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TEMPO-functionalized mesoporous silica particles as heterogeneous oxidation catalysts in flow

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Organocatalysts immobilized on inorganic porous substrates possess fundamental benefits, e.g., a high catalyst/reactant ratio, easy scalability as well as work-up, and continuous processing. Here we report the development of a heterogeneous (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) catalyst immobilized on mesoporous SiO₂ and demonstrate its feasibility in the oxidation of benzyl alcohol to benzaldehyde. Our catalyst system is based on commercially available mesoporous silica particles that are optimized for flow applications (LiChrospher® Si 100 from Merck). The transition from well-known silica materials like MCM-41 and SBA-15 to specialized high-performance materials such as the used LiChrospher® particles is of great value for getting closer to industrial applications on large scale. We functionalized the material by applying clickchemistry and employed a packed HPLC column for the investigation of the catalyst performance and stability in continuous flow. The material shows the best performance with low catalyst loadings. The catalytic activity can be improved significantly by conversion of the TEMPO radical to an oxoammonium salt prior to the reaction. The material is well suited for applications in continuous flow syntheses, as the spherical shape of the particles results in low back pressures. The organic catalyst produces yields up to 89% with a flow rate of 0.05 mL min⁻¹. The mild reaction conditions allow the use of the material in multi-step reactions. This option was demonstrated by combining the TEMPO-functionalized column with an aminopropylfunctionalized column and performing a TEMPO-mediated oxidation followed by a Knoevenagel condensation in a continuous flow setup for the first time. Long-term tests and post-catalytic analysis show a previously neglected decomposition pathway of TEMPO due to the co-catalyst.

Introduction

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The immobilization of organocatalysts on solid supports allows for easy separation and reuse of the catalysts and prevents product contamination with catalyst traces. Since work-up and purification as well as synthesis of the organocatalyst itself are often laborious and expensive, immobilized catalysts are a desirable goal from an ecological and economic point of view.^{1,2} Mesoporous silica has several properties making it an excellent carrier material for immobilized organocatalysts. It is mechanically stable, inexpensive, does not swell in organic solvents, and high catalyst loadings are possible through functionalization of its large surface area. For a good carrier material, not only the area of the surface is important, but the pores must also be easily accessible. The structure of mesoporous silica combines its high surface area with good accessibility of immobilized catalyst molecules for substrates and regeneration reagents. Other carrier materials, e.g., polymers, magnetic nanoparticles, ionic liquids or carbon structures, have also been investigated and used with good results. $^{\rm 3-8}$

Compared to heterogeneous batch catalysis, reactions in continuous flow have additional advantages. As main benefits, catalyst separation and recycling are replaced by a continuous process, which simplifies work-up. A reaction in continuous flow is scalable and allows the extension to a continuous multistep synthesis by adding different reactor columns in one setup. At the same time, the requirements for the carrier material are challenging. Immobilized organocatalysts in high throughput reactors must be equipped with a carrier material that is suitable for high flow rates and does not produce high pressures inside the column. Silica particles designed for HPLC applications provide these properties and should be considered as alternatives to conventional silica materials.

In this work, the organocatalyst (2,2,6,6 tetramethylpiperidin-1yl)oxyl (TEMPO) is immobilized on mesoporous silica particles designed for HPLC applications, aiming at high yields, easy separation of the products, and recycling of the catalyst by continuous flow catalysis. Packing the material into a stainless steel HPLC column produces a dense, homogeneous reactor bed with good flow properties and low pressure build-up and the possibility for scale-up with longer or parallel column setups. The oxidation of benzyl alcohol to benzaldehyde with TEMPO is used as a model reaction to demonstrate that flow-

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optimized mesoporous silica particles are well suited as carrier materials for immobilized organocatalysts.

The oxidation of alcohols to aldehydes is an important reaction, since a wide range of functionalities can be integrated into a molecule starting from aldehydes. A variety of reagents can be used for the oxidation of alcohols to carbonyl groups. The preparation of aldehydes requires a careful selection of reaction conditions in order to prevent over-oxidation to carboxylic acids; the key is the meticulous exclusion of water. This is possible with chromate reagents, but they generate toxic and carcinogenic chromium(VI) waste in stoichiometric quantities. Alternative synthesis routes without the use of heavy metals include Swern oxidation and oxidation by Dess-Martin periodinane.

