65 %. TMS = trimethylsilyl.

As expected, the fluoroalcohols **4a** and **4b** are strong hydrogen-bond donors, comparable to their "mother compound" HFIP. Figure 3 shows the X-ray crystal structures of their 2:1 adducts with 1,4-diazabicyclo[2.2.2]octane (DABCO).[14] The salient feature of both structures are the relatively short (ca. 2.65 Å) and almost linear hydrogen bonds between the fluoroalcohols and the *tert*-amine acceptor. Similarly, ^{1}H NMR spectroscopic titration of alcohols **4a** and **4b** with THF as a hydrogen-bond acceptor provided an association constant of (12 ± 1) L mol^{-1} for **4a** and (16 ± 1) L mol^{-1} for **4b**. These numbers are within the same range as those determined previously for HFIP itself (65 L mol^{-1}).[3,15]

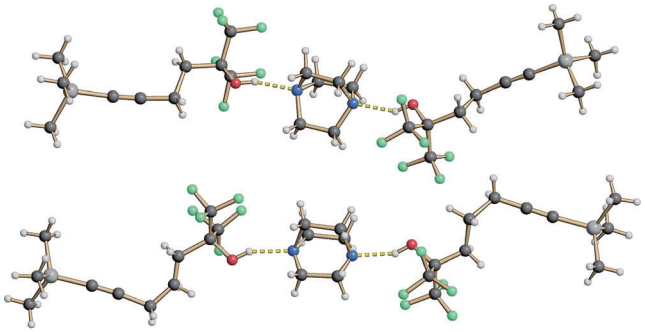
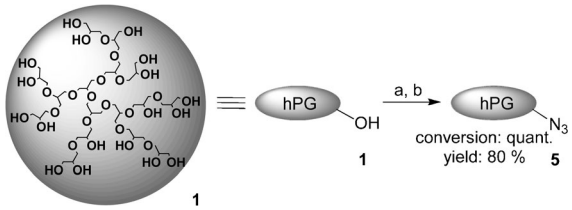
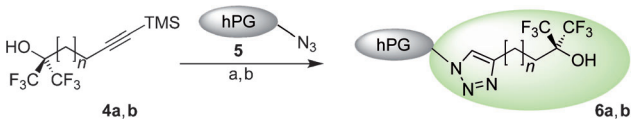


Figure 3. X-ray crystal structures of the DABCO adducts of the fluorinated alkynol **4a** (top) and **4b** (bottom). Dark gray C, white H, blue N, red O, green F, light gray Si.

We chose azide-modified hPG (hPG-N_3, **5**) for the polymeric support, which was prepared from hPG (**1**) (M_n = 10 kDa) in two steps, that is by mesylation and subsequent nucleophilic substitution using sodium azide (Scheme 2). The two alkynols **4a** and **4b** were coupled in high yield to hPG-N_3 (**5**) by using "click chemistry"[16] (Scheme 3). The final



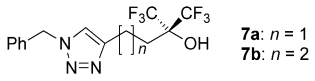
Scheme 2. Modification of the functional groups of dendritic polyglycerol. Reagents and conditions: a) MsCl, pyridine, 0 °C, 16 h; b) NaN_3, DMF, 100 °C, 16 h. Ms = methanesulfonyl.



Scheme 3. Synthesis of the hPG-HFIP catalysts **6a** and **6b**. Reagents and conditions: a) TBAF, THF, RT, 20 min; b) sodium ascorbate, $CuSO_4$, THF/H_2O, RT, 24 h; **6a** 84%, **6b** 81%. TBAF = tetra-*n*-butylammonium fluoride.

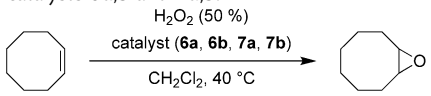
polymeric catalysts (**6a**,**b**) were purified by membrane ultrafiltration (using a Millipore stirred cell) and analyzed by ^1H, ^{13}C, and ^{19}F NMR as well as IR spectroscopy.

