Heterogeneous Catalysis

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Functionalized Chitosan as a Green, Recyclable, Biopolymer-Supported Catalyst for the [3+2] Huisgen Cycloaddition**

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In memory of Charles Mioskowski

Owing to increasing concern about environmental impact, tremendous effort has been made towards the development of new processes that minimize pollution in chemical synthesis. For this reason and others (catalyst removal, recovery, and recycling), heterogeneous catalysis is clearly on the rise, including in industry.[1] Of the many systems that have been developed over the past decades, metallic species supported on inorganic materials (e.g. SiO_2, Al_2O_3) or on charcoal are the most common.[2] The immobilization of transition metals on polymer supports derived from petrochemicals (e.g. polystyrenes) has also been the focus of many efforts.[3]

Recent developments for cleaner, sustainable chemistry are being driven by a shift from petrochemical-based feedstocks to biological materials. There is considerable interest in exploiting natural polymer macrostructures, and in particular those of polysaccharides, to create high-performance and environmentally friendly catalysts. Indeed, polysaccharides present many advantages that may stimulate their use as polymeric supports for catalysis: 1) They are present in enormous quantity on earth, 2) they contain many functionalities that can be used readily for the anchoring of organometallic species, 3) they contain many stereogenic centers, and 4) they are chemically stable but biodegradable.[4] Surprisingly, although there has been a worldwide realization that nature-derived polysaccharides can provide the raw materials needed for the production of numerous industrial consumer goods, their use as supports for catalysis is still in its infancy.

Chitosan (Figure 1 A) is a particularly attractive polysaccharide for application in catalysis[5] owing to the presence of readily functionalizable amino groups and its insolubility in organic solvents. A copolymer of β(1→4)-2-amino-2-deoxy-D-glucopyranose and 2-acetamido-2-deoxy-D-glucopyranose, chitosan results from incomplete deacetylation of chitin. At least 10 gigatons of chitin are constantly present in the biosphere; thus, chitosan is a renewable green material.[6] Of the numerous methods that have been used to chemically modify chitosan,[7] Schiff base formation through the reaction of amine groups on the chitosan backbone with aldehydes is one of the most straightforward. For example, chitosan derivatives obtained by treatment with acetylacetone, salicylaldehyde, and pyridine-2-carboxaldehyde have been prepared to enhance copper adsorption[8] or to promote copper-catalyzed cyclopronation[9] or oxidation[10] reactions.

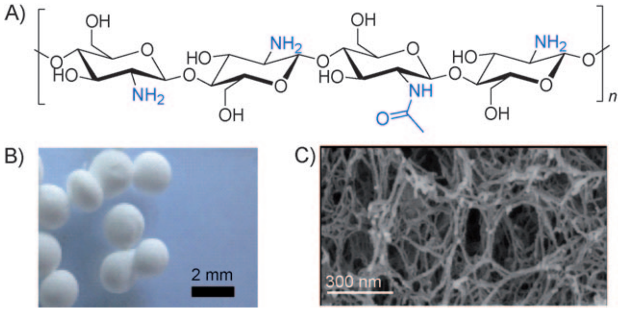

Figure 1. A) Chemical structure of chitosan. B) Photograph of chitosan aerogel beads. C) Scanning electron microscopy image of the chitosan aerogel.

The capacity of imine derivatives of chitosan to strongly chelate copper salts prompted us to study the ability of this type of complex to catalyze the azide–alkyne Huisgen [3+2] cycloaddition reaction. This reaction, the most robust and useful of the so-called "click" reactions, affords triazoles with high chemoselectivity.[11] The typical reaction conditions involve the use of copper salts, introduced directly as Cu^I salts[12] or generated in situ by the reduction of Cu^{II} (usually by sodium ascorbate)[13] or the oxidation of Cu^0,[14] in conjunction with an added base. Heterogeneous Cu^I sources have recently emerged as more practical systems that enable catalyst removal and recycling. A series of heterogeneous Cu^I systems have recently been reported, including Cu^I salts supported on basic Amberlyst,[15] cationic polystyrene,[16] cross-linked poly(ethyleneimine),[17] alumina,[18] and zeolites,[19] and copper nanoparticles in charcoal.[20] Although these heterogeneous catalysts proved their high efficiency and practicability, the cycloaddition reaction often required 1–10 mol % of the catalyst to proceed.