An alternative approach is the use of the persistent radical TEMPO, either as a stoichiometric oxidant or as a catalyst with a co-oxidant, which may allow control of reaction conditions and selectivity. The most widely used experimental procedure using sodium hypochlorite was developed by Anelli *et al.*⁹ For continuous flow applications, a major drawback of the Anelli oxidation is the use of a two phase system. These disadvantages can be avoided by the use of (diacetoxyiodo)benzene (DAIB), a mild co-catalyst that also tolerates many functional groups like amines, base-labile compounds, and alkenes that usually lead to side products when using sodium hypochlorite. Due to its wide substrate scope, DAIB has been used in various homogeneous^{10,11,12} and heterogeneous TEMPO-mediated oxidations.^{13,14,15}

While the oxidation of alcohols using immobilized TEMPO has already been investigated intensively for discontinuous batch systems, $^{3,7,16-27}$ only few studies investigate continuous flow experiments with immobilized TEMPO. Bogdan *et al.* and Okuno *et al.* both reported polymer-supported TEMPO and a two-phase flow system for the Anelli oxidation of various substrates.^{28,29} Aellig *et al.* used a silica-based TEMPO catalyst combined with a co-catalyst system based on O₂ and HNO₃ in a three phase continuous flow reaction under relatively high pressures (up to 5 bar), but thorough characterization of the catalyst material was not carried out.³⁰

There are two main approaches to synthesize organofunctionalized silica: co-condensation to imbed the organic moieties directly into the silica framework during synthesis of the porous silica or post-synthetic grafting, whereby the surface of porous silica materials is functionalized with organosilanes. The latter approach allows for the synthesis of a pure and stable mesoporous silica matrix, which is not impeded by the presence of organic groups. Furthermore, there are no organic molecules trapped inside the silica framework, which leads to well-defined catalyst loading. Organocatalysts can be immobilized subsequently through functionalization of the organosilane, preferably with low by-product generation, e.g., by clickchemistry approaches.^{31–36} The preservation of activity during immobilization requires careful selection of the reaction parameters. Additionally, it is a demanding task not to mechanically damage the material during grafting. Since the literature mostly deals with ordered pore systems or structurally undefined silica gels, 23, 25-27, 37-39 we performed a

thorough investigation of the functionalization of the silica particles. DOI: 10.1039/C9TA12416K

We aim to demonstrate the potential of the system by investigating the activity of the material in heterogeneous and continuous flow oxidation of benzyl alcohol and a two-step synthesis of ethyl-2-cyano-3-phenylacrylate in a continuous setup. By choosing a catalyst system with a co-catalyst, we address the importance of good accessibility of the surface through the mesopores and the long-term effects of the cocatalyst on the immobilized catalyst. Particular emphasis is put on the comprehensive characterization of the system consisting of mesoporous silica and organocatalyst. The successful immobilization of the organocatalyst was verified by infrared spectroscopy, thermogravimetric analysis, and elemental analysis, while the influence of functionalization on the mesoporosity was studied with physisorption experiments. The macroscopic structure was monitored with scanning electron microscopy (SEM). By measuring the radical character of the catalyst with electron paramagnetic resonance (EPR), we monitored the effect of catalyst activation. Basic organocatalyst performance parameters were determined, especially the impact of the catalyst loading on the yield, the dependence on the flow rate, and the stability. Finally, we discuss the performance of the functionalized particles in relation to a heterogeneous batch reaction, in order to scrutinize the potential of organocatalysts applied in continuous flow.

Experimental

Materials

Chemicals were purchased from Sigma-Aldrich (benzyl alcohol \geq 99%; (3-chloropropyl)trimethoxysilane \geq 97%, *N*-chlorosuccinimide \geq 98%, ethyl cyanoacetate \geq 98%, 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl \geq 97%, copper(I) iodide \geq 97%, sodium azide \geq 99%, Amberlite IRA-96), Carl-Roth (*N*,*N*-diisopropylethylamine 99.5%, ethylenediaminetetraacetic acid disodium salt 99%) or Alfa-Aesar (propargyl bromide, 80 w.-% % in toluene). Dry solvents were purchased from Acros Organics (water < 50 ppm). Non-water free solvents were purchased from VWR (HPLC grade). The silica material was purchased from Merck (LiChrospher[®] Si 100, particle size 5 µm).

Preparation of catalyst

Synthesis of propargylether-TEMPO. 0.85 g (21.3 mmol) of sodium hydride were dispersed in 100 mL dry DMF under argon. The mixture was cooled to 0 °C. 3.00 g (17.4 mmol) 4-Hydroxy-TEMPO were added and the solution was stirred for 30 min. 2.5 mL propargyl bromide (22.4 mmol, 80 w.-% in toluene) were slowly added and the mixture was stirred for 3 h at room temperature. 100 mL water were added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with water. After removing the solvent, the product was purified via column chromatography (ethylacetate/hexane 1:9). 2.38 g (11.3 mmol) of propargylether-TEMPO was obtained as an orange solid (65%).

