DOI: 10.1002/ejoc.201001507

Immobilized DMAP Derivatives Rivaling Homogeneous DMAP

Valerio D'Elia,[a] Yinghao Liu,[a] and Hendrik Zipse*[a]

Keywords: Acylation / Homogeneous catalysis / Immobilization / Supported catalysis / Organocatalysis

The copper-catalyzed Huisgen reaction between azides and alkynes was utilized to covalently attach derivatives of 4-(dimethylamino)pyridine (DMAP) to a polystyrene resin (PS) support. The catalytic potential of these constructs as determined in acylation and aza-Morita–Baylis–Hillman reactions far exceeds that of commercially available DMAP-PS resins and is fully competitive with DMAP in homogeneous solution.

Introduction

For decades 4-(dimethylamino)pyridine (DMAP; **1**) and its derivatives,[1] such as 4-pyrrolidinopyridine (PPY; **2**), have belonged to the synthetic chemist's toolbox as versatile and efficient nucleophilic catalysts for fundamental chemical transformations, including acylation,[1,2] synthesis of esters[3] and sulfonamides,[4] silylation,[5] Morita–Baylis–Hillman reaction,[6] CO_2 fixation,[7] and kinetic resolutions.[8] Moreover, such reagents have been widely used in reactor chemistry.[9] With the advent of the "green chemistry" concept[10] and the rising call for better sustainability, factors such as catalyst recoverability[11] and recyclability are becoming increasingly important. Efforts have therefore been undertaken to support DMAP on cross-linked polystyrene beads.[12] Although these catalysts showed a good degree of recoverability and can apparently be reused without any dramatic loss of activity, the catalytic performance of these heterogeneous catalysts is often significantly lower than those of their homogeneous equivalents. In the last few years, new, elegant immobilization strategies have been explored, including the immobilization of DMAP on mesoporous silica nanospheres,[6h] on silica-coated magnetic particles,[13] or the microencapsulation of linear DMAP polymers.[14] In spite of these remarkable advances, a heterogeneous system able to approach or even surpass the performance of the homogeneous catalysts has not yet been reported. Tricyclic DMAP derivatives **3** and **4** (Figure 1) have recently been shown to exhibit excellent activity in acylation reactions in homogeneous solution.[2b,3d] We now report that immobilization of catalyst **4** on a polystyrene support leads to catalysts of unprecedented catalytic activity, while preserving the benefits of facile recoverability and recyclability.

[a] Department of Chemistry, LMU München,
Butenandtstrasse 5-13, 81377 München, Germany
Fax: +49-89-218077738
E-mail: zipse@cup.uni-muenchen.de

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001507.

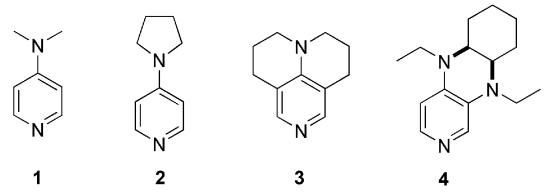
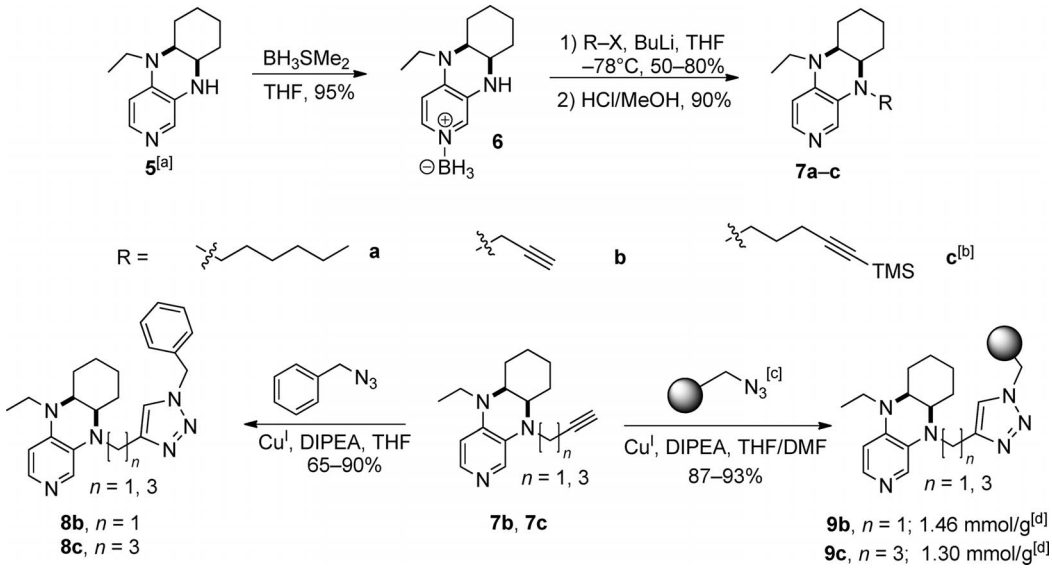


Figure 1. Selected nucleophilic catalysts based on the DMAP motif.

Results and Discussion

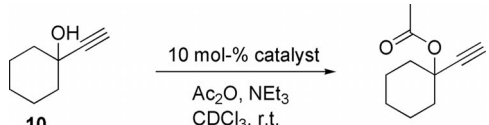
The catalytically active pyridine units were attached to the polystyrene support by using the copper-catalyzed Huisgen reaction between azides and alkynes. A number of alkyne-substituted derivatives of 3,4-diaminopyridine catalyst **4** were therefore synthesized in racemic form and attached to an azide-modified Merrifield resin as shown in Scheme 1. In order to characterize the influence of the linker structure on the catalytic activity in acylation reactions, soluble catalysts with variable side chains were also synthesized according to the synthetic protocol shown in Scheme 1. This included soluble catalyst **7a**, with a simple *n*-hexyl side chain, as well as catalysts **8b** and **8c**, with triazolyl-substituted side chains of variable length. The catalytic potential of the immobilized catalysts and their soluble counterparts were first explored in the acetylation of tertiary alcohol **10** (Table 1). All reactions eventually proceeded to full conversion, and the rate of reaction could thus be characterized by the reaction half-life $t_{1/2}$ using the approach described previously.[2c] For the sake of comparison, we also include kinetic data for the commercially available DMAP (**1**) and its immobilized version DMAP-PS (**12**). Perusal of the kinetic data for the soluble 3,4-diaminopyridine catalysts shows that variation of the side chain attached to the nitrogen substituent at the C-3 position of the pyridine ring had no major influence on the catalytic activity. All of these systems react significantly faster than with DMAP (**1**) itself. This is not the case for immobilized catalyst **9b**, the kinetics of which are comparable to those of homogeneous