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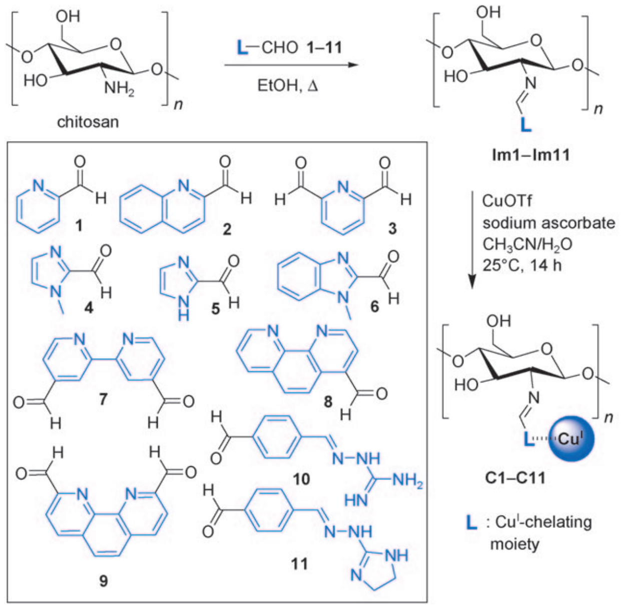
On the basis of the well-known ligand-acceleration effect on the kinetics of this reaction,[21] we hypothesized that more-active heterogeneous systems might be obtained by anchoring appropriate Cu^I ligands onto chitosan microspheres. An added bonus of these hybrid systems results from the textural properties of chitosan aerogels, which should be well-suited to the development of highly efficient hybrid catalysts. Indeed, we showed in previous studies[22] that chitosan microspheres dried in supercritical CO_2 (Figure 1 B) provided a porous support with large surface areas (over 100 $m^2 g^{-1}$) that were entirely accessible as a result of the open-pore structure of the network (pore size >10 nm; Figure 1 C). Moreover, this drying technique makes the amine groups of the polymer (loading: 5 $mmol\,g^{-1}$) more accessible to reactants.

A series of 11 aldehydes were chosen to be anchored to chitosan (Scheme 1). After Schiff base formation between chitosan and aldehydes **1**, **2**, **4**, **5**, and **6**, the corresponding imines should coordinate Cu^I salts as bidentate *N,N* ligands close to the sugar backbone. Aldehydes **8**, **10**, and **11**, which contain phenanthroline or guanidine moieties (known for their ability to chelate copper), and dialdehydes **3**, **7**, and **9**, designed to induce cross-linking throughout the chitosan network,[23] were also selected.



Scheme 1. Preparation of the hybrid catalysts. Tf = trifluoromethanesulfonyl.

Upon the treatment of chitosan with aldehyde reactants (1.5 equiv with respect to the NH_2 groups in chitosan) in EtOH, quantitative conversion of the amine groups on the polysaccharide support into imines was observed, as indicated by gas chromatographic quantification of the remaining aldehydes. Only half an equivalent of dialdehydes **3**, **7**, and **9** was consumed, even in the presence of an excess of the reactants. These results suggest that ligand anchoring occurred throughout the entire internal surface area of porous chitosan, and that cross-linking might occur in the case of functionalization with dialdehydes. The corresponding imine solids (**Im1–Im11**) were characterized by IR spectroscopy, and their surface areas, S_{BET}, were determined from the adsorption–desorption isotherms of N_2 on the corresponding aerogels.[24] The results (Table 1) indicate that the solids have high surface areas, which should enable efficient metal complexation. The Cu^I complexes **C0–C11** were obtained after the incubation of **Im0–Im11** with a solution of CuOTf and sodium ascorbate at room temperature, followed by repeated washing (see the Supporting Information). All functionalized chitosan derivatives, **Im1–Im11**, displayed higher complexation capabilities than that of chitosan itself (Table 1). The percentage of anchored ligands that chelated copper varied from 23 to 83 %; thus, chelation resulted in various metal loadings ranging from 0.5 to 2.1 mmol of Cu^I per gram of the hybrid catalyst.

Table 1: Textural and copper(I)-complexation properties of the functionalized chitosan solids **Im0–Im11**.