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¹H NMR (400 MHz, CDCl₃): δ = 4.17 (d, *J* = 2.3 Hz, 2H), 3.89–3.82 (m, 1H), 2.42 (app t, J = 2.3 Hz, 1H), 2.00–1.88 (m, 2H), 1.53 (app t, *J* = 12.0 Hz, 2H), 1.25 (s, 6H), 1.19 (s, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 80.2, 74.2, 69.8, 59.8, 55.4, 44.3, 32.0, 20.8 ppm; HRMS (ESI–TOF): [M + Na]⁺ calculated for C₁₂H₂₀NO₂Na: *m/z* = 233.1386; found: *m/z* = 233.1393; EA: calculated for C₁₂H₂₀NO₂: C 68.54; H 9.59; N 6.66%; found: C 68.72; H 9.66; N 6.64%.

Synthesis of (3-azidopropyl)trimethoxysilane. 0.806 g iodide (2.18 mmol) tetrabutylammonium and 7.06 g (109 mmol) sodium azide were dried in a desiccator. The solids were transferred into a flask and 25 mL of dry acetonitrile were added under argon. 4.00 mL (21.8 mmol) (3chloropropyl)trimethoxysilane were added and the mixture was refluxed for 72 h. The solids were filtered off and the solvent was evaporated under reduced pressure. The resulting solid was dissolved in pentane and solid residues were removed by filtration. 3.103 g (15 mmol, 70%) of a colourless liquid was obtained. The purity of the product was determined to be 87% by NMR. The crude product was used without further purification.

¹H NMR (400 MHz, CDCl₃): δ = 3.57 (s, 9H), 3.26 (t, *J* = 6.8 Hz, 2H), 1.74–1.67 (m, 2H), 0.71–0.68 (m, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 52.8, 49.7, 21.6, 5.5 ppm; HRMS (ESI–TOF): [M + Na]⁺ calculated for C₆H₁₅N₃O₃Si: *m/z* = 228.0775; found: *m/z* = 228.0775.

Functionalization of silica particles with (3-azidopropyl)trimethoxysilane. 50 mg of the material (LiChrospher® Si 100, particle size 5 μ m) were heated to 80 °C under argon overnight. After cooling to room temperature, 2 mL dry toluene and the chosen amounts of water (e.g., 10 μ L, 20 w.-%) and (3azidopropyl)trimethoxysilane (e.g., 18 μ L, 0.098 mmol) were added. The mixture was heated to 80 °C overnight in a shaking water bath. The solvent was removed via centrifugation. The material was washed with dichloromethane, methanol, methanol:water 1:1 and dried at 40 °C under reduced pressure. The azide loading of the functionalized material was calculated from the nitrogen content obtained by elemental analysis.

$$X_{azide} = \frac{\%N}{N(N) \cdot M(N)} \tag{1}$$

Xazide azide loading

%N nitrogen content

N(N) number of nitrogen atoms in immobilized azide (3)

M(N) molar mass of nitrogen

Functionalization of silica-azide with propargylether-TEMPO. 50 mg of azide functionalized silica particles were suspended in 3 mL toluene. 0.92 mg copper iodide (4.85 μ mol), 98.9 μ L *N*,*N*-diisopropylethylamine (582 μ mol) and 18.36 mg propargylether-TEMPO (87.3 μ mol) were added and the mixture was heated to 50 °C in a shaking water bath for 72 h. The solvent was removed via centrifugation. The material was washed with acetonitrile, methanol, Na₂EDTA (5 w.-%), water and dried at 40 °C under reduced pressure.

When determining the TEMPO loading of the functionalized particles by elemental analysis, non-reacted azide $3^{\circ}/60^{\circ}$ for the beincluded in the calculation. The nitrogen content originating from TEMPO molecules N_{TEMPO} was calculated from the measured CHN contents X_{EA} and the CHN content of the preliminary azide stage X_{azide} .

