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Tetrahedron 60 (2004) 8703–8709

Tetrahedron

High loading polymer reagents based on polycationic Ultraresins. Polymer-supported reductions and oxidations with increased efficiency

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Received 17 November 2003; accepted 15 January 2004

Abstract—Ultraresin **1** was prepared from highly branched polyethylene imine (M_n=10,000) via reductive cross-linking with terephthaldialdehyde. Following quaternization with methyl iodide, the polycationic Ultraresin **2**, with iodide as a counterion, was obtained. These novel resins combine low swelling with high mechanical stability. By anion exchange polycationic Ultraresins carrying borohydride (**3**) and periodate (**22**) were generated and were investigated as very high loading polymer reagents. Ultra-borohydride resin **3** had a reducing activity of up to 12 mmol/g depending on the substrate. It proved successful in diverse reductions including those of aldehydes, ketones, and nitroolefines. The resin was employed in the reductive amination of aldehydes with an excess of amines, which were removed by the use of a scavenger resin. Periodate resin **22** was obtained with an active loading of up to 5.4 mmol/g and was employed in oxidations of sulfides, diols, hydroquinones, and hydrazines.

1. Introduction

Complex organic molecules can be constructed in homogeneous solution, however, for diversity-oriented purposes it is often advantageous to employ a multiple phase system which greatly facilitates isolation and separation procedures as well as the removal of excess reagents and the completion of reactions. Solid phase synthesis is the most widely applied example for multiple phase systems in combinatorial chemistry, possessing significant advantages in comparison to homogeneous single phase synthesis.

Synthesis in solution, however, possesses indisputable advantages in respect to the versatility of applicable reactions, the ease of analytical monitoring, and the accumulated knowledge of synthetic protocols. Thus, an ideal synthetic strategy would combine these merits with the advantages of solid-phase synthesis protocols, such as the possibility of using reagents in large excess and of removing them by filtration. This combination is realized in polymer-assisted solution phase (PASP) synthesis either by using scavenger resins or by the implementation of polymer reagents.[1–4] Polymer reagents can be used in excess and removed by filtration, the products can be easily analyzed and further transformed in solution. They are especially suitable for automated parallel synthesis. They allow preparation of complex libraries by multi-step syntheses in solution, they can be utilized in automated and in flow-through systems, finally they can be employed to transform single compounds as well as complex mixtures obtained by split-mix combinatorial synthesis.

Many advanced polymer reagents have been developed for demanding reactions over recent years. One significant limitation of current polymer reagents, however, remains their relatively low loading (0.5–2 mmol/g for most commercial reagents). Due to their high price, polymer reagents are not very economical confining the method to small scale or microchemistry applications. High loading and economically produced resins would increase the efficiency and the atom economy[5] of polymer-supported methods considerably. In addition, in high loading and low swelling reagents the concentration of the polymer-supported reactants is enhanced, thus reducing the amount of solvents and of polymer backbone employed. Higher concentrations of the supported reactants should accelerate reaction rates and increase yields.

The first, but still important polymer reagents, were based on anion exchange resins loaded with anionic reagents. Classical ion exchange based polymer reagents, however,

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Keywords: Combinatorial chemistry; Polymer reagents; Oxidation; Reduction.

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0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.104

suffer from several drawbacks. Standard anion exchange resins are obtained from cross-linked chloromethyl polystyrene by nucleophilic substitution with trimethylamine.[6] The maximum loading of such resins is at first limited by the weight of the polymer backbone. If the chloromethyl groups are generated in the resin under Friedel–Crafts conditions, the maximum loading is further restricted by Lewis-acid catalyzed methylene cross-linking of chloromethyl groups within the resin.