Scheme 1. Synthesis of immobilized catalysts and their soluble counterparts: [a] See Held et al.[2b] [b] The TMS protecting group was removed in K_2CO_3/MeOH before performing the "click reaction", see Exp. Sect. [c] 1% crosslinked polystyrene. [d] Catalyst loading expressed as mmol of catalyst per g of polymer.

DMAP and more than ten times slower than its soluble analogue **8c**. Loss of activity represents a common drawback of catalyst immobilization and is attributed to changes in the micro-environment of the catalyst and to the increased difficulty for the reactants to diffuse to the catalytically active core. It has been shown[12d,15] that extending the distance between the pyridine moiety and the bulky polystyrene beads has beneficial effects on the activity of the catalyst.

Table 1. Catalytic activity of immobilized and soluble pyridine catalysts.[a]



Entry	Catalyst	$t_{1/2}$ [min]
	Soluble catalysts	
1	DMAP (**1**)	151 ± 2[b]
2	PPY (**2**)	67 ± 0.1[b]
3	**4**	18 ± 0.1[b]
4	**7a**	21 ± 0.1
5	**8b**	16 ± 0.1
6	**8c**	18 ± 0.1
	Immobilized catalysts	
7	DMAP-PS (**12**)	504 ± 8
8	**9b**	166 ± 3
9	**9c**	58 ± 2

[a] Reagents and conditions: **10** (0.2 M), Ac_2O (2.0 equiv.), NEt_3 (3.0 equiv.), catalyst (0.1 equiv.), $CDCl_3$, room temp. [b] Data from Held et al.[2c]

In our case, after inclusion of a longer linker unit (catalyst **9c**), the catalytic performance of the immobilized catalyst approached that of its soluble counterparts. Catalyst resin **9c** was more than eight times more effective than the commercially available DMAP-PS resin under otherwise identical reaction conditions by using the same molar amount of catalyst. This difference closely parallels that of the soluble counterparts DMAP and **8c** and thus indicates that resin support and linker structure lead to only minor perturbations in the intrinsic catalytic potential of these catalysts.

Whether the immobilized catalysts synthesized here could be used repeatedly after separation from the reaction mixture by filtration, was explored with repeated runs of the reaction shown in Table 1 with catalyst **9c**. These experiments were conducted such that the catalyst was filtered off from the reaction mixture after 12 h, washed thoroughly with dichloromethane and methanol, dried in vacuo for 12 h and then reused without any further modification (Table 2). This procedure was accompanied by only minimal loss of catalyst (approx. 1–2%) per cycle. Analogous results were obtained for catalyst **9b** within ten catalytic cycles in 24 h (see the Supporting Information).

Table 2. Yields for the benchmark reaction shown in Table 1 for the repeated use of catalyst **9c** by keeping a constant reaction time of 12 h.

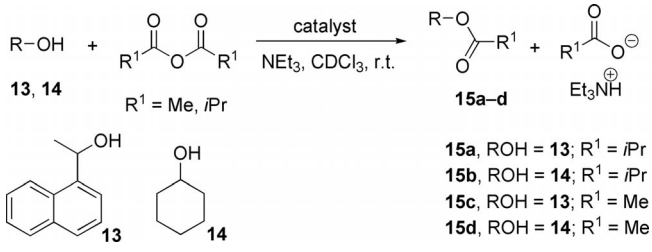
Run	Yield [%][a]	Run	Yield [%][a]
1	100 (95)[b]	6	92
2	100	7	93
3	99	8	95
4	98	9[c]	96 (91)[b]
5	93	10[c]	92

[a] Determined by ^1H NMR spectroscopy. [b] Isolated yield after column chromatography. [c] In 24 h.

The application of supported catalyst **9c** was extended to the reaction between secondary alcohols and anhydrides, because these play a significant role in protecting-group

chemistry and in the kinetic resolution of chiral alcohols. 1-(1-Naphthyl)ethanol (**13**) and cyclohexanol (**14**) were chosen as model substrates and were acylated with acetic or isobutyric anhydride (Table 3). The catalytic performance of **9c** was again compared with that of the commercially available DMAP-PS. Due to the much higher intrinsic reactivity of secondary alcohols compared to their tertiary counterparts,[16] the amount of catalyst employed could be reduced significantly, with **9c** requiring just 0.1–0.5 mol-% to efficiently promote the isobutyrylation of the alcohol substrates within a synthetically useful time. A further reduction of catalytic load, down to just 0.05 mol-% of catalyst **9c**, was possible for the acetylation reaction; however, this reaction shows a significant background rate[16] and smaller differences in catalytic performance between **9c** and DMAP-PS were therefore measured.

Table 3. Results of the acylation of secondary alcohols promoted by catalyst **9c** and DMAP-PS (**12**).[a]



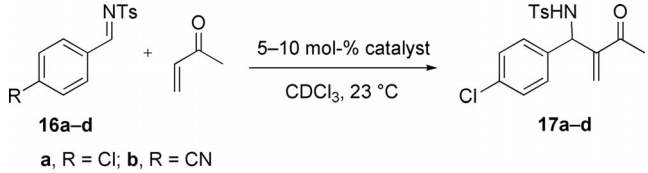
Entry	Product	Catalyst (mol-%)	$t_{1/2}$ [min]	Time [min]	Yield [%][b]
1	**15a**	**9c** (0.1)	40 ± 1	330	100 (93)[c]
2	**15a**	**9c** (0.5)	ca. 15[d]	120	98
3	**15a**	**12** (0.5)	123 ± 2	625	94
4	**15b**	**9c** (0.5)	60 ± 1	340	95 (90)[c]
5	**15b**	**12** (0.5)	270 ± 9	1120	90
6	**15c**	**9c** (0.05)	135 ± 5	1020	97 (93)[c]
7	**15c**	**12** (0.1)	101 ± 2	1045	99
8	**15d**	**9c** (0.1)	96 ± 3	780	97 (88)[c]
9	**15d**	**12** (0.1)	219 ± 4	1045	92

[a] Reagents and conditions: alcohol (0.2 M), Ac_2O (2.0 equiv.), NEt_3 (3.0 equiv.), $CDCl_3$, room temp. [b] Determined by ^1H NMR spectroscopy. [c] Isolated yield after column chromatography. [d] A conversion of 60% was measured after just 20 min of reaction time, but an accurate kinetic study was not possible under the selected conditions (see the Supporting Information).