 $\% N_{TEMPO} =$

$$\frac{\% N_{EA} \cdot \left(100 - (\% N_{azide} + \% C_{azide} + \% H_{azide})\right)}{100 - (\% N_{EA} + \% C_{EA} + \% H_{EA})}$$
(2)

$$X_{TEMPO} = \frac{\% N_{TEMPO} - \% N_{azide}}{N_{add}(N) \cdot M(N)}$$
(1)

X_{TEMPO} TEMPO loading

N(N) number of additional nitrogen atoms from TEMPO functionalization (1)

Characterization methods

The particles were investigated by scanning electron microscopy (SEM, Zeiss Merlin) at an acceleration voltage of 3 kV and a current of 90 pA. The samples were sputter-coated with platinum prior to the analysis. Nitrogen physisorption experiments were performed at 77 K using a Quadrasorb evo (Quantachrome Instruments). Surface areas and pore size distributions were calculated using Brunauer-Emmet-Teller (BET) and Barret-Joyner-Halenda (BJH) models. The particles were degassed for 12 h at 80 °C before the measurement. Elemental analysis (EA) was performed with the CHN-analyzer Flash EA-1112 (Thermo Scientific, microbalance Mettler Toledo UMX2). For quantitative infrared-spectroscopy (IR) pressed KBr pellets made of 2.5 mg sample substance and 197.5 mg KBr were analyzed (Alpha FT-IR, Bruker Optics). The IR spectra were recorded in a measuring range of 400-4000 cm⁻¹ with a resolution of 2 cm⁻¹. Thermogravimetric analysis was done with a continuous heating rate of 5 °C min⁻¹ with a measuring range of 25-800 °C (STA 409 PC Luxx, Netzsch). EPR was performed at room temperature with a microwave frequency of 9.78 GHz and microwave power of 200 mW (Bruker ESP 300). For the determination of the spin concentration, an amorphous carbon sample was used for calibration. ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded in CDCl₃ on a Bruker Advance II 400 MHz at 298 K. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. Data are reported as follows: chemical shift (multiplicity, coupling constants (Hz), integration). HRMS measurements were carried out with a Bruker Daltonics MicroTOF II. Catalytic reactions were monitored via gas chromatography with a flame ionization detector (HP 5890 Series II with capillary column DB-Wax 17, Agilent Technologies). Continuous flow experiments were carried out using an HPLC pump (Hitachi L-600, Merck) and a column oven (Hitachi Column Oven L-7300, Merck).





Fig. 1 SEM images of the mesoporous silica particles used as solid support for the organocatalyst (a and b) and particles damaged by stirring too vigorously (c).

Catalytic tests

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Heterogeneous catalysis. 0.266 g (0.825 mmol) (diacetoxyiodo)benzene were dissolved in 3.67 mL acetonitrile using an ultrasonic bath. 78 μ L (0.75 mmol) benzyl alcohol were added. After addition of the heterogeneous catalyst, the suspension was stirred at room temperature/40 °C for 5 h (350 rpm). To extract an aliquot, the suspension was centrifuged for 2 min at 7500 rpm. After taking the aliquot the mixture was re-suspended. For recycling tests, the material was washed with acetonitrile and dried at 40 °C under reduced pressure.

Heterogeneous catalysis in continuous flow. The catalyst material was packed into stainless steel HPLC columns (diameter 0.46 cm, length 5.0 cm). The column was heated in a column oven and the reaction mixture was pumped through with an HPLC pump.

Catalyst activation. Example for 39 mg of 1.0 mmol g⁻¹ Silica-TEMPO: 30 mg (0.2 mmol) *N*-chlorosuccinimide and 47 μ L HCl in dioxane (4 M) were dissolved in 4 mL dichloromethane. The

Fig. 2 Grafting of azide groups onto the mesoporous silica particles (a) and copper(I)catalyzed cycloaddition between the azide-functionalized support and propargylether-TEMPO (b).







Fig. 3 Correlation of azide band intensity and elemental analysis data.

catalyst material was added and the mixture was shaken gently for 15 min. After the reagents were removed by centrifugation the material was washed with dichloromethane and left to air dry.

Yield determination of benzaldehyde. Aliquots of 150 μ L were taken at 15, 30, 60, 120, and 300 min reaction time. The aliquot was diluted with 450 μ L *tert*-butyl methyl ether and 10 μ L hexadecane were added. The mixture was analyzed via gas chromatography. Yields were determined with a calibration series of benzaldehyde using hexadecane as internal standard.

Results and Discussion

Preparation and characterization

Spherical, porous silica particles (that are commercially used in HPLC) with a particle diameter of 5 to 7 μm and a pore diameter of approx. 100 Å were chosen as the support for the heterogeneous catalyst. An overview of the particles and their porous interior is shown in Fig. 1 a and b. The specific BET surface area was determined to be 400 m² g⁻¹ by a nitrogen physisorption measurement.