Entry	Aldehyde	**Im** (S_{BET} [$m^2 g^{-1}$])	**C** (complexed Cu [%]; loading [$mmol\,g^{-1}$])[a]
1	none	**Im0** (329)	**C0** (11; 0.5)
2	**1**	**Im1** (234)	**C1** (48; 1.5)
3	**2**	**Im2** (258)	**C2** (26; 0.7)
4	**3**	**Im3** (285)	**C3** (49; 0.5)
5	**4**	**Im4** (208)	**C4** (55; 1.7)
6	**5**	**Im5** (407)	**C5** (60; 2.0)
7	**6**	**Im6** (387)	**C6** (64; 1.7)
8	**7**	**Im7** (283)	**C7** (66; 0.5)
9	**8**	**Im8** (387)	**C8** (77; 1.8)
10	**9**	**Im9** (426)	**C9** (83; 0.6)
11	**10**	**Im10** (220)	**C10** (41; 1.0)
12	**11**	**Im11** (166)	**C11** (23; 0.5)

[a] Complexation was carried out with CuOTf (1.2 equiv) at 25 °C for 16 h. The amount of complexed copper (%) was calculated after quantification of the remaining copper salt by UV spectroscopic analysis.

To evaluate the putative catalytic activity of **C0–C11** for the Huisgen [3+2] cycloaddition reaction under different reaction conditions, we decided to use the coumarin-based fluorogenic probe **12**, the design of which was inspired by a previously described study (Figure 2).[25] This probe enabled us to monitor the reaction by a simple fluorescence measurement of the corresponding triazole product **13a** ($\lambda_{ex} = 320$ nm; $\lambda_{em} = 420$ nm). Results summarizing the influence of solvents and the presence of a reducing agent on the efficiency of heterogeneous **C0–C11** and a homogeneous copper–phenanthroline catalyst are presented in a color-code format in Figure 2.

The screening results first indicated a significant solvent effect on all tested catalysts, including the homogeneous catalyst, whereby the highest yields were observed when the reaction was carried out in DMSO. Generally speaking, the hybrid catalysts **C** were most effective in highly polar solvents. The use of EtOH, which is compatible with green chemistry, interested us in particular. Three heterogeneous catalysts, **C6**, **C8**, and **C9**, were found to function efficiently (yields > 95 %)

in EtOH under reducing conditions. Interestingly, only **C9** retained its catalytic efficiency in the absence of sodium ascorbate, which suggests that a particular Cu^I stabilization within the **C9** network avoided the need for a reducing agent.

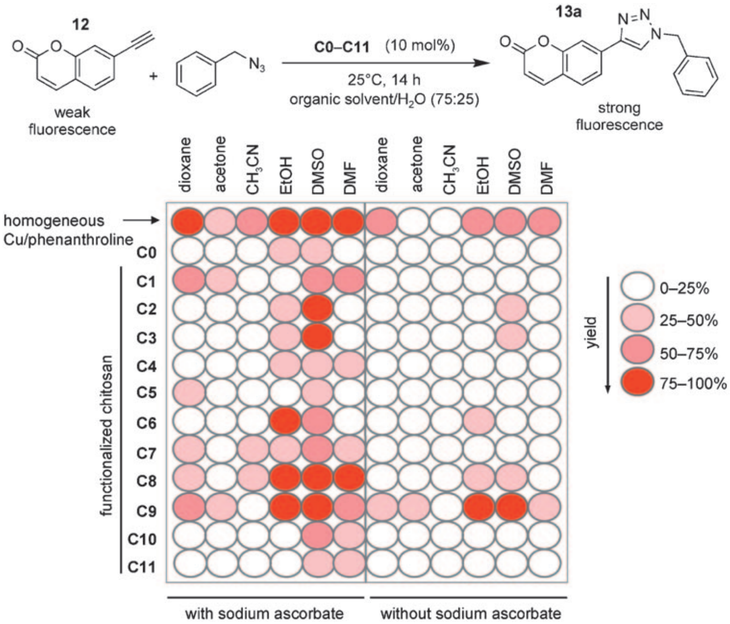
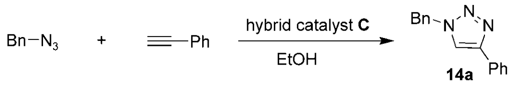


Figure 2. Screening results for a "click" reaction of the fluorophore **12** with a variety of catalysts derived from chitosan (and a homogeneous catalyst), with or without sodium ascorbate (25 mM). Substrate concentration: 10 mM. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide.

Under these conditions, **C9** appeared to be more active than the homogeneous system itself, a result that was confirmed by kinetic experiments (see the Supporting Information).