Given the excellent performance of resin **9c** in acylation reactions, we next turned our attention to the aza-Morita–Baylis–Hillman (aza-MBH) reaction as a synthetically versatile and atom-economic C–C bond-forming reaction.[6k] The use of DMAP-PS resin catalysts for this reaction has been tested previously by Shi et al.[6c] In this case, moderate yields were obtained after up to 72 h of reaction time by employing as much as 20 mol-% of catalyst.

We selected here the reaction of tosyl imines **16a**–**d** with methyl vinyl ketone (MVK) as benchmark, again in combination with selected homogeneous or supported pyridine catalysts (Table 4). Using 5 mol-% of DMAP as a reference (homogeneous) catalyst, we found that the reaction proceeds slowly with a reaction half-life of 745 min. The diaminopyridine catalysts **4**, **7a**, **8b**, and **8c** were significantly more active under otherwise identical conditions, providing essentially complete conversion after 10 h. The shortest reaction half-life (51 min) was determined for catalyst **8c**. Experiments with supported catalysts (10 mol-%) revealed an equally large influence of the catalyst structure: whereas only slow turnover was observed for the DMAP-PS resin, fast reactions and synthetically useful yields were obtained with resin **9c**. Measured $t_{1/2}$ values for both systems indicate an intrinsic activity difference of 10 for the selected substrate pair. After filtration, washing with chloroform, and drying in vacuo for 12 h, catalyst **9c** could be successfully reused for five more runs, although a slight loss of activity was noticed in the last of these cycles (Table 4, Entries 9–13), or for the synthesis of other aza-MBH products (Entries 14–16). The $t_{1/2}$ values assembled in Table 4 also allowed the effect of the resin and linker structure on the catalyst activity to be quantified. By assuming a linear dependence of the reaction rate on the catalyst concentration, the reaction half-lives of 110 min measured for **9c** and of 57 min for catalyst **4**, imply that immobilization reduces the catalyst activity by a factor of 4.

Table 4. Catalytic activity of immobilized and soluble pyridine catalysts in the aza-MBH reaction.



Entry	Catalyst	Product	$t_{1/2}$ [min]	Time [h]	Yield [%][a]
Soluble catalysts (5 mol-% catalyst)[b]					
1	DMAP (**1**)	**17a**	745 ± 4	60	93
2	PPY (**2**)	**17a**	355 ± 2	20	84
3	**4**	**17a**	57 ± 1	10	99
4	**7a**	**17a**	67 ± 1	10	97
5	**8b**	**17a**	60 ± 1	10	98
6	**8c**	**17a**	51 ± 1	10	98
Immobilized catalysts (10 mol-% catalyst)					
7	**12**	**17a**	1125 ± 100	21	54
8	**9c**	**17a**	110 ± 7	12	93 (87)[d]
9[c]	**9c**	**17a**	–	12	92
10[c]	**9c**	**17a**	–	12	90
11[c]	**9c**	**17a**	–	12	92
12[c]	**9c**	**17a**	–	20	95
13[c]	**9c**	**17a**	–	25	90
14[e]	**9c**	**17b**	–	16	94 (81)[d]
15[e]	**9c**	**17c**	–	16	90 (78)[d]
16[e]	**9c**	**17d**	–	16	89 (63)[d,f]

[a] Determined by ^1H NMR spectroscopy. [b] **16** (0.125 M), MVK (1.2 equiv.), $CDCl_3$. [c] Catalyst is recycled from the previous entry. [d] Isolated yield after column chromatography. [e] The catalyst had been already employed for the reactions in Entries 7–12. [f] 20% of benzaldehyde (from hydrolysis of **16d**) was also recovered.

Conclusions

The immobilization of 3,4-diaminopyridines on polystyrene support with aid of the copper-catalyzed Huisgen reac-

tion leads to new catalysts of high activity that can be easily recovered. The measured reaction half-lives depend significantly on both the nature of the pyridine catalyst and on the length of the linker unit. In acylation reactions, the most active combination was found to exceed the catalytic activity of commercially available polystyrene-DMAP eightfold, whereas a tenfold difference was found for the aza-MBH reaction.

Experimental Section

General: Methods and the treatment of kinetic data are described in detail in the Supporting Information. Commercial PS-DMAP polymer (base loading ca. 3.0 mmol/g DMAP, polystyrene crosslinked with 2% DVB) and Merrifield's resin (mesh: 100–200, loading: 2.0–3.0 mmol/g Cl^-, polystyrene crosslinked with 1% DVB) were purchased from Sigma–Aldrich and dried under vacuum at 60 °C overnight before use.

