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Cu(II)−Azabis(oxazoline) Complexes Immobilized on Magnetic Co/C Nanoparticles: Kinetic Resolution of 1,2-Diphenylethane-1,2-diol under Batch and Continuous-Flow Conditions

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Carbon coated cobalt nanoparticles were tagged with azabis(oxazoline)−copper(II) complexes utilizing a copper(I)-catalyzed azide/alkyne cycloaddition (CuAAC) reaction, and the efficacy of the resulting nanomagnetic catalyst was tested in the kinetic resolution of racemic 1,2-diphenylethane-1,2-diol via asymmetric monobenzoylation. The novel semiheterogeneous catalyst was examined under batch conditions and in a continuous flow-type reactor. The extremely high ferromagnetism of the cobalt cores not only facilitates the recycling of the nanobeads via magnetic decantation in the batch reactions but also enables a novel continuous flow-reactor design: This further allowed efficient agitation and containment of the particles to occur without the need for sophisticated separation strategies such as nanofiltration.

Introduction

Magnetic nanoparticles exhibiting a core/shell structure have recently attracted a lot of attention as scaffolds for the grafting of homogeneous compounds, thus resulting in "heterogenized" catalysts, which can be readily dispersed in solvents and recycled by applying an external magnetic field. Especially superparamagnetic iron oxide nanoparticles (SPION), e.g. magnetite particles, have demonstrated their versatility as a support for a plethora of catalysts, albeit under the precondition that a suitable coating for the metaloxide core is provided.[1] However, nanocomposites such as magnetite@silica have the disadvantage of low saturation magnetization when compared to the bulk material. Despite the beneficial implications of superparamagnetism in these nanosized materials, inferior magnetic properties of such nanoparticles hamper the effective recycling of the supported catalyst.

Apart from the magnetic metal oxides, pure metals such as Fe, Co, and Ni and their metal alloys were used in various fields requiring magnetic materials.[2] The saturation magnetization of these ferromagnets exceeds greatly the values obtained with ferrites. In addition, these levels of magnetization are not necessarily diminished upon surface modification. However, nanoparticles out of pure metals are highly sensitive to air and can even be pyrophoric, whereas oxidation of the aforementioned magnetite particles to ferrimagnetic maghemite is potentially less problematic. Graphene layers provide an extremely high level of chemical and thermal stability, thus effectively preventing oxidation of the metal core.[3] Despite this benefit, carbon coated metal nanoparticles are yet to be disclosed as metal−catalyst support since their formation is challenging and was hitherto possible only in small-scale operations (< 1 g/h) via arc discharge techniques,[4] chemical vapor depositions,[5] and pyrolysis of metal complexes.[6] Recently, Stark et al.[7] reported on carbon coated cobalt nanoparticles that can readily be produced (30 g/h) on the kilogram scale in a continuous process via flame-spray[8] pyrolysis.

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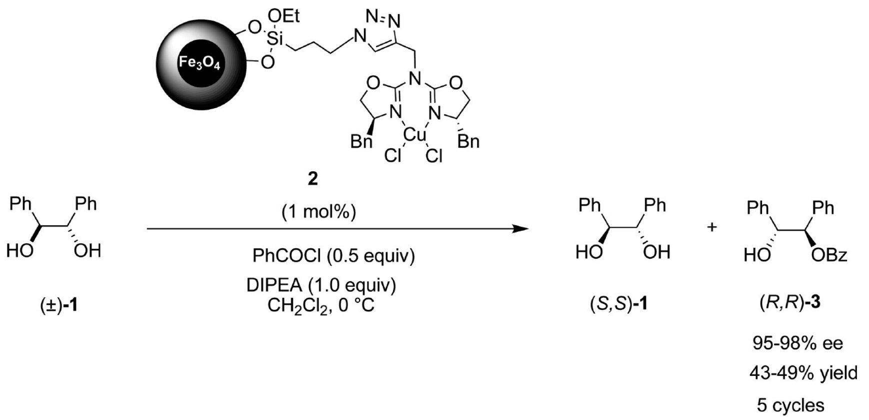
Scheme 1. Monobenzoylation of Racemic Diol (±)-1 Catalyzed by Magnetite@Silica-Immobilized Azabis(oxazoline)−Copper(II) Complex 2.[17]



Co nanoparticles have previously been utilized as supports for various catalysts before.[9] Very recently, the synthesis of cobalt nanoparticles stabilized with oleic acid and long chained carboxylic acids ω-functionalized with chiral β-amino alcohols was reported by Pericàs et al.,[9b] who used those magnetically recyclable ligands for the ruthenium-catalyzed transfer hydrogenation of ketones. However, the reduction of ruthenium by metallic cobalt was an incisive limitation on the recyclability, thus demonstrating once more the importance of a suitable coating.