The uniformity and spherical shape of the particles is of great value because it allows dense and homogeneous packing, leading to low back pressures in continuous flow.⁴⁰ Therefore,





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Fig. 5 Influence of water on azide loading with same amounts of Az-PTMS (left) and correlation between azide loading and intensity of the azide band in IR spectra (right). After functionalization with TEMPO the azide band disappears.

it is important not to destroy the particles during functionalization. SEM images reveal damaged particles after a functionalization experiment using a magnetic stirring bar (Fig. 1c). To avoid damaging of the particles, functionalization experiments were carried out in a shaking water bath.

A click-chemistry approach was used to functionalize the silica material with TEMPO (Fig. 2).33,41 The copper-catalyzed cycloaddition between an azide group and an alkyne group produces high yields under mild reaction conditions with negligible by-product formation.

The first functionalization step is a grafting reaction with (3-azidopropyl)trimethoxysilane (Az-PTMS). The equivalents of Az-PTMS used refer to the number of hydroxyl groups on the silica particles (a surface concentration of 8 µmol m⁻² was assumed).42 The amount of water present in the reaction mixture plays a major role in the resulting loading of the material. Water promotes the condensation reaction between the organosilanol and the silica surface hydroxy groups, but also leads to increased homocondensation between silanols. This reduces the reactivity towards the surface, and no uniform monolayer forms.43-46

To control the amount of water present in the reaction, the silica was heated under reduced pressure and functionalized

Table 1 Summary of experiments with various amounts of Az-PTMS and water, and resulting material loading. Amount of Az-PTMS relative to amount of silica hydroxyl

| amount of Az-PTMS equiv | H₂O w% | N (EA) w% | loading mmol g ⁻¹ | BET m²g⁻¹ | surface loading µmol m ⁻² |
|----------------------------------|-----------|-----------------|---------------------------------|--------------|--|
| 0.5 | 0 | 0.7 | 0.1 | 380 | 0.3 |
| 0.5 | 10 | 4.5 | 0.9 | 330 | 2.3 |
| 0.5 | 20 | 5.9 | 1.1 | 340 | 2.8 |
| 0.2 | 10 | 2.4 | 0.4 | 380 | 1.1 |
| 0.2 | 20 | 3.1 | 0.6 | 340 | 1.5 |
| 0.1 | 10 | 1.9 | 0.3 | 400 | 0.7 |
| 0.1 | 20 | 1.7 | 0.4 | 360 | 1.0 |
| | | | | | |

under inert conditions. Since a completely water-free reaction resulted in materials with negligibly small azide loading, defined amounts of water were added to the reaction. Elemental analysis, IR spectroscopy, and nitrogen physisorption experiments show the influence of different amounts of water on the loading, with higher water content resulting in higher loading of azide groups (Table 1, Fig. 3). The azide loading of the functionalized material was calculated from the nitrogen content obtained by elemental and thermogravimetric analysis (Fig. 4). The EA data reveal good agreement with the integration of the azide band from IR spectroscopy (Fig. 5, left).

In the second functionalization step, propargyl ether-TEMPO was immobilized on the silica-azide particles. The progress of the reaction can be easily followed by the vanishing of the azide band in IR spectroscopy (Fig. 5, right). Thermogravimetric data show the decomposition of immobilized TEMPO at temperatures of 170-470 °C. The catalyst loading calculated from the mass loss is in good agreement with the results

Fig. 6 Effect of normalization to silica content for TEMPO functionalized silica material (1.0 mmol g⁻¹).



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Fig. 7 N₂-physisorption isotherms (top) and BJH pore size distributions (bottom) of functionalized particles with various amounts of water (left), before and after two-step functionalization (middle) and various amounts of immobilized TEMPO catalyst (right).

obtained from elemental analysis, showing a complete functionalization of azide groups with TEMPO moieties.

Maintaining the mesoporosity is important for good accessibility of the catalyst molecules for substrates and regeneration reagents. To study changes of the mesoporous space after the functionalization steps, nitrogen physisorption experiments were carried out. For meaningful comparison, the data for the functionalized particles must be corrected for the mass increase through functionalization so that all samples are normalized to the same silica content (Fig. 6).

$$V_{normalized} = \frac{V_{measured}}{1 - (X \cdot M(\text{TEMPO}))}$$
(3)

Xcatalyst loading of the materialM(TEMPO)molar mass of immobilized species

The BJH method was used to determine the pore size distribution since a DFT kernel for SiO_2 could not depict the change in polarity of the surface after functionalization.

The physisorption data confirm the results from IR spectroscopy and elemental analysis. Higher loading of organic molecules reduces the BET surface area and the pore volume. Larger pores (bigger than 10 nm) are preferably functionalized and show

Fig. 8 Oxidation of benzyl alcohol with co-catalyst DAIB as a test reaction for the heterogeneous catalyst.





higher decrease in the pore size distributions than small pores (<7 nm), which remain constant in their contribution to the volume. This leads to a slight decrease in the mean pore size with higher content of immobilized species (Fig. 7).