The high value of **C9** with regard to its efficiency and practical use under sustainable conditions was further confirmed by a series of experiments conducted on a 1 mmol scale on a model reaction (Scheme 2). Indeed, only 0.1 mol % of **C9** (<1% w/w) was required in EtOH at 70 °C for complete conversion of the starting materials into the 1,4-triazole product (Table 2, entry 3). The benefit of chitosan functionalization on catalytic efficiency (compare entries 3 and 4 in Table 2) and the superior air stability of **C9** (compare entry 3 with entries 5–8 in Table 2) were confirmed. Shorter reaction times were observed in the presence of triethylamine (TEA)[26] or under aqueous basic conditions; other bases had no significant effect (Table 2, entries 9–12). Further experiments showed that **C9** is quite a robust catalyst: reuse of the catalyst for the reaction of phenylacetylene with benzyl azide produced the expected 1,4-triazole in near quantitative yield even after four cycles. Quantitative analysis of the product from each cycle by inductively coupled plasma (ICP) spectrometry revealed no detectable leaching of copper. To further verify whether the observed catalysis is truly heterogeneous or caused by a leached copper species, **C9** was removed from the reaction mixture after 1 h at 70 °C, and the filtrate was heated further for several hours. The formation of **14a** was stopped completely by the removal of **C9** (see the Supporting Information).



Scheme 2. Model reaction. Bn = benzyl.

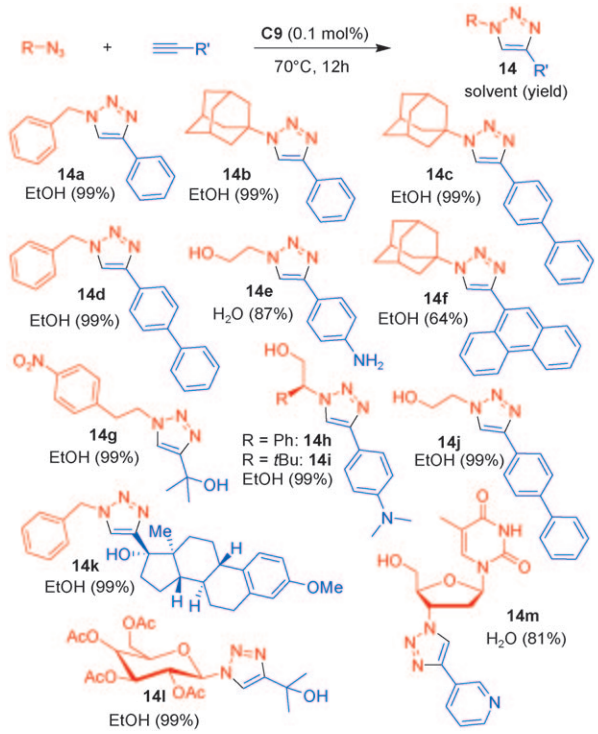
To examine the scope of catalysis by **C9** in the absence of an additive, we conducted a series of reactions with the hybrid catalyst (0.1 mol %). 1,4-Triazoles were obtained in high yields even with hindered and basic nitrogen-containing reactants (Scheme 3). Furthermore, reactions were catalyzed efficiently in pure H_2O.[27] Although the hybrid catalyst **C9** has a sugar backbone, it was found to be thermally quite stable: compound **14c** (pure 1,4-isomer) was formed quantitatively within minutes under microwave irradiation (1 M in EtOH/TEA (95:05), 150 °C, 15 min) in the presence of **C9** (0.1 mol %). No significant macroscopic change in the **C9** beads was observed after this treatment, and **14c** was again obtained quantitatively when the same beads were used to catalyze the reaction a second time. Such thermostability might be explained by the cross-linking of chitosan chains, which should stabilize the fibrous network of **C9**. The physical characterization of **C9** showed a high surface area of $368\ m^2\ g^{-1}$ and a high dispersion of copper within the network.

Table 2: Optimization of the reaction conditions.[a]

Entry	Catalyst (loading [mol %])	Base	Conditions	*t* [h]	Yield of **14a** [%]
1	**C9** (1)	none	air, 25 °C	18	95
2	**C9** (1)	none	air, 70 °C	2	98
3	**C9** (0.1)	none	air, 70 °C	12	99
4	**C0** (0.1)	none	air, 70 °C	12	trace
5	**C8** (0.1)	none	air, 70 °C	12	25
6	**C8** (0.1)	none	N_2, 70 °C	12	98
7	**C6** (0.1)	none	air, 70 °C	12	23
8	**C6** (0.1)	none	N_2, 70 °C	12	92
9	**C9** (0.1)	pyridine[b]	air, 70 °C	12	96
10	**C9** (0.1)	TEA[b]	air, 70 °C	2	97
11	**C9** (0.1)	DBU[b]	air, 70 °C	12	93
12	**C9** (0.1)	NaOH[c]	air, 70 °C	2	90