Herein, we report the synthesis and application of the first transition-metal complex immobilized on carbon coated cobalt nanoparticles via a copper(I)-catalyzed[10] azide/alkyne cycloaddition[11] (CuAAC) reaction, a tagging method that has already proven to be a powerful tool for ligating functional molecules to supporting scaffolds.[12] The power of this novel heterogeneous catalyst was examined in the asymmetric benzoylation of 1,2-diols under batch and continuous-flow conditions, placing emphasis on the advantages provided by the extraordinary high magnetization of this material.[13]

Results and Discussion

The use of a highly magnetic nanoparticle supported catalyst was envisaged to allow a novel design for continuous-flow reactors, which might be able to overcome several restrictions related to conventional fixed-bed reactors. Agitation of the nanomagnets in a rotating external magnetic field might have beneficial influence on the fluid dynamics and surface area within the reactor column. Moreover, due to the pronounced ferromagnetism of carbon coated cobalt particles, the free-floating nanocatalyst might be magnetically retained in the reactor, thus making the application of membranes for nanofiltration dispensable. The latter should be especially advantageous, since nanoparticles tend to aggregate and block membranes owing to their magnetic remanence, thus inevitably provoking a flow collapse.

A continuous-flow setup offers a number of potential advantages over batch techniques.[14] The reaction conditions (flow rate, stoichiometry, and pressure) can be independently varied and precisely controlled. Flow processes are readily scalable by employing multichannel or parallel reactors (number-up vs scale-up). Some notable advances were recently reported for continuous asymmetric processes using either organic or inorganic supports.[15] However, some of these systems suffered from uncontrollable fluid dynamics, because catalysts packed as random fixed-bed reactors might lead to stagnation zones, hot-spot formations, and large residence time distributions.[16] Additional drawbacks might arise from polymer-specific issues such as uncontrollable swelling,[15e] limited accessibility of catalytic sites, and clogging of the sintered funnel by polymerization byproducts (Scheme 1).[15c]

In order to overcome such limitations, magnetite@silica nanoparticles tagged with azabis(oxazoline)−copper(II) complexes were employed in a preliminary

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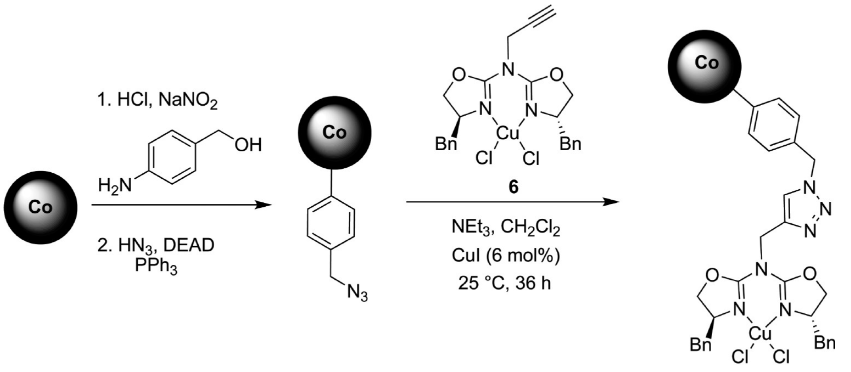
Scheme 2. Copper(I)-Catalyzed Click Reaction of (Azidomethyl) Benzene Functionalized Co/C Nanoparticles 5 with Propargylated Azabis(oxazoline)−Copper Complex 6



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experiment. Azabis(oxazolines) (AzaBOX)[18] represent a subclass of bis(oxazolines),[19] being one of the most successful classes of chiral ligands in asymmetric catalysis. Azabis(oxazolines) are particularly suitable for immobilization on heterogeneous supports due to the greatly reduced tendency of metal leaching from their complexes, contrasting corresponding metal−bis(oxazoline) catalyst.[20] In previous investigations, we had demonstrated that nanocomposite **2** is highly effective in the kinetic resolution of 1,2-diphenylethane-1,2-diol through copper(II)-catalyzed asymmetric benzoylation under batch conditions (Scheme 2).[17] The eminent low catalyst concentration (1 mol %), which is sufficient for high conversions within reasonable reaction times, additionally validates this reaction for a continuous process with inherently limited catalyst loading.