Acylation (Homogeneous Catalysts): The experimental procedure and the kinetic data treatment were carried out as described previously.[2c]

Acylation (Heterogeneous Catalysts) and Catalyst Recovery: Two stock solutions (in anhydrous $CDCl_3$) were prepared in dry, calibrated 10 mL flasks: stock solution A: anhydride (1.2 M); stock solution B: alcohol (0.6 M) and Et_3N (1.8 M). Under N_2, the two solutions were mixed in a dry 50 mL flask, and anhydrous $CDCl_3$ (10 mL) was added to adjust the concentration of the reagents to the same values used in the case of the homogeneous catalysts. The appropriate amount of resin was subsequently added, and the flask was closed with a rubber septum. The reaction vessel was shaken at room temperature at 480 rpm. Periodically, the agitation was interrupted for about 1 min until all the resin floated on top of the solution, thus allowing removal of 100 μL of a solid-free sample from the bottom of the reaction mixture by using a syringe. The sample was placed in a vial; 80 μL of this solution was removed by using a calibrated pipette, placed in a dry NMR tube and diluted with anhydrous $CDCl_3$ (0.8 mL). The sample was subsequently submitted to NMR spectroscopy to obtain the kinetic data, which were treated as described previously.[2c] At the end of the reaction, the heterogeneous mixture was filtered under reduced pressure through a Büchner funnel covered by a disc of filter paper. The catalyst was washed with CH_2Cl_2 (50 mL), CH_2Cl_2/MeOH (1:1; 50 mL), and finally with CH_2Cl_2 (100 mL). It was collected in a dry 50 mL flask and dried under high vacuum at 60 °C overnight. The filtrate was placed in an extraction funnel and washed with saturated aqueous NH_4Cl (30 mL) and with saturated $NaHCO_3$ (30 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was filtered through a plug of silica gel (hexanes/EtOAc, 10:1) to afford the desired ester with high yields and purity.

Morita–Baylis–Hillman Reaction (Homogeneous Catalysts): Two stock solutions were prepared in dry calibrated 5 mL flasks: stock solution A: tosylimine (0.15 M), methyl vinyl ketone (0.18 M) and 1,3,5-trimethoxybenzene (0.1 M) (internal standard) in $CDCl_3$; stock solution B: catalyst (0.0375 M) in $CDCl_3$. Under N_2, stock solution A (0.5 mL) and stock solution B (0.1 mL) were injected into an NMR tube, which was sealed by melting its opening with a flame. The sample was periodically submitted to NMR analysis to collect the kinetic information.

Morita–Baylis–Hillman Reaction (Heterogeneous Catalysts) and Catalyst Recovery: Supported catalyst **9c** (0.375 mmol) was added to a solution of tosylimine **16a**–**d** (3.75 mmol), methyl vinyl ketone (4.5 mmol, 315 mg), and 1,3,5-trimethoxybenzene (1.0 mmol, 168 mg, internal standard) in $CDCl_3$ (30 mL). The reaction vessel was shaken at room temperature (480 rpm). Periodically, the agitation was interrupted for about 1 min until all the resin floated on top of the solution, thus allowing the removal of 100 μL of a solid-free sample from the bottom of the reaction mixture by using a syringe. The sample was diluted with $CDCl_3$ (0.6 mL) and subsequently submitted to NMR spectroscopy to determine the kinetic information. At the end of the reaction, the heterogeneous mixture was filtered under reduced pressure through a Büchner funnel covered by a disc of filter paper. The catalyst was washed with $CHCl_3$ (3×50 mL), collected in a dry 50 mL flask and dried under high vacuum at 60 °C overnight. The filtrate was concentrated under reduced pressure, and the crude material was purified by column chromatography on silica gel (hexanes/EtOAc, 4:1) to afford the desired MBH product, together with 2–20% of aromatic aldehyde derived from the partial hydrolysis of the tosylimine substrates **16a**–**d**.

Synthesis of Homogeneous Catalysts

(5-Ethyl-5,5a,6,7,8,9,9a,10-octahydropyrido[3,4-*b*]quinoxalin-2-ium-2-yl) Trihydroborate (6): Racemic building block **5**[2b] (0.41 g, 1.90 mmol, 1.0 equiv.) was dissolved in anhydrous THF (10 mL), and the temperature of the solution was set to –10 °C by using an ice/NaCl bath. To this solution, a solution of BH_3SMe_2 (2 M in THF, 0.95 mL, 1.9 mmol, 1.0 equiv.) was added dropwise through a rubber septum by using a syringe within 10 min. After the addition was complete, the ice/NaCl bath was removed, and the reaction mixture was warmed to room temperature for 5 min. TLC analysis (EtOAc/NEt_3/MeOH, 10:1:1; R_f = 0.90) showed complete conversion of the starting material. The reaction solvent was removed under reduced pressure, and the residual oil was purified by filtration through a silica gel plug (EtOAc/NEt_3/MeOH, 10:1:1) to afford **6** (0.42 g, 1.82 mmol, 95%) as a white solid; m.p. 190–193 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, J = 6.4 Hz, 1 H, 3-H), 7.50 (s, 1 H, 1-H), 6.28 (d, J = 6.4 Hz, 1 H, 4-H), 3.61 (br. s, 1 H, N-H), 3.46–3.28 (m, 4 H, NCH_2CH$_3$, 5a-H, 9a-H), 2.90–2.00 (br. s, 3 H, BH_3), 1.93 (m, 1 H), 1.81–1.68 (m, 3 H), 1.61–1.37 (m, 3 H), 1.32 (m, 1 H), 1.19 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.3, 138.9, 130.5, 129.4, 103.4, 59.1, 47.6, 43.7, 30.7, 27.3, 24.9, 19.1, 12.0 ppm. IR (solid): $\tilde{\nu}$ = 3228, 2935, 2294, 1686, 1611, 1532, 1173, 1096 cm^{-1}. HRMS (ESI$^-$): calcd. for [$C_{13}H_{22}BN_3$ + HCOO]$^-$ 276.1889; found 276.1893.