Heterogeneous catalysis

Benzyl alcohol was chosen to test the performance of the immobilized TEMPO catalyst in oxidation reactions (Fig. 8). Importantly, benzaldehyde formed in the oxidation reaction is sensitive to over-oxidation to benzoic acid, but the GC-spectrum of a test reaction with benzyl alcohol (Fig. 9) does not show benzoic acid formation, meaning that the immobilized TEMPO

Fig. 9 Typical GC signals of a reaction mixture aliquot.



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Fig. 10 Regeneration of TEMPO with the secondary oxidation agent DAIB.

catalyst has retained its ability to oxidize substrates to the corresponding aldehydes.

Since TEMPO was not intended to be used stoichiometrically, a co-catalyst was needed to regenerate TEMPO during the reaction. Diacetoxyiodobenzene (DAIB) was chosen as a mild secondary oxidation agent. Fig. 10 summarizes the reaction cycle of TEMPO during the oxidation.

Fig. 11 The EPR spectrum of silica-TEMPO shows a partially resolved structure (top). The conversion of the hydroxylamine species to the oxoammonium of TEMPO is accompanied by a color change (bottom).



Table 2 Calculated spin content for the immobilized TEMPO catalyst before and after activation with NCS/HCI.

| | Spin content g ⁻¹ | % of maximum spin content |
|-------------------|---------------------------------|---------------------------|
| before activation | 1.1·10 ²⁰ | 30 |
| after activation | 2.6·10 ¹⁸ | 1 |

Due to the reaction conditions during functionalization the catalyst is initially present mostly as the mattive mythology species. It is possible to use the catalyst as synthesized, but the conversion to the active species by the co-catalyst takes some time, thus slowing the reaction. The treatment of the material

time, thus slowing the reaction. The treatment of the material with *N*-chlorosuccinimide (NCS) and HCl in dioxane ensures rapid transformation of the material into the active species.⁴⁷ This change can be traced by the color change from white to orange (Fig. 11).

To quantify the effect of the activation on the catalyst, an electron paramagnetic resonance (EPR) spectrum was recorded. The EPR signal of TEMPO consists of three lines (due to the unpaired electron interactions with the nitrogen nucleus) that merge into a broad single line at high concentrations. For the catalyst material, a partially resolved EPR structure was observed.^{26,48–51} The spin content of the material before and after activation was calculated (Table 2), enabling an estimation what proportion of the immobilized TEMPO is present as a radical.

In the untreated material, about one third of the TEMPO molecules is present in radical form, which means that twothirds exist in the hydroxyl form. After activation, the measured spin content is about 1% of the maximum spin content. This suggests that virtually all molecules are converted into the oxoammonium species through activation. After activation, the material needs to be washed thoroughly because NCS residues can disturb the reaction by converting benzyl alcohol to benzoic acid.

Fig. 12 shows the catalyst performance (batch mode) after activation for three different TEMPO loadings (0.3, 0.6, and 1.0 mmol g^{-1}). At 40 °C with 5 mol% catalyst high yields are

Fig. 12 Performance of the heterogeneous TEMPO catalyst for the oxidation of benzyl alcohol to benzaldehyde (top) and recycling tests carried out with 0.6 mmol g^{-1} silica-TEMPO (bottom).





Fig. 13 Photograph of a stainless steel column filled with the immobilized catalyst.

achieved with the heterogeneous catalyst system. Surprisingly, the material with the highest loading shows the worst performance in catalytic tests, presumably because of diffusion limitation due to the narrowing of the pore entrances, or steric impairment of the individual TEMPO functionalities. Furthermore, it cannot be guaranteed that the functionalization is largely immobilized in form of a monolayer on the particle. Inner layers of a multilayer contribute to loading calculations in characterization methods such as elemental analysis, but do not participate in the oxidation reaction. The effective particle loadings can therefore be much lower than the calculated loading of 1 mmol g⁻¹. The material with a medium catalyst loading of 0.6 mmol g⁻¹ shows the best performance and is a good compromise between activity and material consumption. As expected, the control experiment with homogeneous TEMPO proceeds faster: the two-phase system of solvent and immobilized solid catalyst limits the contact area compared to a homogeneous mixture.

Since the immobilized catalyst was envisaged to be used in a continuous flow setup, recycling experiments were performed first. For this, the material was centrifuged, washed, and reused five times after the initial test reaction. The activation reaction with NCS and HCl does not need to be repeated after the first time. The first three cylces show no decrease in yield. In the fourth and fifth reuse, the performance of the catalyst declines from 97% to 77% and 65%, respectively.