Hence, a glass column (Omnifit, 10 cm length, 3.4 mL volume) was charged with the magnetite@silica immobilized catalyst **2** and placed vertically between adjacent parallel flanks of two standard magnetic stir motors (Heidolph) with a distance of 4 cm to each other (Figure 1). The glass column was equipped with adequate joints to be connected to a piston pump that allowed the reactor to be floated with anhydrous CH_2Cl_2. A PE frit (25 μm pore size) was mounted into the lower thread of the glass column to prevent excessive sedimentation of the particles to the piston pump after shutdown. Because of the small flow rates required in these experiments, a diaphragm metering pump (KNF STEPDOS 03-RC) was chosen as the delivery assembly for reactants and reagents. Residence times of the reactants in the flow reactor were not expected to be sufficient for satisfying

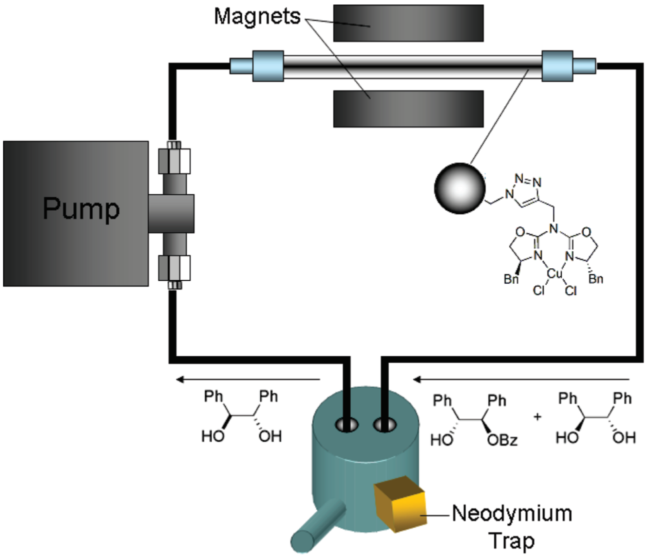

Figure 1. Representation of a closed circuit type reactor for the asymmetric monobenzoylation of racemic diol (±)-**1** catalyzed by azabis(oxazoline)−copper(II) complexes tagged to magnetic nanobeads.

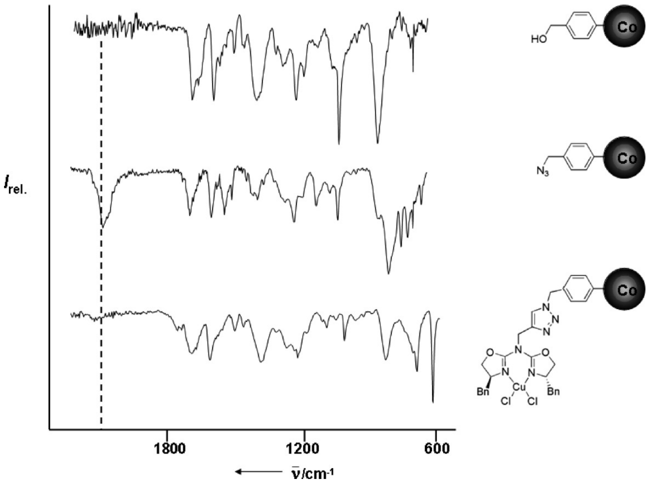

Figure 2. IR-spectra of Co/C powder after functionalization with phenylmethanol, (azidomethyl) benzene, and after subsequent click reaction of the latter with propargylated azabis(oxazoline)−copper complex **6**.

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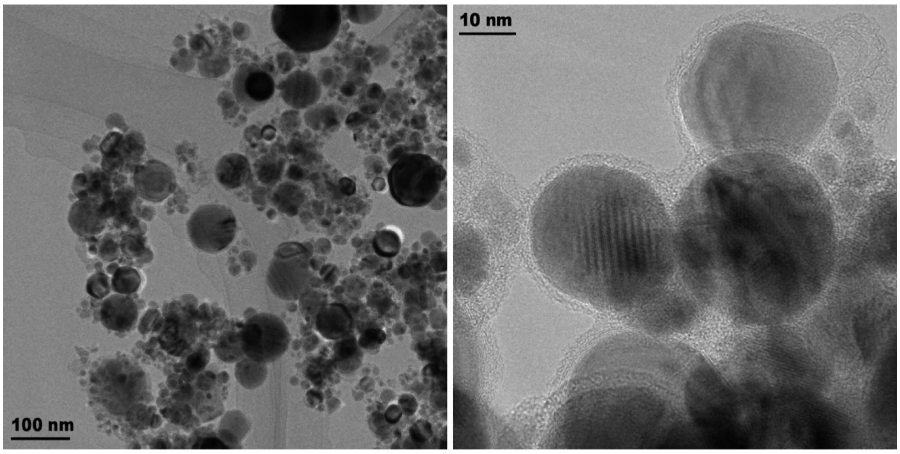