5-Ethyl-10-hexyl-5,5a,6,7,8,9,9a,10-octahydropyrido[3,4-*b*]quinoxaline (7a): Compound **6** (0.82 g, 3.55 mmol, 1.0 equiv.) was dissolved in anhydrous THF (15 mL). Butyllithium (2.5 M in hexanes, 1.7 mL, 4.25 mmol, 1.2 equiv.) was added dropwise to this solution through a rubber septum at –78 °C. After 15 min, hexyl bromide (0.75 mL, 5.32 mmol, 1.5 equiv.) was added, and the reaction mixture was warmed to room temperature overnight. The reaction was quenched by adding EtOH (1 mL), and the solvent was subsequently removed under reduced pressure. The raw material was taken up in MeOH (10 mL), and concentrated HCl (0.32 mL, 1.1 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at this temperature for 5 min, then the solvent was removed under reduced pressure, and the crude material was taken up in CH_2Cl_2 (20 mL) and saturated aqueous K_2CO_3 (10 mL). The aqueous layer was washed with CH_2Cl_2 (5 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to yield an oil, which was purified by column chromatography on silica gel (EtOAc/NEt_3/MeOH, 20:2:1) to

afford **7a** (0.64 g, 2.12 mmol, 60%) as a pale-yellow oil together with unprotected starting material **6** (0.30 g, 1.38 mmol, 39%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, J = 5.5 Hz, 1 H, 3-H), 7.70 (s, 1 H, 1-H), 6.37 (d, J = 5.5 Hz, 1 H, 4-H), 3.54–3.29 (m, 3 H, NCH_2CH$_3$, 5a-H), 3.22 [m, 2 H, NCH_2(C$_5$H$_{11}$)], 3.04 (m, 1 H, 9a-H), 1.86 (m, 2 H), 1.59 (m, 6 H), 1.33 (m, 8 H), 1.16 (t, J = 7.1 Hz, 3 H, NCH$_2$CH_3), 0.90 [m, 3 H, N(C$_5$H$_{10}$)CH_3] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5, 140.1, 132.0, 130.9, 104.5, 55.4, 54.5, 47.2, 41.1, 31.7, 28.0, 27.0, 26.9, 25.5, 22.7, 22.3, 22.2, 14.0, 11.5 ppm. IR (film): $\tilde{\nu}$ = 2928, 2855, 1580, 1514, 1354, 1266, 1074 cm^{-1}. HRMS (ESI$^+$): calcd. for [C$_{19}$H$_{31}$N$_3$ + H]$^+$ 302.2591; found 302.2590.

5-Ethyl-10-(prop-2-ynyl)-5,5a,6,7,8,9,9a,10-octahydropyrido[3,4-*b*]-quinoxaline (7b): Compound **6** (1.76 g, 7.61 mmol, 1.0 equiv.) was dissolved in anhydrous THF (40 mL), and butyllithium (2.5 M in hexanes, 3.35 mL, 8.37 mmol, 1.1 equiv.) was added dropwise to this solution through a rubber septum at –78 °C. After 15 min, propargyl bromide (80 wt.-% in toluene, 1.0 mL, 9.13 mmol, 1.2 equiv.) was added, and the reaction mixture was warmed to room temperature overnight. The reaction was quenched by adding EtOH (3 mL), and the solvent was subsequently removed under reduced pressure. The raw material was taken up in MeOH (20 mL), and concentrated HCl (0.70 mL, 1.1 equiv.) was added dropwise to this solution at 0 °C. The reaction mixture was stirred at this temperature for 5 min, then the solvent was removed under reduced pressure and the crude material was taken up in CH_2Cl_2 (40 mL) and saturated K_2CO_3 (20 mL). The aqueous layer was washed with CH_2Cl_2 (10 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to yield an oil, which was purified by column chromatography on silica gel (EtOAc/NEt$_3$/MeOH, 20:2:1) to afford **7b** (1.58 g, 6.19 mmol, 80%) as a pale-yellow solid; m.p. 162–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (m, 2 H, 1-H, 3-H), 6.36 (d, J = 5.5 Hz, 1 H, 4-H), 4.17 (dd, J = 18.3, 2.3 Hz, 1 H, NCH_2C≡CH), 3.92 (dd, J = 18.3, 2.3 Hz, 1 H, NCH_2C≡CH), 3.52–3.13 (m, 4 H, NCH_2CH$_3$, 5a-H, 9a-H), 2.20 (s, 1 H, NCH$_2$C≡C*H*), 2.01 (m, 1 H), 1.85–1.57 (m, 4 H), 1.54–1.23 (m, 3 H), 1.17 (t, J = 7.1 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.0, 141.0, 133.0, 129.5, 104.0, 78.5, 72.4, 57.6, 52.6, 42.1, 35.2, 28.0, 27.2, 23.5, 20.9, 11.7 ppm. IR (solid): $\tilde{\nu}$ = 3096, 2932, 2095, 1587, 1524, 1440, 1274, 1240, 1184, 1076 cm^{-1}. HRMS (ESI$^+$): calcd. for [C$_{16}$H$_{21}$N$_3$ + H]$^+$ 256.1808; found 256.1806.

5-Ethyl-10-[5-(trimethylsilyl)pent-4-ynyl]-5,5a,6,7,8,9,9a,10-octahydropyrido[3,4-*b*]quinoxaline (7c′, Precursor of 7c): Compound **6** (2.10 g, 9.1 mmol, 1.0 equiv.) was dissolved in anhydrous THF (40 mL), and butyllithium (2.5 M in hexanes, 4.40 mL, 10.92 mmol, 1.2 equiv.) was added dropwise to this solution through a rubber septum at –78 °C. The reaction mixture was stirred at –78 °C for 15 min and then warmed to 0 °C in an ice bath. After 15 min, (5-iodo-1-pentynyl)trimethylsilane (11.4 mmol, 1.25 equiv.) was added dropwise, and the reaction mixture was warmed to room temperature overnight. The reaction was quenched by adding EtOH (5 mL), and the solvent was subsequently removed under reduced pressure. The raw material was taken up in MeOH (20 mL), and concentrated HCl (0.85 mL, 1.1 equiv.) was added dropwise to this solution at 0 °C. The reaction mixture was stirred at this temperature for 5 min, then the solvent was removed under reduced pressure, and the crude material was taken up in CH_2Cl_2 (50 mL) and saturated K_2CO_3 (20 mL). The aqueous layer was washed with CH_2Cl_2 (10 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to yield an oil, which was purified by column chromatography on silica gel (EtOAc/NEt$_3$/MeOH, 20:2:1; R_f = 0.90) to afford **7c′** (0.90 g, 4.58 mmol, 50%) as a pale-yellow oil together with unprotected starting material **6** (0.90 g, 3.89 mmol, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, J = 5.5 Hz, 1 H, 3-H), 7.72 (s, 1 H, 1-H), 6.38 (d, J = 5.5 Hz, 1 H, 4-H), 3.48 (m, 3 H, NCH_2CH$_3$, 5a-H), 3.25 (m, 3 H, NCH_2CH$_2$CH$_2$C≡CSiMe$_3$, 9a-H), 2.30 (t, J = 6.8 Hz, 2 H, NCH$_2$CH$_2$CH_2C≡CSiMe$_3$), 1.82 (m, 4 H), 1.59 (app. d, 4 H), 1.40 (m, 2 H), 1.26 (t, J = 7.1 Hz, 3 H, CH$_3$), 0.18 [s, 9 H, Si(CH$_3$)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.7, 140.3, 131.9, 130.6, 106.4, 104.6, 85.4, 55.2, 54.9, 45.9, 41.1, 28.0, 26.8, 24.2, 22.3, 22.2, 17.4, 11.5, 0.14 ppm. IR (film): $\tilde{\nu}$ = 2935, 2857, 2173, 1580, 1515, 1355, 1248 cm^{-1}. HRMS (ESI$^+$): calcd. for [C$_{21}$H$_{33}$N$_3$Si + H]$^+$ 356.2517; found 356.2514.