Various post-catalytic measurements were performed to determine why the activity of the material decreases. Leaching of the catalyst can be excluded by EA and physisorption analysis of the used material, hence a change in the catalyst at the molecular level is more likely to occur. Ciriano et al. investigated the stability of TEMPO and its derivatives.⁵² According to their research. TEMPO can decompose to 2.2.6.6tetramethylpiperidine (TEMPH) via hydroxylamine at temperatures above 105 °C. Acids such as ascorbic acid catalyze this reaction. It is plausible that prolonged contact with acetic acid formed during the reaction causes similar decomposition Table 3 Key data of the continuous flow experiments with calculated turnover frequency.

| flow rate | residence time | back pressure | yield | TOF |
|----------------------|----------------|---------------|-------|-----------------|
| mL min ^{−1} | S | bar | % | h ^{−1} |
| 0.05 | 816 | 1 | 89 | 3.2 |
| 0.1 | 408 | 2 | 73 | 5.3 |
| 0.5 | 82 | 7 | 48 | 17.5 |



Fig. 14 Schematic illustration of the continuous flow experiment.

at room temperature. To test this hypothesis, the reaction conditions were simulated by stirring a solution of TEMPO and acetic acid with appropriate concentrations for two days. Analysis with ESI-MS showed an intense m/z signal not present in the reference measurement. The signal indicates the presence of TEMPH (m/z 142.1590 [M+H⁺], found: 142.1592). From this, we conclude that the immobilized TEMPO decomposes on the silica surface in a similar way.

Flow catalysis

The silica particles used in this paper are designed to withstand HPLC applications with high pressures and high flow rates. To take advantage of these benefits, we chose to use a classic stainless steel column for continuous flow experiments. The particles can be packed into the column with high pressure, creating a dense and homogeneous bed with good flow characteristics. The material loaded with 0.6 mmol g⁻¹ catalyst was packed in HPLC columns (Fig. 13). Before packing, the material was treated with the activation reagent. 310 mg of material was used for a column with a diameter of 0.4 cm and a length of 5 cm (volume = 0.63 mL). Alcohols such as methanol or isopropanol are typically used as packing solvents; in order to avoid oxidation with the immobilized TEMPO, the columns were packed using acetone as solvent. For catalyst tests in continuous flow, the same concentrations and temperatures as in heterogeneous batch catalysis were used. The reaction solution containing the substrate benzyl alcohol and the co-catalyst DAIB was pumped through the column with an HPLC pump. Fig. 14 shows a schematic illustration of the experiment.

The oxidation of benzyl alcohol was carried out in continuous flow at different flow rates and the conversion of the reaction product was determined by GC (Fig. 15, Table 3). The turnover frequency (TOF) was calculated based on the concentration of the product c_{product} , the flow rate F, and the amount of catalyst n_{cat} .

$$TOF = \frac{n_{product}}{n_{cat} \cdot t_{reaction}} = \frac{c_{product} \cdot F}{n_{cat}}$$
(4)

At the lowest flow rate of 0.05 mL min⁻¹ (and therefore a residence time of approximately twelve minutes) the highest conversion of 89% was obtained. As the flow rate increases, the conversion of benzaldehyde decreases, while the TOF increases. The benzaldehyde formed was not oxidized to benzoic acid as evident in the gas chromatogram.

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Fig. 15 Yield of benzaldehyde for continuous flow oxidation with different flow rates and corresponding pressure built-up (left); long-term catalytic test of a second column filled with silica-TEMPO (right, flow rate 0.05 mL min⁻¹).

Particularly remarkable are the low back pressures of the system. At low flow rates, nearly no pressure build-up is measurable. When switching to higher flow rates, the pressure only rises slightly, which means longer columns (that will produce even higher yields due to higher contact times) could be used without running into pressure limitations.

The flow rate tests were followed by a long-term test with a second column (Fig. 15, right). The activity of the column material remains constant for 6 h, after which the yield of benzaldehyde decreases.

Comparison to the homogeneous reaction

The direct comparison of heterogeneous catalysis in continuous flow with the homogeneous reaction can be problematic and is therefore usually not discussed. One method is to scale the homogeneous reaction so that it uses the same amount of catalyst as the heterogeneous column reactor. This leads to a homogeneous reaction using 0.186 mmol TEMPO to oxidize 3.7 mmol benzyl alcohol.

The two highest flow rates produce more benzaldehyde than the homogeneous experiment at the end of the batch experiment (5 h), and the TOF of the highest flow rate is comparable to the homogeneous reaction.