Furthermore, the chemical lability of the ammonium salt has to be considered. Typically anion exchange resins display the fishy odor of released trimethylamine. Thus for several reasons, the molar activity of the supported reagents can decrease considerably during storage and can be significantly lower than the original loading as specified by the supplier. Another general problem of polystyrene is its chemcial lability under strong Lewis acidic and oxidative conditions that have been documented thoroughly.[7]

In principle, the maximum loading of carrier materials is obtained in polymers constructed from low molecular weight functional monomers such as polyvinylalcohol, polyethylene imine, or polyvinylamine. Realizing this fact, polyethylene imine (PEI) was selected as the starting material for very high loading polymer supports (Ultraresins).[8]

2. Results and discussion

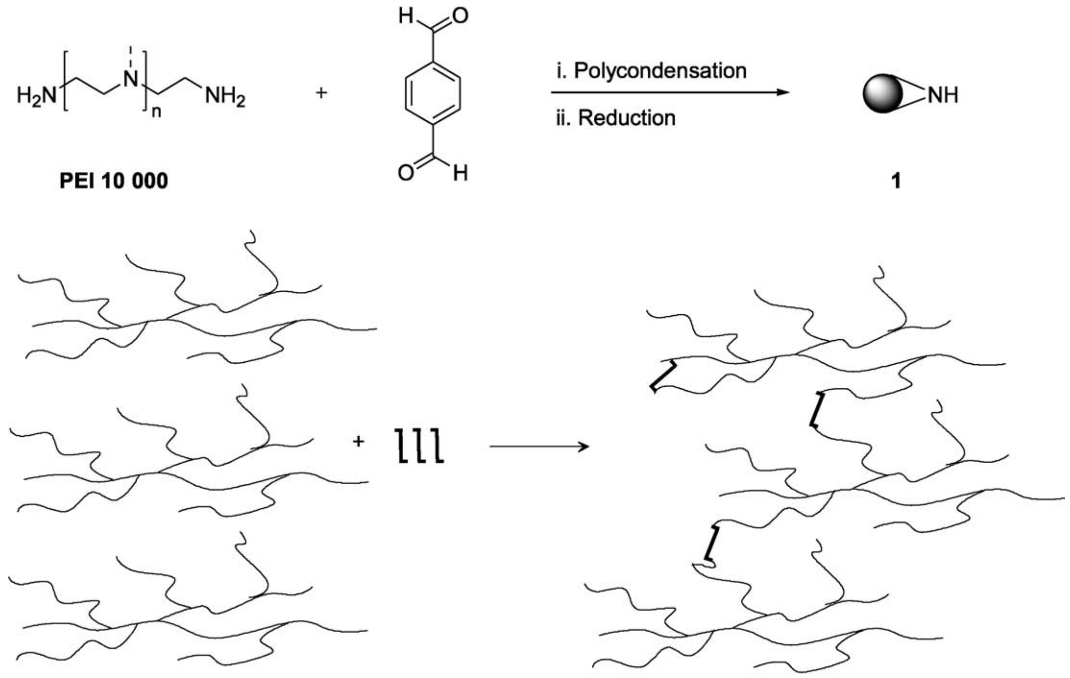
In a recent publication, a collection of Ultraresins with varied cross-linking were constructed from various PEIs and were investigated in respect to their swelling volumes, mobility and synthetic accessibility.[9] Ultraresins constructed from short, prepondarably linear, PEIs were ideally suited for solid phase organic synthesis of peptides and heterocycles.[8] Low-crosslinked Ultraresins displayed large swelling volumes, unless they were chemically derivatized with a linker moiety. Especially when swollen in aqueous hydrochloric acid, the free-amine resins had a swelling volume of up to >100 ml/g resin. This enormous swelling was attributed to the presence of multiple protonated amines. Such very strongly extending resins were not desirable for use as polycationic reagents, as they required larger reaction volumes and led to reduced concentrations.

Thus for use as polycationic polymer reagents, Ultraresins had to be developed with reduced swelling yet retain good accessibility. The swelling of polycationic Ultraresins could be reduced by increasing the amount of the cross-linker. As an undesired side-effect, high cross-linking ratios would however reduce the loading. Thus, as an alternative, highly branched PEI was investigated as the starting material for very high loading resins.

Therefore, polycationic Ultrresins were prepared starting from large, statistically branched polyethyleneimine (M_n=10,000; M_w=25,000). This material contained a mixture of 38% tertiary, 24% secondary, and 38% primary amines and was reacted with terephthalic dialdehyde as the cross-linker to yield the Ultraresin **1**. The cross-linker ratio was 42:1 per equivalent of the starting PEI (Scheme 1).