[a] Experiments were carried out at a substrate concentration of 1 M. [b] The reaction was carried out with 1 equivalent of the base. [c] The reaction was carried out in ethanol/aqueous NaOH (9:1; pH 9). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

In conclusion, we have described new readily recoverable hybrid catalysts which combine the catalytic power of transition-metal complexes with the architecture of polysaccharides and display particularly high efficiency for the Huisgen [3+2] cycloaddition. The reaction conditions



Scheme 3. Scope of the reaction with the catalyst **C9** (0.1 mol %).

(0.1 mol %, EtOH or H_2O as solvent, no additive) and the sustainability of the catalyst make the described heterogeneous system highly desirable from the point of view of green chemistry.

Experimental Section

General procedure (no precautions were taken to exclude oxygen): Two beads of **C9** (1.4 mg, 0.87 μmol, 0.1 mol %), the alkyne (1 mmol, 1.1 equiv), and the azide (0.9 mmol, 1 equiv) were heated in EtOH or H_2O (0.9 mL) at 70 °C for 14 h in a closed vial. The mixture was separated from the catalyst with a pipette, and the solvent was removed in vacuo to afford the pure product **14**, except in the case of triazoles **14 e**, **f**, and **m**, which needed recrystallization.

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[1] a) J. M. Thomas, W. J. Thomas in *Principles and Practice of Heterogeneous Catalysis*, VCH, Weinheim, **1997**; b) H. U. Blaser, A. Baiker, R. Prins in *Heterogeneous Catalysis and Fine Chemicals IV*, Elsevier, Netherlands, **1997**.
[2] a) A. Corma, H. Garcia, *Chem. Rev.* **2003**, *103*, 4307–4365; b) B. H. Lipshutz, B. A. Frieman, A. E. Tomaso, *Angew. Chem.* **2006**, *118*, 1281–1286; *Angew. Chem. Int. Ed.* **2006**, *45*, 1259–1264; c) A. Corma, *Chem. Rev.* **1995**, *95*, 559–614; d) L. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133–173; e) B. H. Lipshutz, T. Butler, E. Swift, *Org. Lett.* **2008**, *10*, 697–700; f) B. H. Lipshutz, J. B. Unger, B. R. Taft, *Org. Lett.* **2007**, *9*, 1089–1092; g) B. H. Lipshutz, D. M. Nihan, E. Vinogradova, B. R. Taft, Ž. V. Bošković, *Org. Lett.* **2008**, *10*, 4279–4282; h) B. H. Lipshutz, H. Ueda, *Angew. Chem.* **2000**, *112*, 4666–4668; *Angew. Chem. Int. Ed.* **2000**, *39*, 4492–4494; i) B. H. Lipshutz, B. A. Frieman, T. Butler, V. Kogan, *Angew. Chem.* **2006**, *118*, 814–817; *Angew. Chem. Int. Ed.* **2006**, *45*, 800–803.
[3] a) N. E. Leadbeater, M. Marco, *Chem. Rev.* **2002**, *102*, 3217–3274; b) P. Hodge, *Chem. Soc. Rev.* **1997**, *26*, 417–424; c) S. J. Shuttleworth, S. M. Allin, P. K. Sharma, *Synthesis* **1997**, 1217–1239; d) 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] S. Dumitriu in *Polysaccharides: Structural Diversity and Functional Versatility*, Marcel Dekker, New York, **2005**.
[5] a) R. Valentin, K. Molvinger, F. Quignard, D. Brunel, *New J. Chem.* **2003**, *27*, 1690–1692; b) K. Molvinger, F. Quignard, D. Brunel, M. Boissière, J. M. Devoisselle, *Chem. Mater.* **2004**, *16*, 3367–3372; c) E. Guibal, *Prog. Polym. Sci.* **2005**, *30*, 71–109, d) D. J. Macquarrie, J. J. E. Hardy, *Ind. Eng. Chem. Res.* **2005**, *44*, 8499–8520.
[6] C. Jeuniaux, M. F. Voss-Foucart, *Biochem. Syst. Ecol.* **1991**, *19*, 347–356.