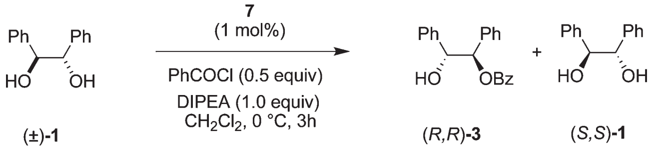
Figure 3. TEM images of azabis(oxazoline)·$CuCl_2$ tagged Co/C nanoparticles **7** at different resolutions.

conversion of the racemic diol (±)-**1** into the enantioenriched monobenzoylated **3** product even at very low flowrates. In principle, for a given amount of catalyst, reaction rates in a continuous-flow reactor depend on the feed composition, mean residence time, and reaction temperature. However, raising the temperature in order to increase rates up to a level adequate for a single pass is usually prohibitive for an enantioselective process. Hence, adopting recirculation appeared more feasible. In order to control the temperature, the whole setup was operated in a cooling chamber (4 °C), which was envisaged to secure an isothermal reaction rather than applying a column jacket with a circulating cooling fluid. Furthermore, a column jacket would demand space that was required by the stir motors for the effective containment of the particles.

Charging the closed circuit type reactor with solvents and reagents was carried out without special precautions such as ensuring strict oxygen or moisture free conditions. A nitrogen filled balloon was applied to create an inert atmosphere in the septum-sealed vessel containing the dissolved reactants. In addition, the flask was equipped with an external neodymium based magnet that would trap any catalyst leached from the reactor along with the circulating reactants (Figure 1).

A flow of 0.2 mL/min was maintained in order to avoid leaching of the magnetic nanoparticles. However, in the case of the magnetite@silica-supported catalyst **2**, excessive leaching occurred already at these moderate flowrates. Thus, SPIO nanoparticles with their comparatively low saturation magnetization (20 $A \cdot m^2/kg$)[21] appear ineligible for such a continuous-flow setup using magnetic stirrers commonly used in synthetic laboratories. Since the magnetism of the ferrite core is obviously insufficient for such an application, we expected to remedy this by using highly ferromagnetic carbon coated cobalt nanoparticles (saturation magnetization: 158 $A \cdot m^2/kg$), which can be generated on the kilogram scale in a continuous process at a high production rate (30 g/h).[7]

Table 1. Cu(II)-Catalyzed Monobenzoylation of (±)-1 under Batch Conditions: Recycling Experiment Using Azabis(oxazoline)−$CuCl_2$ Complexes Immobilized on Co/C Nanoparticles[a]



entry	run	yield (%)[b]	ee (%)[c]	s[d]
1	1	47	97	183
2	2	43	96	100
3	3	49	97	227
4	4	48	99	645
5	5	46	99	536

[a] Reagents and conditions: DL-Diol (1 mmol), benzoylchloride (0.5 mmol), DIPEA (1 mmol), 0 °C, 3 h, CH_2Cl_2. [b] Yield of isolated product **3**. [c] Determined by chiral HPLC. [d] References 23 and 24.

In order to achieve the functionalization of the Co/C-nanoparticles **4** in a way being suitable for applying the CuAAC for ligation, grafting of in situ created diazonium salt of 4-aminobenzylic alcohol onto the carbon layer was accomplished following a well-established route.[9a] The (azidomethyl)phenyl derivatized particles **5** were subsequently subjected to a "click" reaction with propargylated azabis(oxazoline)−copper(II)chloride complex **6** to afford the heterogenized catalyst **7** (Scheme 2). The loading typically obtained under these conditions was determined via elemental microanalysis to be approximately 0.1 mmol/g, a value being consistent with previous investigations.[9a]

The immobilization of preformed transition metal complex **6** which can be conveniently separated from any residual copper(II)chloride by simple filtration after complexation was envisaged to be more promising than coordination of grafted azabis(oxazolines) with $CuCl_2$. The latter method inherits the severe disadvantage that any metal salt outlasting complexation and purification is capable of acting as an unselective catalyst. In this regard, the mild reagents and conditions required during the click