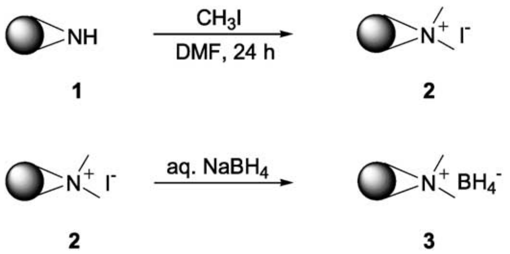
Following the reported condensation–reduction sequence, stacked sieves with calibrated mesh size were used to obtain a size distribution of 90–180 mesh (80–170 μm) or >180 mesh (<80 μm), respectively (Fig. 1).

Quaternization of the secondary and tertiary amines within the resin network of **1** was attained by alkylation with methyl iodide at rt (Scheme 2). The conversion was assessed by elemental analysis of iodine in the washed and dried resin sample yielding an iodine content of 47.5%. The



Scheme 1. Synthesis of Ultraresin **1** from highly branched polyethylene imine yielding a high-loading, low-swelling, and mechanically stable support material.

Figure 1. Polycationic Ultraresin loaded with 12 mmol/g borohydride (effective activity with 4-nitroaldehyde, rt, 16 h). The resin was sieved to a particle size of 80–170 μm (90–180 mesh). The reaction vessel to the left contains 1 mequiv. borohydride resin (82 mg).



Scheme 2. Preparation of polycationic Ultraresin **2** in the iodide form. Loading of polycationic Ultraresin **2** with borohydride anions yielded the reducing resin **3** with up to 12.0 mmol/g reductive activity.

obtained polycationic Ultraresins **2** displayed unique swelling properties, as well as chemical and mechanical stability. The synthetic protocols allowed the preparation of 50 g of **2** without difficulties.

As the first polymer reagent based on the polycationic Ultraresin, the borohydride resin **3** was generated by the exchange of iodide anions from **2**. The swelling volume of **3** was considerably reduced compared to the Ultraresins based on short PEIs. The maximum swelling volume was found in methanol with 10.7 ml/g. The swelling volume was essentially constant when switching from DCM to water. The swelling factor (volume of swollen resin / volume of dry resin) was below 2 for most solvents (Table 1).

Table 1. Swelling properties of borohydride resin **3**

Solvent	Resin volume (ml/g)	Swelling factor
none (dry resin)	5	1
Methanol	10.7	2.14
DCM	8.2	1.64
Water	8.8	1.76
THF	6.0	1.2
DMF	7.5	1.5
Toluene	7.0	1.4

Polystyrene-supported borohydride is one of the classical polymer reagents. Introduced in 1961,[10] it has been employed broadly in polymer-assisted solution phase synthesis in recent years.[11,12] Standard resins are supplied with nominal loadings of ca. 3 mmol/g. Before using these resins in synthesis, it is usually advisable to determine the actual reductive activity in a standardized test reaction, as the active loading can be significantly lower than reported.

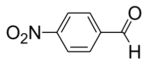
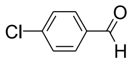
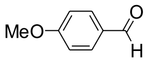
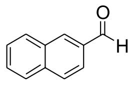
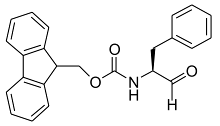
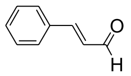
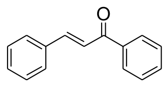
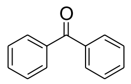
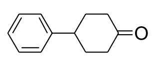
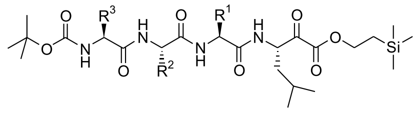
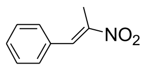
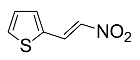
The reduction of 4-nitrobenzaldehyde was selected as a test reaction for activity determination and indicated a reducing activity of 8.0 mmol/g for resin **3** after 0.5 h (1 equiv., Table 2). By increasing the reaction time to 16 h the reducing activity of resin **3** was even 12 mmol/g. Subsequently, a selection of aromatic and aliphatic aldehydes, activated carboxylic acids, aromatic and aliphatic ketones, and α,β-unsaturated nitro-olefines were subjected to polymer-supported reduction with reagent **3** (Scheme 3). As the reaction rates depended strongly on the substrates, reaction times and reagent excess were adapted in order to achieve complete consumption of the starting materials (Table 2). The products were analyzed for purity by HPLC (214 nm) and by NMR-spectroscopy. Aldehydes reacted much faster than ketones and were reduced selectively in the presence of a double bond in α-β-position. On the contrary the double bonds in nitroolefines were reduced without affecting the nitro group. An α-ketoamide-containing fully protected tetrapeptide[13] was reduced to the norstatine product **13** bearing four aliphatic side chains. The products were obtained in good to excellent yields with only few equivalents excess (Table 2), showing that the superior loading of the Ultraresin **3** could be fully exploited in polymer-assisted transformations.