The surface loading (amount of fluoroalcohol groups on the polymer) was determined to be 3.0 mmol "HFIP" g^{-1} for catalyst **6a** and 2.9 mmol "HFIP" g^{-1} for catalyst **6b** by ^{19}F NMR spectroscopy with 4-trifluoroaniline used as an internal standard. For comparison, the monomeric catalysts **7a**,**b** were synthesized starting from benzylazide instead of hPG-azide (**5**).



We then compared the catalytic activity of the dendritic fluoroalcohols **6a** and **6b** with that of their monomeric analogues **7a** and **7b** as well as that of HFIP itself. The epoxidation of *cis*-cyclooctene[17] with aqueous hydrogen peroxide was chosen as the test reaction, and the results are summarized in Table 1. We were delighted to see that both

Table 1: Epoxidation of cyclooctene with hydrogen peroxide in the presence of catalysts **6a**,**b** and **7a**,**b**.[a]



Entry	Cat.	*t* [h]	Conv. [%][b]	Yield [%][b]
1	hPG-HFIP (**6a**)	24	quant.	quant.
2	hPG-HFIP (**6b**)	24	quant.	quant.
3	Bn-HFIP (**7a**)	24	13	11
4	Bn-HFIP (**7b**)	24	11	< 10
5	HFIP	24	16	14

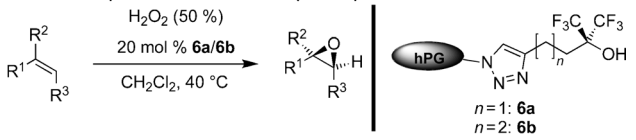
[a] Reaction conditions: see the general epoxidation method (Experimental Section), 20 mol% of "HFIP equivalents". [b] determined by GC.

dendritic HFIP analogues **6a** and **6b** were catalytically significantly more active than the monomers **7a**,**b** or HFIP itself (applied at the same concentration as the other fluoroalcohols, that is, 20 mol%, relative to the olefin). This positive dendritic effect not only validates the initial catalyst design concept, but in retrospect supports the transition-state model with multiple HFIP molecules for the epoxidation of olefins catalyzed by HFIP (Figure 1).[1,3]

Next, we optimized the reaction conditions by screening a range of solvents, reaction temperatures, hydrogen peroxide solutions (with respect to pH and concentration), and alkene/catalyst concentrations. In nonpolar solvents (such as *n*-hexane or toluene), the catalyst was completely insoluble and epoxide yields were typically very low, identical to those of the background reaction. In polar, hydrogen-bond-acceptor solvents, such as ethanol, 1,4-dioxane, or ethyl acetate, the epoxide yields again did not differ significantly from those of the background, although the catalyst was completely soluble in most of those solvents. As in the case of HFIP itself, catalyst inhibition results in the presence of hydrogen-bond acceptors.[18] The best results were obtained at alkene concentrations of 0.125 M and catalyst concentrations of 0.025 M (20 mol% with respect to the fluoroalcohol monomers attached to the polymer) in a biphasic system with halogenated solvents, such as dichloromethane, and unbuffered hydrogen peroxide (50 wt%) at 40 °C.

We then submitted various alkenes to the optimized reaction conditions. As summarized in Table 2, excellent olefin conversions and epoxide yields were achieved with as

Table 2: Scope of hPG-HFIP-catalyzed epoxidation of alkenes.[a]



Entry	Substrate	*t* [h]	Cat.	Conv. [%][b]	Yield [%][b]
1		15	**6a**	98	95
		16	**6b**	97	93
2		15	**6a**	98	10–26[c]
3		19	**6a**	97	94
		19	**6b**	95	90
4		24	**6a**	quant.	quant.
		23	**6b**	quant.	quant.
5		72	**6a**	48	35
		72	**6b**	98	28
6		72	**6a**	37	28
		70	**6b**	42	32

[a] Reaction conditions: see the general epoxidation method (Experimental Section). [b] Determined by GC. [c] Product epoxide not stable under the reaction conditions.

