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TEMPO Supported on Magnetic C/Co-Nanoparticles: A Highly Active and Recyclable Organocatalyst

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Abstract: TEMPO was grafted on graphene-coated nanobeads with a magnetic cobalt core by using a general applicable "click"-chemistry protocol. The new heterogeneous CoNP–TEMPO emerged as a highly active catalyst for the chemoselective oxidation of primary and secondary alcohols using bleach as terminal oxidant. The outstanding stability of the C/Co nanoparticles enables the nanopowder to tolerate several TEMPO-mediated iterative oxidation reactions without any significant loss in catalyst activity. Furthermore, the excellent magnetic properties enable the rapid separation and quantitative recycling of CoNP–TEMPO out of the reaction mixture by simple magnetic decantation. The recovered nanoparticles can be subsequently reused without any further purification.

Keywords: cobalt · heterogeneous catalysis · magnetic nanobeads · nanoparticles · supported catalysts

Introduction

The selective oxidation of primary and secondary alcohols into the corresponding carbonyl compounds is one of the most important transformations in organic chemistry.[1] Common reagents for these oxidations are usually toxic chromium(VI) salts in stoichiometric amounts causing a severe environmental problem.[2] Therefore, the development of systems displaying high atom efficiency using comparatively harmless oxidants such as oxygen, peroxide or hypochlorite is desired.[3] The stoichiometric oxidation of primary alcohols to the corresponding aldehydes by the oxoammonium cation was first reported by Golubev and coworkers in 1965.[4] The oxoammonium cation could also be generated from TEMPO in situ using single oxygen donors such as *m*-chloroperbenzoic acid,[5] sodium bromite,[6] persulfate,[7] or sodium hypochlorite.[8] The stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) exhibits benign properties such as low toxicity[9] and a reversible redox behavior which motivated its application in combination with these diverse primary oxidants. Especially the protocol developed by Anelli et al. in 1987, using household bleach buffered at pH 9 at 0 °C in combination with 10 mol % sodium bromide and 1 mol % 4-methoxy-TEMPO in dichloromethane/water is widely applied in organic synthesis.[8] Both primary and secondary alcohols are converted to carbonyl compounds in high yields, even in large-scale operations. Whichever oxidant is used, product isolation and catalyst recovery remain key issues. Moreover, although low catalyst concentrations are required (typically 1–2.5 mol %), TEMPO is quite expensive. Consequently, it is highly desirable to separate and reuse the catalyst after the oxidation reaction. Several groups have addressed this problem by anchoring TEMPO to solid supports such as polymers,[10] silica[11] or by entrapping TEMPO in a silica sol–gel.[12]

Nanoparticles are also being increasingly recognized as supports for catalysts.[13] In particular, the use of magnetic nanobeads[14] promises easy recycling of the catalyst by magnetic separation with the advantages of a nanostructured powder. Connon et al.[15a] as well as Sato et al.[15b] have recently demonstrated the convenience of such an approach for organocatalysts, disclosing the anchoring of 4-*N*,*N*′-dimethylaminopyridine or quaternary ammonium salts to silica coated magnetite particles. So far, TEMPO was only immobilized on thiol-protected gold nanoparticles utilizing a ligand-exchange reaction.[16] However, no existing nanoparticle support has proven yet to be stable under conditions required for the TEMPO mediated oxidation. Especially, ini-

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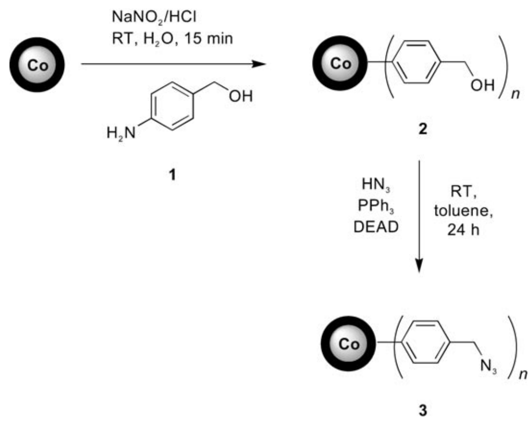
tial screening by us revealed that both thiol protected gold particles (oxidation of thiols) as well as silica coated magnetite particles (oxidation of iron(II) to iron(III)[17]) are affected under the reaction conditions used for TEMPO oxidations although its not clear yet if the oxidation of magnetite is necessarily a disadvantage.