Reductive amination was investigated by treatment of an excess of the amine (1.3 equiv.) with an aldehyde followed by addition of polycationic borohydride resin **3** (Scheme 3, Table 3). A small excess of resin (2 equiv.) sufficed to furnish clean products in good yields, that were obtained by scavenging of the amine excess. Following to the reaction the excess of the primary amine was removed by scavenging with a polymer-supported aromatic aldehyde. Currently, reductions of alternative substrates with resin **3** are under investigation including amides, nitriles, nitro compounds, and azides.

The next target of research was the preparation of an oxidizing polymer. Polycationic Ultraresins such as **2** could be especially valuable as carriers for oxidative species as the oxidative sensitivity of polystyrene has been documented well and has limited the extended use of polymer-supported oxidants so far. Recently, this group during the synthesis of supported IBX-resin has reported on the partial oxidation of polystyrene by treatment with tetrabutylammonium oxone at 80 °C[14] and by oxoammonium salts.[15]

Before the loading of resin **2** with oxidative species, the iodide anions had to be exchanged for chloride in order to avoid the formation of iodine by oxidation. For this purpose, **2** was washed with aqueous HCl (1 M) until no residual iodide could be detected in the washing solution by the addition of hydrogen peroxide. The resin **21** obtained was then treated with sodium periodate solution, washed, and dried yielding periodate resin **22** (Scheme 4). The presence of periodate was assessed qualitatively by IR and by reaction of a resin sample with sulfuric acid and

Table 2. Reactions employing reducing Ultraresin **3**

Product	Starting material	Equivalents[a]	Time (h)	Yield (%)	Purity (%)
4		1	0.5	98	100
5		1.3	1	98	100
6		2	4	100	99
7		1	2	100	99
8		2	3	95	90
9		1.6	4	100	99
10		4	16	100[b]	81
11		4	16	98	100
12		4	16	100[c]	100
13		8	16	65[c]	90
14		2	2	77[d]	100
15		2	2	52[d]	93

As determined by ^1H NMR-spectroscopy.

[a] Calculated for an effective loading of 8 mmol/g.

[b] 19% reduced to the corresponding saturated alcohol.

[c] Obtained as mixture of 2 diastereomers.

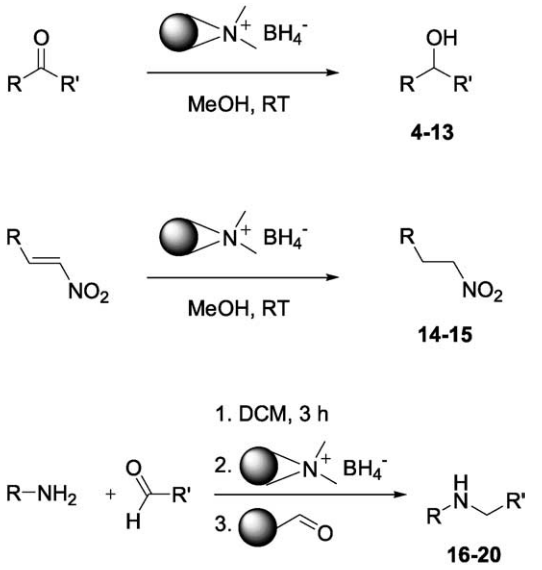
[d] Reduction to the saturated nitroalkane.

o-phenylenediamine leading to a red precipitate.[16] The oxidative activity of resin **22** was measured by the partial oxidation of an excess of 1,4-hydroquinone to quinone **25** as quantified by NMR-spectroscopy. The active loading in this reaction was 5.4 mmol/g resin. This value exceed the maximum loading obtainable with the periodate ion. The supported periodate ion thus can be assumed to perform a two step oxidation via the intermediary iodate (Scheme 5, Table 4).