little as 20 mol% of the dendritic fluoroalcohols **6a** and **6b**. As the loading of 20 mol% refers to the amount of fluoroalcohol present, our goal of providing a substoichiometric catalytic system—as opposed to using fluoroalcohols as a solvent—has been reached. Similar to epoxidations in fluoroalcohol solvents,[19–21] the dendritic catalysts **6a**,**b** perform particularly well with cycloalkenes as substrates, as exemplified by cyclohexene, 1-methyl- and 1-phenylcyclohexene, and cyclooctene (Table 2, entries 1–4). As shown by control experiments, the poor epoxide yield in the case of 1-methylcyclohexene (Table 2, entry 2) is due to product instability under the reaction conditions—again in accord with earlier studies with this substrate in fluoroalcohol solvents.[19–21] Similarly, open-chain alkenes such as styrene (Table 2, entry 5) and 1-octene (Table 2, entry 6) are epoxidized with moderate efficiency.

As an example of the oxidation of thioethers, we subjected thioanisol to the reaction conditions (not shown in Table 2). We were delighted to see that the very high sulfoxide selectivity typical for sulfoxidations in fluoroalcohol solvents was maintained by the dendritic catalysts **6a**,**b**, as only the sulfoxide PhS(O)Me was formed in quantitative yield, and no sulfone.

An additional advantage of the dendritic catalysts is their potential recovery for multiple uses. In the current case, the catalysts **6a**,**b** were successfully recovered by ultrafiltration. The catalysts were re-used twice without noticeable losses in the yield of the product epoxide when cyclooctene was used as the test substrate.

In conclusion, we could show that immobilization of fluoroalcohol monomers on a soluble dendritic support is a suitable method for the generation of organocatalysts that promote transformations by multiple hydrogen-bond networks. In the current case, the high local concentration of fluoroalcohol groups on the polymeric surface was exploited for the electrophilic activation of hydrogen peroxide. Epoxidations with hydrogen peroxide, hitherto attainable in fluoroalcohol solvents, were achieved for the first time with catalytic amounts of fluoroalcohol units. This positive dendritic effect not only validates the multifunctional catalyst design concept, but also supports the transition-state model with multiple HFIP molecules for the catalytic epoxidation of olefins. Similarly, the selective sulfoxidation of thioethers with H_2O_2 could be achieved with our catalytic dendritic polymers. We are convinced that this novel catalytic principle will find further use, for example, in further electrophilic oxidations using peroxide as a terminal O donor, or in other transformations requiring substrate activation/transition-state stabilization by multiple hydrogen bonding.[21]

Experimental Section

a) "Click reaction" and characterization of polymeric catalysts:

1. In situ deprotection of the TMS-protected alkyne: Tetra-*n*-butylammonium fluoride trihydrate (1.8 g, 5.72 mmol, 1.1 equiv) and **4a** (1.52 g, 5.2 mmol) were stirred in THF until TLC showed complete deprotection (ca. 30 min).

2. Click coupling: Diisopropylethylamine (88 μL, 0.52 mmol, 0.1 equiv) and polyglycerol azide **5** (515 mg, 5.2 mmol azide, 1 equiv) in THF were added to the deprotected fluorinated alcohol. After the mixture had been stirred for 5 min, sodium ascorbate (103 mg, 0.52 mmol, 0.1 equiv) in 1.5 mL Millipore water was added, followed by copper(II) sulfate pentahydrate (130 mg, 0.52 mmol, 0.1 equiv) in 1.5 mL Millipore water. The reaction mixture was stirred overnight at RT. TLC analysis indicated complete consumption of the fluorinated alcohol. The solution was concentrated and the residue was diluted in water and extracted with ethyl acetate. The combined organic layers were washed several times with small portions of saturated EDTA solution until the blue color of the aqueous phase had disappeared. The crude product was further purified by ultrafiltration (Millipore solvent-resistant stirred cell (XFUF07601); solvent: methanol; membrane material: regenerated cellulose, molecular-weight cut-off (MWCO) of the membrane: 5 kDa). The polymeric catalyst **6a** was obtained in 84% yield (1.4 g) with a loading of 3.0 mmol fluoroalcohol head groups per gram.