To take into account how much substrate is used for a given amount of product, it is useful to consider the reactions under normalization to the amount of benzyl alcohol used. The homogeneous reaction thereby determines the amount of reactant for the comparison. The time it takes this amount of benzyl alcohol to flow through the column is calculated for the three flow rates. With high flow rates, the reaction time is shorter, but the product quantity is smaller due to incomplete conversion. These approaches can only give a rough overview of the performance of the catalyst column in comparison to homogeneous catalysis; further studies need to take into account additional aspects like operating costs and different column lengths.

Multi-step reaction in continuous flow

The wide substrate scope of oxidations catalyzed by immobilized TEMPO has been well established,⁵³ so we decided to focus on the possibilities of continuous flow catalysis instead. In order to take advantage of the continuous flow synthesis, a second reaction step was added to the reactor setup. The twostep synthesis of ethyl-2-cyano-3-phenylacrylate from benzyl alcohol was carried out in continuous flow (Fig. 16). The TEMPOfunctionalized silica column was combined with an aminofunctionalized silica column that was synthesized using (3aminopropyl)trimethoxysilane. This second column had a catalyst loading of 1.1 mmol g⁻¹. It can catalyze the Knoevenagel condensation of an aldehyde with an active hydrogen compound bearing an electron withdrawing functional group.54,55 The amino-functionalized silica column achieved a yield of 90% when tested separately in the condensation reaction of benzaldehyde with ethyl cyanoacetate (0.2 mol L⁻¹, 0.05 mL min⁻¹).

In order to carry out the oxidation with TEMPO and the Knoevenagel reaction in one continuous setup, an acid scavenger column needed to be inserted between the two catalyst columns. Amberlite® IRA-96 was used to trap acetic acid formed from DAIB, as the acid interferes with Knoevenagel

Table 4: Comparison of homogeneous batch and heterogeneous flow catalysis. The batch experiment was scaled to the same amount of catalyst the flow experiment used (0.186 mmol). The reaction was carried out with 0.2 mmol mL⁻¹ substrate and 5 mol% catalyst.

| flow rate mL min ⁻¹ | yield % | product amount at end of batch (5 h) mmol | TOF h ⁻¹ | t for 3.7 mmol BnOH use min | product amount mmol |
|-----------------------------------|------------|---|------------------------|--------------------------------------|---------------------------|
| batch | 99 | 3.7 | 19.7 | 300 | 3.7 |
| 0.05 | 89 | 2.7 | 3.2 | 372 | 3.3 |
| 0.1 | 73 | 4.4 | 5.3 | 186 | 2.7 |
| 0.5 | 48 | 14.4 | 17.5 | 37 | 1.8 |

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Fig. 16 Schematic illustration of the multi-step synthesis step.

condensation by deactivating the catalyst. The scavenger can be regenerated by treatment with sodium hydroxide in ethanol and be reused without loss of capacity.

The yield over both steps for a substrate concentration of 0.2 mol L⁻¹ and a flow rate of 0.05 mL min⁻¹ is 72%. Despite the combination of three columns, the back pressures remain at low levels while the yield of the reaction is comparable to the total yield of the individual steps.

Conclusions

A heterogeneous organocatalyst was prepared by immobilizing TEMPO on mesoporous silica particles, which are optimized for HPLC applications. With IR, elemental, and nitrogen physisorption analysis, we show that the amount of water during functionalization has significant influence on the resulting catalyst loading and performance. The material was investigated with EPR spectroscopy, suggesting performance enhancement by activation with NCS. In catalytic tests, the silica-TEMPO catalyst showed good conversion of benzyl alcohol to benzaldehyde. Long-term tests and post-catalytic analyses reveal that the co-catalyst DAIB leads to catalyst decomposition over time, therefore other co-catalysts should be considered for long-term use. In flow experiments only little pressure build-up in the column was detected. With the highest flow rate, about $0.3 \text{ g} \text{ h}^{-1}$ benzaldehyde is produced by one column. A novel two-step continuous flow synthesis with the immobilized catalysts TEMPO and aminopropyl delivered ethyl-2-cyano-3-phenylacrylate in good yields. The successful combination with another catalyst column in a continuous twostep synthesis demonstrates the great potential of combining a flow-optimized carrier material and an organocatalyst for both good material properties and catalyst activity.

Conflicts of interest

There are no conflicts to declare.

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TEMPO was immobilized on continuous-flow-optimized mesoporous silica particles and a TEMPO/DAIB mediated oxidation followed by Knoevenagel condensation was investigated.