We envisaged a support different from those mentioned above, that is, carbon-coated cobalt nanoparticles,[18] which we expected to be more stable and which in addition exhibit excellent magnetic properties. In contrast to the well studied behavior of the nitroxyl radical on silica surfaces,[11,12] to the best knowledge no report has addressed its catalytic activity on carbon surfaces so far although examples of TEMPO grafted on carbon, that is, fullerenes,[19] are known. We report here the simple and efficient covalent functionalization of such particles with the preparation of a recyclable magnetic nanobead-supported TEMPO utilizing a copper-catalyzed[20] azide/alkyne cycloaddition[21] (CuAAC) reaction as tagging method and demonstrate its high activity for the oxidation of alcohols using a modified Anelli protocol.

Results and Discussion

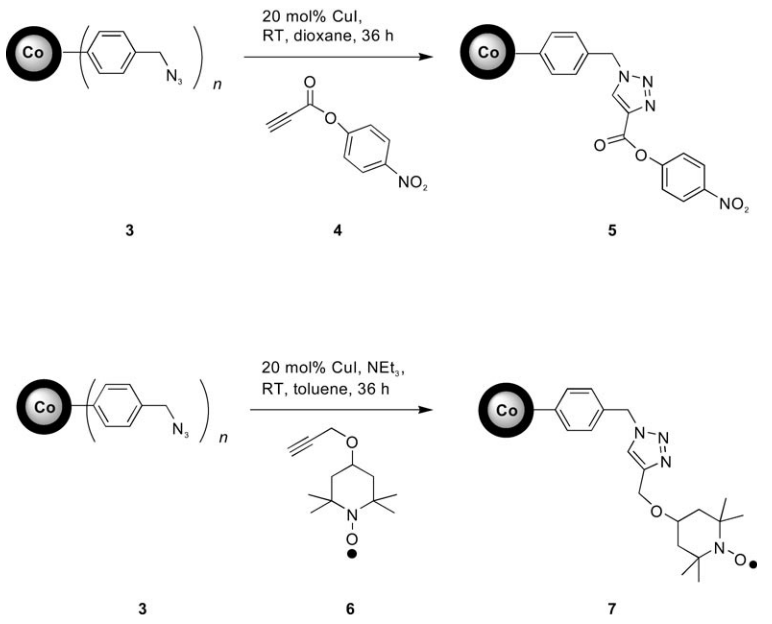
The carbon-coated cobalt particles could be created on a large scale by reducing flame synthesis as recently reported.[18] In order to achieve their functionalization suitable for applying the CuAAC for ligation, grafting of in situ created diazonium salts of 4-(aminophenyl)alkylalcohols onto the carbon layer of the nanoparticles by sonication was investigated. Initial attempts to use aniline derivatives with a long alkyl chains such as 12-(4-aminophenyl)dodecan-1-ol in order to create a spacer between the support and the catalyst, were met without success. No covalently bound aryl compounds thereof could be traced in the IR. However, no problems were encountered when **1**, which lacks such a spacer, was covalently grafted on the particles following literature precedent developed for the grafting of diazonium salts on carbon surfaces (Scheme 1).[22]

Keeping in mind the various possible side reactions with the sensitive diazonium moiety created in situ and the excess of reagent that has to be applied in the course of the reaction, the grafting is apparently limited to quite simple aniline-derivatives. To functionalize the nanoparticles with more complex molecules, the covalently bound phenylethanol **2** was transformed into the (azidomethyl)phenyl derivative **3** using a modified Mitsunobu reaction to enable a copper(I) iodide catalyzed azide/alkyne cycloaddition[20b] on the particle surface. The loading typically obtained under these conditions was assessed by reacting **3** with alkyne **4** bearing a *para*-nitrophenolester[23] (Scheme 2).



Scheme 1. Grafting of the diazonium salt of 4-aminobenzyl alcohol (**1**) onto carbon coated cobalt particles and subsequent substitution of the alcohol against an azide under modified Mitsunobu conditions.