^{1}H NMR (700 MHz, [D$_6$]DMSO): $\delta = 8.16$–7.42 (m, 1H, triazole), 5.30–4.60 (functionalized primary/secondary PG groups), 4.09–3.01 (PG), 2.89–2.66 (m, 2H, H$_4$), 2.26–2.03 ppm (m, 2H, H$_3$). ^{13}C NMR (176 MHz, [D$_6$]DMSO): $\delta = 145.6$ (s, triazole), 123.9 (s, C-1), 122.1 (s, triazole), 78.5 (br, PG), 75.7 (m, C-2), 70.1 (br, PG), 60.2 (br, PG), 50.3 (br, PG), 30.3 (s, C-3), 18.6 ppm (s, C-4). ^{19}F NMR (376 MHz, [D$_4$]MeOH): $\delta = -77.01$ ppm (s). IR (neat): $\tilde{\nu}$ =3145, 3079, 2956, 2882, 2736, 1732, 1704, 1556, 1454, 1283, 1199, 1137, 1035, 967, 930 cm^{-1}.

In the same fashion, the polymeric catalyst **6b** was prepared from the TMS-protected alkyne **4b** and polyglycerol azide **5** in 81% yield (1.4 g), with a loading of 2.9 mmol fluoroalcohol head groups per gram.

^{1}H NMR (700 MHz, [D$_6$]DMSO): $\delta = 7.88$–7.30 (m, 1H, triazole), 5.30–4.63 (functionalized primary/secondary PG groups), 4.07–3.03 (PG), 2.68–2.43 (m, 2H, H$_5$), 1.97–1.83 (m, 2H, H$_3$), 1.83–1.65 ppm (m, 2H, H$_4$). ^{13}C NMR (176 MHz, [D$_6$]DMSO): $\delta = 146.4$ (s, triazole), 123.9 (s, C-1), 122.3 (s, triazole), 78.4 (br, PG), 75.9 (m, C-2), 70.2 (br, PG), 60.2 (br, PG), 50.2 (br, PG), 30.3 (s, C-3), 25.3 (s, C-5), 22.1 ppm (s, C-4). ^{19}F NMR (376 MHz, [D$_4$]MeOH): $\delta = -76.92$ ppm (s). IR (neat): $\tilde{\nu}$ =3148, 3089, 2952, 2875, 1728, 1704, 1552, 1462, 1444, 1375, 1286, 1273, 1206, 1178, 1137, 1053, 989, 930, 871, 808 cm^{-1}.

b) General procedure for the catalytic epoxidation of alkenes: The alkene (50 μmol, 1 equiv), bromobenzene (50 μmol, internal standard), and the catalyst (0.2 equiv) were suspended in CH_2Cl_2 (0.4 mL, $c = 0.125$ mol L^{-1}) in a GC vial (1.5 mL). Hydrogen peroxide (1 mmol, 50 wt% in H_2O, 20 equiv) was added and the reaction mixture was stirred at 40°C for 15–72 h. 20 μL samples were frequently taken, eluted over Al_2O_3/MnO_2 with CH_2Cl_2 to quench any remaining hydrogen peroxide, and analyzed by gas chromatography. GC Method: Chiraldex γ-TA column; flow 0.9 mL min^{-1}, 40°C for 5 min, then 4°C min^{-1} up to 120°C, 120°C for 15 min, then 5°C min^{-1} up to 140°C.