5-Ethyl-10-(pent-4-ynyl)-5,5a,6,7,8,9,9a,10-octahydropyrido[3,4-*b*]-quinoxaline (7c): Compound **7c′** (1.50 g, 4.22 mmol, 1.0 equiv.) was dissolved in MeOH (15 mL), and K_2CO_3 (0.87 g, 6.33 mmol, 1.5 equiv.) was added. The reaction mixture was stirred at room temperature overnight, then the solvent was removed under reduced pressure, and the crude material was partitioned between water (100 mL) and CH_2Cl_2 (200 mL). The aqueous layer was washed with CH_2Cl_2 (50 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound as a greenish oil (1.15 g, 4.06 mmol, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (app. d, 2 H, 3-H, 1-H), 6.37 (d, J = 5.4 Hz, 1 H, 4-H), 3.47 (m, 3 H, NCH_2CH$_3$, 5a-H), 3.22 (m, 3 H, NCH_2CH$_2$CH$_2$C≡CH, 9a-H), 2.24 (t, J = 10.9 Hz, 2 H, NCH$_2$CH$_2$CH_2C≡CH), 2.00 (s, 1 H, NCH$_2$CH$_2$CH$_2$C≡C*H*), 1.83 (m, 4 H), 1.58 (m, 4 H), 1.39 (m, 2 H), 1.15 (t, J = 7.1Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.8, 140.3, 131.9, 130.6, 104.6, 83.6, 69.0, 55.2, 54.9, 46.3, 40.9, 28.0, 26.7, 24.4, 22.4, 22.0, 16.0, 11.4 ppm. IR (film): $\tilde{\nu}$ = 3289, 2932, 2856, 2116, 1579, 1514, 1355, 1266, 1065 cm^{-1}. HRMS (ESI$^+$): calcd. for [C$_{18}$H$_{25}$N$_3$ + H]$^+$ 284.2121; found 284.2121.

10-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-5-ethyl-5,5a,6,7,8,9,9a,10-octahydropyrido[3,4-*b*]quinoxaline (8b): Compound **7b** (0.26 g, 1.0 mmol, 1.0 equiv.) was dissolved in anhydrous THF (10 mL), and the solution was degassed by purging with N_2 for 5 min. Benzyl azide (0.16 g, 1.2 mmol, 1.2 equiv.) was added, followed by a catalytic amount of CuBr and *N*,*N*-diisopropylethylamine (DIPEA; 0.34 mL, 2.0 mmol, 2.0 equiv.). The reaction mixture was stirred at room temperature for 2 h, then the solution was partitioned between CH_2Cl_2 (20 mL) and saturated K_2CO_3 (10 mL). The aqueous layer was washed with CH_2Cl_2 (10 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to yield an oil that was purified by column chromatography on silica gel (EtOAc/NEt$_3$/MeOH, 20:2:1) to afford **8b** (350 mg, 0.90 mmol, 90%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 2 H, 3-H, 1-H), 7.34 (s, 1 H, triazole-H), 7.33–7.22 (m, 2 H), 7.24–7.07 (m, 3 H), 6.32 (d, J = 5.5 Hz, 1 H, 4-H), 5.43 (d, J = 7.5 Hz, 1 H, CH_2Ph), 5.39 (d, J = 7.5 Hz, 1 H, CH_2Ph), 4.65 (d, J = 16.7 Hz, 1 H, NCH_2-triazole), 4.43 (d, J = 16.7 Hz, 1 H, NCH_2-triazole), 3.44–3.09 (m, 4 H, NCH_2CH$_3$, 5a-H, 9a-H), 2.08 (s, 1 H), 1.77 (m, 1 H), 1.65–1.41 (m, 4 H), 1.40–1.27 (m, 2 H), 1.11 (t, J = 6.9 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 141.1, 140.4, 134.8, 131.7, 130.6, 129.0, 128.6, 127.8, 122.2, 104.3, 56.3, 54.0, 53.7, 42.3, 41.7, 27.7, 27.2, 22.9, 21.4, 11.6 ppm. IR (solid): $\tilde{\nu}$ = 2931, 2856, 1361, 1267, 1200, 1047 cm^{-1}. HRMS (ESI$^+$): calcd. for [C$_{23}$H$_{28}$N$_6$ + H]$^+$ 389.2448; found 389.2442.