3. Conclusions

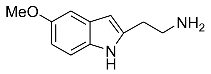
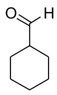
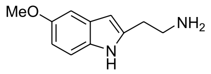
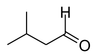
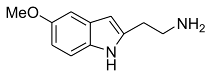
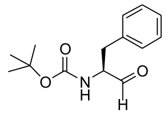
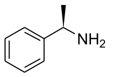
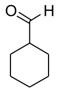
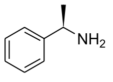
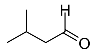
The original Ultraresin concept was successfully extended towards the generation of polycationic Ultraresins **2** which could be used as polymer reagents in a broad selection of oxidation and reduction reactions. By selecting highly branched high molecular weight PEI as starting material a polymer was obtained that was chemically and mechanically stable and was tailored to swelling volumes well-suited for use as anion-carrying polymer reagents. The resin was produced with narrow particle size distribution and low swelling factors in most solvents. Thus, it might be useful in continuous flow reactors that allow operation with low back pressures.

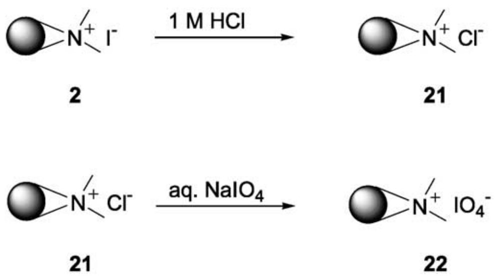
The economic preparation of the support is noteworthy. All starting materials are inexpensive industrial bulk products. Resin production can be up-scaled with ease and does not require the addition of emulgators and multiple phase



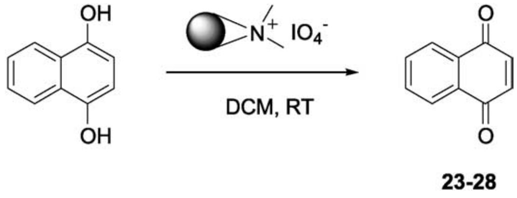
Scheme 3. The borohydride resin **3** was employed for the conversion of various aldehydes, ketones and nitro-olefines and for reductive amination yielding products **4**-**20**.

Table 3. Reductive aminations with resins **3**: following to 3 h, 2 equiv. of borohydride resin **3** was used and reacted 16 h at room temperature. Scavenging of the primary amine with 10 equiv. of formyl-PS (0.57 mmol/g) for 6 h at 40 °C

Product	Amine	Aldehyde	Yield (%)	Purity (%)
16			85	99
17			83	91
18			94	94
19			92	90
20			72	85



Scheme 4. The oxidizing periodate resin **22** was obtained via the chloride-loaded polycationic Ultraresin **21**.



Scheme 5. The oxidizing resin **22** was employed for the conversion of various sulfides, hydroquinones, diols, and hydrazines yielding products **23**-**28**.

systems as for polystyrenes. In addition, the obtained Ultraresins are chemically and mechanically robust; the lability towards oxidants and Lewis acids is strongly reduced in comparison with standard support materials.

The demonstrated applications of the novel resin include a reducing borohydride resin **3** which was generated with an active loading of up to 12.0 mmol/g, significantly higher than for conventional borohydride exchange resins. The resin performed successfully in reductions of aldehydes, ketones and in reductive aminations. The polymer-supported periodate resin was obtained with an active loading of up to 5.4 mmol/g and very efficient in the oxidation of sulfides, hydroquinones, hydrazines, and in periodate-cleavage of diols.