After consumption of **3**—conveniently monitored by IR tracking the vanishing azide peak at 2100 cm^{-1} (Figure 1)—the particles were separated from excess of **4** in the supernatant, washed copiously and dried. Subsequently, **5** was subjected to basic hydrolysis (1 M NaOH$_{aq}$/dioxane 1:1 v/v, 1 h) and the concentration of nitrophenolate was detected by UV/Vis spectroscopy measured against a standard solution. Since it is known that phenolates can be adsorbed on



Scheme 2. Copper(I)-catalyzed “click” reaction of (azidomethyl) benzene functionalized nanoparticles **3** with 1-(nitrophenyl)-2-propyn-1-one (**4**) and propargyl ether TEMPO **6**, respectively (top to bottom).

carbon surfaces to some extent,[24] a reference solution was prepared in which a standard solution of nitrophenolate was incubated together with **2** for 1 h. No significant difference in the concentration of the standard and the reference solution was detected, indicating that no phenolates are retained.

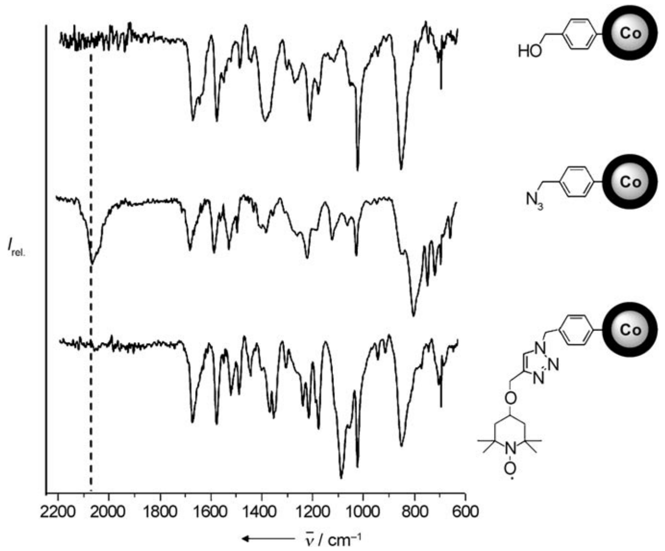


Figure 1. IR spectra of C/Co powder after functionalization with phenylmethanol, (azidomethyl)benzene and after subsequent "click" reaction of the latter with **4** and **6**, respectively (top to bottom).

The loading of the azide-functionalized cobalt-nanoparticles **3** thus determined was approximately 0.1 mmol g^{-1} which agrees with earlier functionalizations.[18] Propargyl ether TEMPO[10e] **6** was attached to the particle surface likewise quantitatively in respect to azide (Scheme 2). Elemental microanalysis confirmed a loading of 0.1 mmol g^{-1}. Previous studies have demonstrated the highly versatile "click" protocol developed by Meldal et al.[20b] being applicable for substrates such as TEMPO, for example, no oxidation of Cu$^{(I)}$ occurs.[10e,25] The necessity of a rather high concentration of copper salt (20 mol %) for a quantitative reaction course within 36 h might be attributed to solvation effects since the reaction proceeds within a heterogeneous environment (proximity of the particle surface).

The new heterogeneous CoNP–TEMPO **7** was found to be highly efficient in the iterative oxidation of benzylic and aliphatic alcohols using a modified Anelli protocol.[8b] 1.25 equivalents of sodium hypochlorite were used as primary oxidant together with 30 mol % KBr and 2.5 mol % of **7** allowing complete and chemoselective conversion of primary benzylic alcohols into the corresponding aldehydes within 1 h (TOF 20–40 cycles h^{-1} [not optimized]; Tables 1 and 2). No overoxidation to the corresponding carboxylic acids was observed.

The advantage of the new heterogeneous CoNP–TEMPO **7** lies in the ease of separation and recyclability provided by the catalyst support. Simply by applying an external magnet to the reaction vessel a separation of the magnetic nanobeads is achieved within seconds and the resulting clear supernatant can be decanted (Figure 2).