10-[3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propyl]-5-ethyl-5,5a,6,7,8,9,9a,10-octahydropyrido[3,4-*b*]quinoxaline (8c): Compound **7c** (0.38 g, 1.3 mmol, 1.0 equiv.) was dissolved in anhydrous THF (15 mL), and the solution was degassed by purging with N_2 for

5 min. Benzyl azide (0.34 g, 2.6 mmol, 2.0 equiv.) was added, followed by a catalytic amount of CuBr and DIPEA (0.44 mL, 2.6 mmol, 2.0 equiv.). The reaction mixture was stirred at room temperature for 2 h, then the solution was partitioned between CH_2Cl_2 (25 mL) and saturated K_2CO_3 (10 mL); the aqueous layer was washed with CH_2Cl_2 (10 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to yield an oil that was purified by column chromatography on silica gel (EtOAc/NEt_3/MeOH, 20:2:1) to afford **8c** as a pale-yellow foam (0.35 g, 0.85 mmol, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 5.4 Hz, 1 H, 3-H), 7.63 (s, 1 H, 1-H), 7.36 (m, 3 H), 7.26 (m, 3 H), 6.37 (d, J = 5.4 Hz, 1 H, 4-H), 5.49 (s, 2 H, CH_2Ph), 3.53–3.34 (m, 3 H, NCH_2CH$_3$, 5a-H), 3.29–3.17 (m, 2 H, 9-NCH_2R), 3.17–3.04 (m, 1 H, 9a-H), 2.74 (t, J = 7.7 Hz, 2 H, NCH$_2$CH$_2$CH_2-triazole), 1.95 (m, 3 H), 1.73 (m, 1 H), 1.55 (app. s, 4 H), 1.36 (app. s, 2 H), 1.14 (t, J = 7.5 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9, 140.8, 140.1, 134.9, 131.7, 130.7, 129.1, 128.6, 128.0, 120.7, 104.6, 55.1, 54.8, 54.0, 46.6, 41.0, 28.0, 26.7, 25.4, 23.3, 22.3, 22.1, 11.4 ppm. IR (film): $\tilde{\nu}$ = 2930, 2854, 1579, 1514, 1455, 1354, 1266, 1214, 1048 cm^{-1}. HRMS (ESI$^+$): calcd. for [$C_{25}H_{32}N_6$ + H]$^+$ 417.2761; found 417.2760.

Synthesis of Polystyrene-Supported Catalysts

Supported Catalyst 9b: Polystyrene-azide (**PS-N$_3$**; 0.80 g, 2.1 mmol N_3^-, 1.0 equiv.) was suspended in an anhydrous THF/DMF mixture (1:1; 20 mL), and the suspension was degassed by purging with N_2 for 5 min. Compound **7b** (0.70 g, 2.7 mmol, 1.3 equiv.) was added, followed by a catalytic amount (10 mol-%) of CuBr-(PPh_3)$_3$ (0.19 g, 0.2 mmol, 0.1 equiv.) and DIPEA (0.72 mL, 4.2 mmol, 2.0 equiv.). With the mixture still under N_2, the reaction vessel was rotated in a water bath at 40 °C for 24 h, during which time the color of the reaction mixture turned to brown and then to black. The resin was filtered and washed with DMF (80 mL), water/DMF (1:1; 80 mL), water (80 mL), water/MeOH (1:1; 80 mL), MeOH (80 mL), THF/MeOH (1:1; 80 mL), and finally THF (150 mL). It was dried under vacuum at 60 °C for 24 h to give a dark-red resin (**9b**; 1.30 g, 96%). The FTIR spectrum of the solid showed the disappearance of the azide stretching band at 2093 cm^{-1} and the presence of new absorption bands at $\tilde{\nu}$ = 1532, 1264, 1197, 1183 cm^{-1}, belonging to the backbone of the supported catalyst. Elemental analysis: found C 78.24, H 7.53, N 12.26. On the basis of the nitrogen content it was possible to calculate a loading of 1.46 mmol/g catalyst and an efficiency of 93% for the "click reaction".

Supported Catalyst 9c: Polystyrene-azide (**PS-N$_3$**; 0.65 g, 1.7 mmol N_3^-, 1.0 equiv.) was suspended in an anhydrous mixture of THF/DMF (1:1, 12 mL), and the suspension was degassed by purging with N_2 for 5 min. Compound **7c** (0.72 g, 2.5 mmol, 1.5 equiv.) was added, followed by a catalytic amount (10 mol-%) of CuBr(PPh_3)$_3$ (0.16 g, 0.17 mmol, 0.1 equiv.) and DIPEA (0.73 mL, 4.25 mmol, 2.5 equiv.). With the mixture still under N_2, the reaction vessel was rotated in a water bath at 50 °C for 2 d, during which time the color of the reaction mixture turned to brown and then black. The resin was filtered and washed with DMF (80 mL), water/DMF (1:1; 80 mL), water (80 mL), water/MeOH (1:1; 80 mL), MeOH (80 mL), THF/MeOH (1:1; 80 mL), and finally THF (150 mL). It was dried under vacuum at 60 °C for 24 h to give a brown resin (**9c**; 1100 g, 97%). The FTIR spectrum of the solid showed the disappearance of the azide stretching band at $\tilde{\nu}$ = 2093 cm^{-1} and the presence of new absorption bands at $\tilde{\nu}$ = 1668, 1580, 1513, 1266, 1064 cm^{-1}, belonging to the backbone of the supported catalyst. Elemental analysis: found C 82.13, H 6.93, N 10.91. On the basis of the elemental analysis it was possible to calculate a catalyst loading of 1.30 mmol/g catalyst and an efficiency of 87% for the "click reaction".

Supporting Information (see footnote on the first page of this article): General methods, kinetic data and graphics, NMR and IR frequencies, copies of ^{1}H and ^{13}C NMR spectra, supporting references.

Acknowledgments

Financial support for this project by the Deutsche Forschungsgemeinschaft through the focus program SPP 1179 "organocatalysis" is gratefully acknowledged.

[1] a) L. M. Litvinenko, A. I. Kirichenko, *Dokl. Akad. Nauk SSSR* **1967**, *176*, 97–100; b) L. M. Litvinenko, A. I. Kirichenko, *Chem. Abstr.* **1968**, *68*, 68325u; c) W. Steglich, G. Höfle, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 981.

[2] a) M. R. Heinrich, H. S. Klisa, H. Mayr, W. Steglich, H. Zipse, *Angew. Chem. Int. Ed.* **2003**, *42*, 4826–4828; b) I. Held, S. Xu, H. Zipse, *Synthesis* **2007**, 1185–1196; c) I. Held, E. Larionov, C. Bozler, F. Wagner, H. Zipse, *Synthesis* **2009**, 2267–2277.