As found for applications in solid phase synthesis, the accessibility of the novel Ultraresin-based polymer reagents **3** and **22**—despite of their high loading—remain fully accessible for soluble reactants. This is shown not only by the determined activity of the reagents but as well by the efficiency in less-favored transformations. Therefore, Ultraresin-based polymer reagents should be a viable alternative to current support materials.

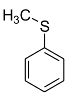
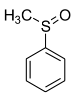
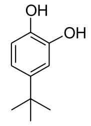
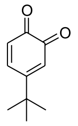
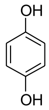
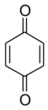
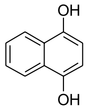
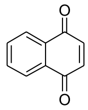
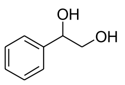
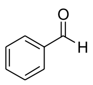
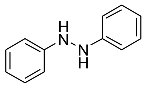
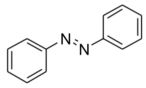
4. Experimental

4.1. General procedures

Polyethylene imine (PEI) (M_n=10,000, M_w=25,000) was obtained from Sigma Aldrich. Solvents were purchased in HPLC grade or freshly distilled before use. Formyl polystyrene resin was a gift from Merck Biosciences, Läufelfingen, Switzerland. All reactions were carried out in glass tubes. The NMR measurements were conducted on a Bruker Avance 400 MHz spectrometer. The IR spectra were measured on a Bruker Vector 22 FT-IR spectrometer employing a split-pea ATR unit. For HPLC analysis a Beckman Gold system was used with a diode array detector and an analytic reversed phase column (Nucleosil 100 C-18, 5 μm, 2×250 mm, Fa. Grom, Herrenberg) operated with acetonitril–water mixtures containing 0.1% trifluoroacetic acid.

4.1.1. Synthesis of ultra resin (1). PEI 10,000 (21 g) was dissolved in THF (150 ml) in a 500 ml round-bottom flask. Terephthalic dialdehyde (11.9 g, 0.088 mol, dissolved in 125 ml THF) was added rapidly to the stirred solution. The reaction mixture solidified spontaneously and was shaken for one hour. The cross-linked polymer was washed with THF, crushed, and suspended again in a mixture of THF

Table 4. Oxidations employing the periodate resin **22**

Product	Starting material	Product	Equivalents[a]	Time (h)	Yield (%)	Purity (%)
23			1.63	1[b]	94	97
24			2.2	0.5[c]	100	100
25			1.4	1[d]	100	99
26			2.1	0.33[d]	100	93
27			2.1	10[d]	91	93
28			2.1	4[c]	88	85

[a] Calculated for an effective loading of 3 mmol/g.

[b] In MeOH.

[c] In DCM.

[d] In DCM/MeOH 2:1.

(300 ml) and methanol (150 ml). Sodium borohydride (6.7 g, 0.17 mol) was added and the mixture was stirred for 2 h. To remove excess sodium borohydride the polymer was transformed in its hydrochloride form by treatment with 1 N hydrochloric acid for one hour. The polymer was passed through a frit, washed with water and was stirred in 2 N sodium hydroxide solution for 15 min to convert the polymer to the free amine form **1**. After washing with water, THF and dichloromethane (DCM) the polymer was dried in vacuo at 60 °C for 5 h. The polymer was sieved to get particles of 90–180 mesh (80–170 μm). Yield 28 g (90%) of **1**. Elemental analysis C 53.1%, H 9.9%, N 21.1%, Cl 0.1%. Loading of amine 15 mmol/g. FT-ATR-IR: 798, 1114, 1460, 1508, 2817, 2937, 3220.

4.1.2. Synthesis of polycationic Ultraresin 2. Ultraresin **1** (20 g) was swollen in N,N-Dimethylformamide (DMF) (500 ml) and methyl iodide (426 g, 3 mol) was added. After shaking for 24 h at room temperature, the quaternized polymer was transferred to frit (glass filter), washed with DMF and DCM and dried in vacuo at 60 °C for 5 h. Yield: 42.7 g of a pale yellow polymer. Elemental analysis C 31.3%, H 5.8%, N 9.2%, I 47.5%. FT-ATR-IR: 1460, 1612, 2784, 2949, 3402.