[7] a) M. N. V. Ravi Kumar, R. A. A. Muzzarelli, C. Muzzarelli, H. Sashiwa, A. J. Domb, *Chem. Rev.* **2004**, *104*, 6017–6084; b) K. Kurita, *Prog. Polym. Sci.* **2001**, *26*, 1921–1971.
[8] a) Y. Koyama, A. Taniguchi, *J. Appl. Polym. Sci.* **1986**, *31*, 1951–1954; b) M. Gomez-Guillen, A. Gomez-Sanchez, M. E. Martin-Zamora, *Carbohydr. Res.* **1994**, *258*, 313–319.
[9] a) W. Sun, C. G. Xia, H. W. Wang, *New J. Chem.* **2002**, *26*, 755–758; b) H. Wang, W. Sun, C. Xia, *J. Mol. Catal. A* **2003**, *206*, 199–203.
[10] a) Y. Chang, Y. Wang, F. Zha, R. Wang, *Polym. Adv. Technol.* **2004**, *15*, 284–286; b) Y. Chang, Y. Wang, Z. Su, *J. Appl. Polym. Sci.* **2002**, *83*, 2188–2194.
[11] For reviews, see: a) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952–3015; b) V. D. Bock, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2006**, 51–68.
[12] a) L. V. Lee, M. L. Mitchell, S. J. Huang, V. V. Fokin, K. B. Sharpless, C.-H. Wong, *J. Am. Chem. Soc.* **2003**, *125*, 9588–9589; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064.
[13] 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.
[14] F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210–216.
[15] C. Girard, E. Önen, M. Aufort, S. Beauvière, A. Samson, J. Herscovici, *Org. Lett.* **2006**, *8*, 1689–1692.
[16] U. Sirion, Y. J. Bae, B. S. Lee, D. Y. Chi, *Synlett* **2008**, 2326–2330.
[17] L. Bonami, W. van Camp, D. van Rijckegen, F. E. Du Prez, *Macromol. Rapid Commun.* **2009**, *30*, 34–38.
[18] T. Katayama, K. Kamata, K. Yamaguchi, N. Mizuno, *ChemSusChem* **2009**, *2*, 59–62.
[19] a) S. Chassaing, M. Kumarraja, A. Sani Souna Sido, P. Pale, J. Sommer, *Org. Lett.* **2007**, *9*, 883–886; b) A. Alix, S. Chassaing, P. Pale, J. Sommer, *Tetrahedron* **2008**, *64*, 8922–8929; c) S. Chassaing, A. Sani Souna Sido, A. Alix, M. Kumarraja, P. Pale, J. Sommer, *Chem. Eur. J.* **2008**, *14*, 6713–6721.
[20] B. H. Lipshutz, B. R. Taft, *Angew. Chem.* **2006**, *118*, 8415–8418; *Angew. Chem. Int. Ed.* **2006**, *45*, 8235–8238.
[21] W. G. Lewis, F. G. Magallon, V. V. Fokin, M. G. Finn, *J. Am. Chem. Soc.* **2004**, *126*, 9152–9153.
[22] a) R. Valentin, K. Molvinger, C. Viton, A. Domard, F. Quignard, *Macromolecules* **2005**, *6*, 2785–2792; b) R. Valentin, B. Bonelli, E. Garrone, F. Di Renzo, F. Quignard, *Biomacromolecules* **2007**, *8*, 3646–3650.

[23] Dialdehyde cross-linking has been used previously with chitosan to provide supports for enzyme immobilization: a) R. Vazquez-Duhalt, R. Tinoco, P. D'Antonio, L. D. Timmie Topoleski, G. F. Payne, *Bioconjugate Chem.* **2001**, *12*, 301 – 306; b) L. Iyengar, A. V. S. P. Rao, *Biotechnol. Bioeng.* **1979**, *21*, 1333 – 1343; c) J. Synowiecki, Z. E. Sikorski, M. Naczk, *Biotechnol. Bioeng.* **1981**, *23*, 2211 – 2215.

[24] R. Valentin, K. Molvinger, F. Quignard, F. Di Renzo, *Macromol. Symp.* **2005**, *222*, 93 – 101.

[25] Z. Zhou, C. J. Fahrni, *J. Am. Chem. Soc.* **2004**, *126*, 8862 – 8863.

[26] The particular effect of TEA on the kinetics of the "click" reaction has been described by Lipshutz and Taft.[20]

[27] However, the catalyst is not compatible with acidic aqueous solutions. In the case of substrates containing acidic moieties, the pH value of the aqueous solution should be controlled and, if necessary, adjusted to pH > 5.