Table 1. Recycling experiment in the CoNP–TEMPO mediated oxidation of 4-methylbenzyl alcohol.[a]

Run	Conversion [%][b]	Yield [%][c]	Purity [%][b]
1	>98	89	>98
2	>96	92	>96
3	>98	95	>98
4	>98	87	>98
5	>93	90	>93
6	>98	96	>98

[a] 4-Methylbenzyl alcohol (3 mmol) in CH_2Cl_2 (6 mL), KBr (1 mmol), CoNP–TEMPO (2.5 mol %), NaOCl (3.8 mmol), $NaHCO_3$ (0.6 mmol), 0 °C, 60 min. [b] Determined by ^1H and ^{13}C NMR. [c] Yields of isolated products.

Figure 2. CoNP–TEMPO dispersed in dichloromethane before (left) and after the application of an external neodymium based magnet (right).

For maximum yield it is required to redisperse the particles in the appropriate solvent and repeat the magnetic decantation several times. After drying the resulting catalyst can be reused for the next cycle without further activation. Due to this very efficient recycling mode and the extraordinary stability of the powder virtually no loss of catalyst was observed. The possibility for recovery of the catalyst by magnetic decantation is clearly advantageous in comparison to conventional filtration protocols of heterogeneous catalysts, which in our experience always goes along with some loss of catalyst. Moreover, in six subsequent runs 4-methylbenzyl alcohol was oxidized chemoselectively without any loss in activity (Table 1).

Electron microscopy confirmed the remarkable stability of the nanopowder support (Figure 3). Consequently, recycled catalyst was used for all subsequent oxidations (Table 2), again, quantitative recovery was achieved after each run.

2-Phenylethanol showed diminished reaction rates allowing no complete conversion within 60 minutes (entry 5, Table 2). However, applying 5 mol % of CoNP–TEMPO afforded 2-phenylacetaldehyde in very good yield and purity and proved furthermore to be efficient for the oxidation of aliphatic alcohols (entry 6 and 7, Table 2). A peculiarity of

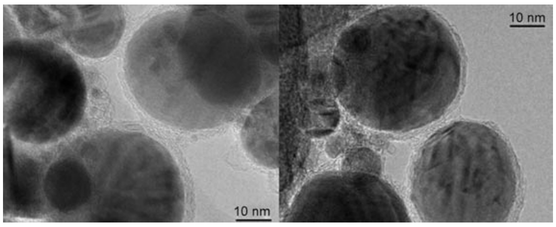


Figure 3. Transmission electron images of CoNP–TEMPO **7** before (left) and after (right) the recycling experiment: The structure of the nanoparticles is not affected by iterative oxidation reactions.

TEMPO-mediated oxidations is the different activity towards primary and secondary alcohols, the latter being oxidized much slower. Indeed, the secondary alcohol proved to be oxidized significantly slower demanding a reaction time of 3 h at an elevated hypochlorite concentration to reach quantitative conversion (entry 8, Table 2).

Table 2. CoNP–TEMPO mediated oxidation of different alcohols to aldehydes. The catalyst was recycled after each iterative run and reused.[a]

Entry	Alcohol	Conversion [%][b]	Yield [%][c]	Purity [%][b]
1	4-methylbenzyl alcohol	>98	89	>98
2	4-bromobenzyl alcohol	>98	92	>98
3	4-methoxybenzyl alcohol	>98	96	>98
4	benzyl alcohol	>98	85	>98
5	2-phenylethanol	>83 (>98)[d]	77 (94)[d]	>83 (>98)[d]
6[d]	1-octanol	>98	87	>98
7[d]	1-dodecanol	>98	92	>98
8[e]	cyclohexanol	>98	96	>98

[a] Alcohol (3 mmol) in CH_2Cl_2 (6 mL), KBr (1 mmol), CoNP–TEMPO (2.5 mol %), NaOCl (3.8 mmol), $NaHCO_3$ (0.6 mmol), 0 °C, 60 min. [b] Determined by ^1H and ^{13}C NMR. [c] Yields of isolated products. [d] 5 mol % CoNP–TEMPO. [e] 5 mol % CoNP–TEMPO, 7.5 mmol NaOCl, 3 h.