[3] a) B. Neises, W. Steglich, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522–524; b) K. Takeda, A. Akiyama, H. Nakamura, S. Takizawa, Y. Mizuno, H. Takayanagi, Y. Harigaya, *Synthesis* **1994**, 1063–1066; c) L. J. Gooßen, A. Döhring, *Synlett* **2004**, 263–266; d) I. Held, P. von den Hoff, D. S. Stephenson, H. Zipse, *Adv. Synth. Catal.* **2008**, *350*, 1891–1900.

[4] J. Habermann, S. V. Ley, J. S. Scott, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1253–1255.

[5] S. K. Chaudary, O. Hernandez, *Tetrahedron Lett.* **1979**, *20*, 99–102.

[6] a) F. Rezgui, M. M. El Gaied, *Tetrahedron Lett.* **1998**, *39*, 5965–5966; b) V. K. Aggarwal, A. Mereu, *Chem. Commun.* **1999**, 2311–2312; c) M. Shi, C. Q. Li, J. K. Jiang, *Chem. Commun.* **2001**, 833–834; d) M. Shi, Y.-M. Xu, *Eur. J. Org. Chem.* **2002**, 696–701; e) J. W. Huang, M. Shi, *Adv. Synth. Catal.* **2003**, *345*, 953–958; f) A. Corma, H. Garcia, A. Leyva, *Chem. Commun.* **2003**, 2806–2807; g) Y. Sotohme, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589–5592; h) H.-T. Chen, S. Huh, J. W. Wiench, M. Pruski, V. S.-Y. Lin, *J. Am. Chem. Soc.* **2005**, *127*, 13305–13311; i) B. Helms, S. J. Guillaudeu, Y. Xie, M. McMurdo, C. J. Hawker, J. M. J. Frechet, *Angew. Chem. Int. Ed.* **2005**, *44*, 6384–6387; j) C. K. W. Kwong, R. Huang, M. Zhang, M. Shi, P. H. Toy, *Chem. Eur. J.* **2007**, *13*, 2369–2376; k) D. Basavaiah, B. S. Reddy, S. S. Badsara, *Chem. Rev.* **2010**, *110*, 5447–5674; l) I. Deb, M. Dadwal, S. M. Mobin, I. N. N. Namboothiri, *Org. Lett.* **2006**, *8*, 1201–1204; m) I. Deb, P. Shanbhag, S. M. Mobin, I. N. N. Namboothiri, *Eur. J. Org. Chem.* **2009**, 4091–4101.

[7] a) Y. M. Shen, W. L. Duan, M. Shi, *Adv. Synth. Catal.* **2003**, *345*, 337–340; b) Y. M. Shen, W. L. Duan, M. Shi, *Eur. J. Org. Chem.* **2004**, 3080–3089; c) R. A. Shiels, C. W. Jones, *J. Mol. Catal. A* **2007**, *261*, 160–166; d) D. J. Darensbourg, *Chem. Rev.* **2007**, *107*, 2388–2410; e) G. W. Coates, D. R. Moore, *Angew. Chem. Int. Ed.* **2004**, *43*, 6618–6639; f) W. L. Dai, S. L. Luo, S. F. Yin, C. T. Au, *Appl. Catal., A* **2009**, *366*, 2–12.

[8] a) R. Wurz, *Chem. Rev.* **2007**, *107*, 5570–5595; b) T. A. Duffey, S. A. Shaw, E. Vedejs, *J. Am. Chem. Soc.* **2009**, *131*, 14–15; c) C. Kanta De, E. G. Klauber, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 17060–17061; d) O. Gleeson, R. Tekoriute, Y. K. Gun'ko, S. J. Connon, *Chem. Eur. J.* **2009**, *15*, 5669–5673; e) T. A. Duffey, J. A. MacKay, E. J. Vedejs, *J. Org. Chem.* **2010**, *75*, 4674–4685.

[9] a) C. Wiles, P. Watts, S. J. Haswell, E. Pombo-Villar, *Tetrahedron* **2003**, *59*, 10173–10179; b) A. R. Bogdan, B. P. Mason, K. T. Sylvester, D. T. McQuade, *Angew. Chem. Int. Ed.* **2007**, *46*, 1698–1701.

[10] P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York **1998**.
[11] a) F. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 1367–1390; b) *Recoverable and Recyclable Catalysts* (Ed.: M. Benaglia), John Wiley & Sons, Chichester, UK, **2009**.
[12] a) S. Shinkai, H. Tsuji, Y. Hara, O. Manabe, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 631–632; b) J. Yoshida, J. Hashimoto, N. Kawabata, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 309–310; c) F. M. Menger, D. J. McCann, *J. Org. Chem.* **1985**, *50*, 3928–3931; d) A. Deratani, G. D. Darling, D. Horak, J. M. J. Frechet, *Macromolecules* **1987**, *20*, 767–772; e) F. Gendouz, R. Jacquier, J. Verducci, *Tetrahedron* **1988**, *44*, 7095–7108; f) M. Tomoi, Y. Akada, H. Kakiuchi, *Makromol. Chem. Rapid Commun.* **1982**, *3*, 537–542.
[13] C. O'Dalaigh, S. A. Corr, Y. Gun'ko, S. J. Connon, *Angew. Chem. Int. Ed.* **2007**, *46*, 4329–4332.
[14] a) K. E. Price, B. P. Mason, A. R. Bogdan, S. J. Broadwater, J. L. Steinbacher, D. T. McQuade, *J. Am. Chem. Soc.* **2006**, *128*, 10376–10377; b) B. P. Mason, A. R. Bogdan, A. Goswami, D. T. McQuade, *Org. Lett.* **2007**, *9*, 3449–3451.
[15] a) M. Tomoi, E. Ogawa, Y. Hosokawa, H. Kakiuchi, *J. Polym. Sci. Polym. Chem. Ed.* **1982**, *20*, 3015–3019; b) M. Tomoi, M. Goto, H. Kakiuchi, *Makromol. Chem. Rapid Commun.* **1985**, *6*, 397–401.
[16] C. B. Fisher, S. Xu, H. Zipse, *Chem. Eur. J.* **2006**, *12*, 5779–5784.

Received: November 10, 2010
Published Online: January 27, 2011