4.1.3. Loading of polycationic Ultraresin 2 with borohydride anions yielding reducing resin 3. Quaternized ultra resin (**2**, 32 g) was swollen in water and a 1 M aqueous solution of sodium borohydride was poured over the resin for 15 min. After repeating this procedure for two times the resin was washed with distilled water until free from excess sodium borohydride. The resin was dried in vacuo at 80 °C for 5 h to yield 16 g of borohydride exchange Ultraresin **3** as a white polymer. FT-ATR-IR: 1070, 1456, 1578, 2223, 2814, 2939. The polymer was stored at 4 °C and the hydride content was stable for 3 months.

4.1.4. Reduction of carbonyl compounds and nitroolefines to products 4–15. The following reduction of 4-chlorobenzaldehyde is representative for the reduction of carbonyl compounds and nitroalkenes. 4-Chlorobenzaldehyde (23.6 mg, 0.168 mmol) was dissolved in 2 ml methanol. After adding 28 mg of borohydride Ultra resin **3** (0.22 mmol with an effective loading 8 mmol/g) the reaction mixture was shaken for one hour at room temperature. The completion of the reaction was indicated by thin layer chromatography. After adding 4 ml of DCM the resin was removed by filtration and washed for three times with 2 ml of DCM. The solvent was removed by evaporation to get pure 4-chlorobenzylalcohol. The purity was checked by ^{1}H and ^{13}C NMR-spectroscopy and HPLC analysis (detection wavelength 214 nm).

4.2. General procedure for the reductive amination to amines 16–20

5-Methoxytryptamine (25.2 mg, 0.133 mmol) and cyclohexanecarboxyaldehyde (11.4 mg, 0.102 mmol) were dissolved in 2 ml methanol. After shaking for 3 h at room temperature borohydride Ultra resin **3** (51 mg, 2 equiv.) was added and the reaction mixture was shaken for 16 h at room temperature. The resin was removed by filtration, washed three times with 2 ml of DCM. To remove excess amine a formyl polystyrene resin (0.57 mmol/g, 10 equiv.) was used. The mixture was shaken for 6 h at 40 °C. After filtration of the resin and washing with 15 ml of DCM the solvent was evaporated to get the secondary amine **16**. Purity was checked by ^{1}H and ^{13}C NMR-spectroscopy and HPLC analysis (detection wavelength 214 nm).

4.2.1. Loading of polycationic Ultraresin 2 with chloride anions yielding resin 21. Quaternized ultra resin (**2**, 2 g) was swollen in water and a 1 M aqueous solution of hydrochloric acid was added then the reaction mixture was shaken for 30 min at room temperature. After repeating this procedure for five times the resin was washed with distilled water until free from excess hydrochloric acid. The resin was dried in vacuo overnight to yield 1.8 g of chloride exchange Ultra resin **21** as a white polymer. FT-ATR-IR: 1021, 1472, 1638, 2821, 2969, 3376.

4.2.2. Loading of polycationic Ultraresin 21 with periodate anions yielding oxidizing resin 22. Quaternized ultra resin (**21**, 1.8 g) was swollen in water and an aqueous solution of sodium periodate (5 equiv.) was added. The reaction mixture was shaken for one hour at room temperature. After repeating this procedure for three times the resin was washed with distilled water until free from excess periodate and finally three times with acetone. The resin was dried in vacuo overnight to yield 1.7 g of periodate exchange Ultra resin **22** as a white polymer. FT-ATR-IR: 780, 841, 1473, 1654, 3022.

4.3. General procedure for the oxidation of diols, sulfides, quinols and catechols to products 23–28

The following oxidation of thioanisole to **23** is representative for the oxidation of diols, sulfides, quinols and catechols. Thioanisole (15 mg, 0.12 mmol) was dissolved in 1 ml methanol. After adding 65 mg of periodate resin (effective loading 3 mmol/g) the reaction mixture was shaken for 1 h at room temperature. The completion of the reaction was indicated by thin layer chromatography. The resin was filtered off and washed for three times with 2 ml of DCM and two times with methanol, all solvent was removed by evaporation to furnish **23**. The purity was checked by ^{1}H and ^{13}C NMR-spectroscopy and HPLC analysis (detection wavelength 214 nm).

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