Conclusion

In summary we have developed a protocol for the functionalization of magnetic C/Co nanoparticles with complex molecules utilizing the versatile copper-catalyzed alkyne/azide cycloaddition. The feasibility of this reaction was demonstrated by grafting the propargyl ether TEMPO **6** onto the particles, which emerged as a highly stable and easy separable heterogeneous catalyst showing neither loss of activity nor chemoselectivity even after multiple runs.

Experimental Section

General methods: 4-Aminobenzyl alcohol,[26] 1-(nitrophenyl)-2-propyn-1-one (**4**),[27] propargyl ether TEMPO **6**[10e] and hydrazoic acid,[28] were prepared according to literature procedures. All other commercially available compounds were used as received. Toluene was dried with CaH_2, distilled and stored over sodium wire. ^1H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 Spectrometer in $CDCl_3$ with $CHCl_3$ (7.27 ppm for ^1H, 77 ppm for ^{13}C) as a standard. The nanoparticles were analyzed by ATR-IR spectroscopy (Excalibur FTS 3000 Spectrometer, Biorad equipped with a Specac Golden Gate Diamond Single Reflection ATR-System), elemental microanalysis (LECO CHN-900) and transmission electron microscopy (CM30 ST-Philips, LaB_6 cathode, operated at 300 kV point resolution ≈4 Å).

Carbon-coated cobalt nanoparticles: A spray nozzle was placed in a glove box (2 m^3) filled with nitrogen (PanGas, 99.999 %). The glove box atmosphere was constantly recycled (recycle stream ≈20 m^3h, Busch, Seco SV1040CV) using two zeolite columns (zeolite 4 Å and 13X, Zeochem). While fresh nitrogen (PanGas, 99.9999 %, ≈2 m^3h) was added, a purge stream avoided the accumulation of other combustion related species (NO_x, H_2, CO) in the glove-box atmosphere. Cobalt(II) 2-ethylhexanoate in mineral spirit (Aldrich) was diluted 2:1 (weight/weight) with tetrahydrofuran (Fluka, tech.) and filtered (Satorius, fluted filter type 288) prior to use. The cobalt carboxylate precursor was delivered to the spray nozzle by a micro annular gear pump (6 mL min^{-1}, HNP Mikrosysteme, mzr-2900) where it was dispersed by oxygen (5 L min^{-1}; PanGas tech.) and ignited by a premixed pilot flame (CH_4: 1.2 L min^{-1}, O_2: 2.2 L min^{-1}, PanGas tech.). The flame was encased in a porous tube allowing optimal combustion conditions, the inflow of additional nitrogen (PanGas, 99.999 %, 45 L min^{-1}) and the addition of acetylene gas (PanGas, 5 L min^{-1}) for the formation of carbon shells. The product particles were separated from the off-gas using glass fiber filters (Schleicher & Schuell, GF6).

Phenylmethanol functionalized carbon coated cobalt nanoparticles (2): The as-prepared carbon coated cobalt nanobeads (1 g) were suspended in H_2O (5 mL) by the use of an ultrasonic bath (Sonorex RK 255 H-R, Bandelin). 4-Aminobenzyl alcohol (**1**) was transformed in the corresponding diazonium salt in situ by adding a cooled solution of sodium nitrite (2.3 mmol, 160 mg in 12 mL H_2O) to a mixture of the alcohol **1** (1.5 mmol, 185 mg), HCl (0.6 mL, concentrated) and H_2O (20 mL) in an ice bath. After addition of the carbon coated nanobeads, the reaction mixture was sonicated for 30 min. The nanobeads were recovered from the reaction mixture with the aid of a neodymium based magnet (N48, W-12-N, Webcraft GmbH, side length 12 mm) and washed with water (3×5 mL) and acetone (6×5 mL). Each washing step consisted of suspending the particles in the solvent, ultrasonication (5 min) and retracting the particles from the solvent by the aid of the magnet. After the last washing step the particles were dried in vacuo. IR: $\tilde{\nu}$ = 2916, 2850, 1698, 1599, 1398, 1276, 1214, 1178, 1015, 835, 681 cm^{-1}.