Received: July 26, 2012
Published online: November 21, 2012

Keywords: alcohols · epoxidation · hyperbranched polymer · organocatalysis · polyglycerol

[1] A. Berkessel in *Modern Oxidation Methods*, 2nd ed. (Ed.: J. E. Bäckvall), Wiley-VCH, Weinheim, **2010**, pp. 117–145.
[2] J.-P. Bégué, D. Bonnet-Delpon, B. Crousse, *Synlett* **2004**, 18–29.
[3] a) A. Berkessel, J. A. Adrio, D. Hüttenhain, J.-M. Neudörfl, *J. Am. Chem. Soc.* **2006**, *128*, 8421–8426; b) A. Berkessel, J. A. Adrio, *J. Am. Chem. Soc.* **2006**, *128*, 13412–13420.
[4] a) A. Berkessel, M. R. M. Andreae, H. Schmickler, J. Lex, *Angew. Chem.* **2002**, *114*, 4661–4664; *Angew. Chem. Int. Ed.* **2002**, *41*, 4481–4484; b) A. Berkessel, M. R. M. Andreae, *Tetrahedron Lett.* **2001**, *42*, 2293–2295.
[5] a) J. Legros, B. Crousse, J. Bourdon, D. Bonnet-Delpon, J.-P. Bégué, *Tetrahedron Lett.* **2001**, *42*, 4463–4466; b) J. Legros, B. Crousse, D. Bonnet-Delpon, J.-P. Bégué, *Tetrahedron* **2002**, *58*, 3993–3998; c) K. S. Ravikumar, Y. M. Zhang, J. P. Bégué, D. Bonnet-Delpon, *Eur. J. Org. Chem.* **1998**, 2937–2940.
[6] S. Roller, H. Zhou, R. Haag, *Mol. Diversity* **2005**, *9*, 305–316.
[7] a) R. Haag, A. Sunder, A. Hebel, S. Roller, *J. Comb. Chem.* **2002**, *4*, 112–119; b) A. Hebel, R. Haag, *J. Org. Chem.* **2002**, *67*, 9452–9455.
[8] C. Hajji, S. Roller, M. Beigi, A. Liese, R. Haag, *Adv. Synth. Catal.* **2006**, *348*, 1760–1771.
[9] a) M. Beigi, R. Haag, A. Liese, *Adv. Synth. Catal.* **2008**, *350*, 919–925; b) M. Beigi, S. Roller, R. Haag, A. Liese, *Eur. J. Org. Chem.* **2008**, 2135–2141; c) M. Meise, R. Haag, *ChemSusChem* **2008**, *1*, 637–642.
[10] a) A. Sunder, R. Hanselmann, H. Frey, R. Mülhaupt, *Macromolecules* **1999**, *32*, 4240–4246; b) A. Sunder, R. Mülhaupt, R. Haag, H. Frey, *Adv. Mater.* **2000**, *12*, 235–239.

[11] See, for example: K. M. Foote, M. John, G. Pattenden, *Synlett* **2001**, 365 – 368.
[12] S. Bräse, H. Wertal, D. Vidovic, A. de Meijere, *Eur. J. Org. Chem.* **2005**, 4167 – 4178.
[13] J. T. Anderson, P. L. Toogood, E. N. G. Marsh, *Org. Lett.* **2002**, *4*, 4181 – 4183.
[14] CCDC 892819 (**4a**) and 892820 (**4b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[15] D. Hüttenhain, Dissertation, Universität zu Köln, **2007**.
[16] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004; for a review, see C. W. Tornøe, M. Meldal, *Chem. Rev.* **2008**, *108*, 2952 – 3015.
[17] U. Neuenschwander, I. Hermans, *J. Org. Chem.* **2011**, *76*, 10236 – 10240.
[18] A. Berkessel, J. A. Adrio, *Adv. Synth. Catal.* **2004**, *346*, 275 – 280.
[19] K. Neimann, R. Neumann, *Org. Lett.* **2000**, *2*, 2861 – 2863.
[20] M. C. A. van Vliet, I. W. C. E. Arends, R. A. Sheldon, *Synlett* **2001**, 248 – 250.
[21] A. Berkessel, K. Etzenbach-Effers in *Hydrogen Bonding in Organic Synthesis* (Ed.: P. M. Pihko), Wiley-VCH, Weinheim, **2009**, pp. 15 – 42.