(Azidomethyl)benzene functionalized carbon coated cobalt nanoparticles (3): The functionalized cobalt particles **2** (0.9 g) were suspended in dry toluene (5 mL) by sonication (10 min) before triphenylphosphine (0.3 mmol, 80 mg), freshly prepared HN_3 (0.3 mmol, 1 M solution in toluene) and diethylazodicarboxylate (0.3 mmol, 40 % in toluene) were added. The resulting slurry was sonicated for 24 h at ambient temperature. The nanoparticles were recovered from the reaction mixture with the aid of a magnet and washed with toluene (3×5 mL) and acetone (3×5 mL) as described above. After the last washing step the particles were dried in vacuo. IR: $\tilde{\nu}$ = 2922, 2854, 2100, 1699, 1599, 1539, 1386, 1217, 1115, 1015, 83, 781, 723, 693 cm^{-1}.

4-Nitrophenyl 1-benzyl-1*H*-1,2,3-triazole-4-carboxylate functionalized carbon coated cobalt nanoparticles (5): The azide-functionalized cobalt particles **3** (0.5 g) were suspended in degassed dioxane (4 mL) by sonication (10 min) before 1-(nitrophenyl)-2-propyn-1-one (**4**) (0.25 mmol, 48 mg) and CuI (0.025 mmol, 5 mg) were added. The resulting slurry was sonicated for 36 h at ambient temperature. Two additional portions of CuI (0.013 mmol, 3 mg) were added after 12 and 24 h. The nanoparticles were recovered from the reaction mixture with the aid of a magnet and washed with dioxane (3×5 mL) and acetone (5×5 mL) as described above. IR: $\tilde{\nu}$ = 2852, 1751, 1699, 1594, 1524, 1346, 1208, 1111, 1014, 861, 831, 746, 682 cm^{-1}.

4-(1-Benzyl-1*H*-1,2,3-triazol-4-yloxy)-2,2,6,6-Tetramethylpiperidine-1-oxyl functionalized carbon coated cobalt nanoparticles (7): The azide-functionalized cobalt particles **3** (1 g) were suspended in degassed toluene (5 mL) by sonication (10 min) before propargyl ether TEMPO **6** (0.5 mmol, 95 mg), NEt_3 (0.5 mmol, 70 µL) and CuI (0.05 mmol, 10 mg) were added. The resulting slurry was sonicated for 36 h at ambient temperature. Two additional portions of CuI (0.025 mmol, 5 mg) were added after 12 and 24 h. The nanoparticles were recovered from the reaction mixture with the aid of a magnet and washed with toluene (3×5 mL) and acetone (5×5 mL) as described above. IR: $\tilde{\nu}$ = 2974, 2935, 1700, 1600, 1541, 1507, 1379, 1363, 1242, 1218, 1177, 1083, 1015, 833, 679 cm^{-1}.

General procedure for the CoNP–TEMPO mediated oxidation of alcohol: 4-Methylbenzyl alcohol (3 mmol, 366 mg) in CH_2Cl_2 (6 mL), KBr (1.0 mmol, 120 mg) and CoNP–TEMPO **7** (0.1 $mmol\,g^{-1}$, 750 mg, 2.5 mol% TEMPO) were merged in a 50 mL round-bottom flask. The reaction mixture was sonicated at 0°C for 15 min using an ultrasonic bath filled with a tempered coolant solution (10% glycol in water) before 2.4 mL of a NaOCl solution (10%, Aldrich) and $NaHCO_3$ (120 mg, 50 $mg\,mL^{-1}$ bleach) were added. The resulting suspension was sonicated at 0°C for 1 h. The reaction mixture was separated from the CoNP–TEMPO by decantation with the aid of a neodymium based magnet. The particles were suspended in CH_2Cl_2 (10 mL), subjected to ultrasound (5 min) and the supernatant was decantated once again after applying an external magnet. This procedure was repeated three times before the solution was dried over $MgSO_4$, filtered and concentrated under vacuum to afford 4-methylbenzaldehyde. CoNP–TEMPO was washed as described above with water (3×5 mL) and acetone (6×5 mL), dried in vacuo and reused without further purification.

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