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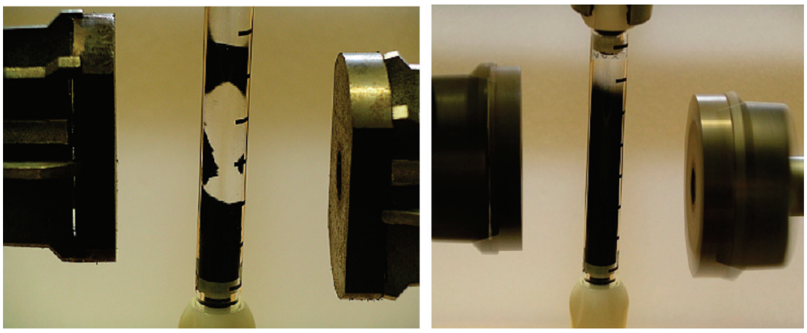

Figure 4. Co/C-supported catalyst **7** in a jointed glass column contained by an external magnetic field (left). The nanomagnets were agitated in the rotating magnetic field while CH_2Cl_2 was passed through the reactor (right).

reaction are a prerequisite for tagging the particle surface with AzaBOX·$CuCl_2$. Moreover, the success of the CuAAC reaction was conveniently monitored using IR spectroscopy, especially by the vanishing azide peak at 2100 cm^{-1} (Figure 2).

In order to test the catalytic potential of the as-prepared nanomagnets **7** (Figure 3), we subjected them first to several consecutive kinetic resolutions[22] of (±)-**1** under batch conditions, following a protocol initially developed by Matsumura and co-workers.[13] The overall magnetism of the particles allowed for efficient dispersion in the reaction vessel without the need for an additional stir bar.

After each run, the ferromagnetic Co/C nanopowder was recovered within seconds from the reaction mixture with the aid of an external neodymium magnet. The attraction was sufficiently strong enough to allow simple decantation of the supernatant (magnetic decantation). For maximum yield of **3**, it was required to redisperse the particles in the appropriate solvent and repeat the magnetic decantation thrice. Due to this extremely efficient recycling mode, virtually no loss of nanomaterial was observed. To our delight, catalyst **7** maintained its high activity for at least 5 runs, affording the resolved alcohol **3** in excellent enantioselectivity (Table 1), thus demonstrating that the novel semiheterogeneous catalyst **7** is at least equally selective as its magnetite-based counterpart **2**, if not superior.

With the highly magnetic nanocatalyst **7** in hand, we further subjected the material that was recovered after five iterative runs under batch conditions, to continuous-flow (Figure 4). In contrast to the magnetite@silica-based nanomagnets, the carbon coated cobalt particles were retained at a moderate flow rate (0.2 mL/min), showing only negligible catalyst leaching. Considering the solvent volume of the whole system (8 mL) and the flow-rate applied, the total volume of the reaction mixture in the vessel would be circulated within 40 min. Three successive batches of a solution of racemic diol (±)-**1** in anhydrous CH_2Cl_2 were fed with intermittent washing of the reactor using dry CH_2Cl_2. The contact of the catalyst with adventitious air during the washing procedure had no mentionable effect on the catalyst efficiency in the next run.

Table 2. Cu(II)-Catalyzed Monobenzoylation of (±)-1 Catalyzed by Azabis(oxazoline)−$CuCl_2$ Complexes Immobilized on Co/C Nanoparticles in a Closed Circuit Type Reactor[a]

entry	batch	yield (%)[b]	ee (%)[c]	s[d]	catalyst leaching (%)[e]
1	1	43	99	449	< 1
2	2	47	98	282	< 1
3	3	39	99	383	< 1

[a] Reagents and conditions: DL-Diol (1 mmol), benzoylchloride (0.5 mmol), DIPEA (1 mmol), catalyst **7** (5 mol %) 4 °C, 20 h, CH_2Cl_2. [b] Yield of isolated product **3**. [c] Determined by chiral HPLC. [d] Reference 23 and 24. [e] Amount of supported catalyst **7** which was extruded from the reaction chamber during the denoted reaction time and collected in the neodymium magnet trap.

By this procedure, 1,2-diol (±)-**1** was effectively resolved using catalyst **7**. The Co/C-immobilized azabis(oxazoline)−copper(II) complex **7** delivered essentially unaltered enantioselectivities in **3** for at least three consecutive runs (Table 2).

Hence, the containment and agitation of the nanomagnets in a microreactor via an external magnetic field provides an interesting alternative to fixed-bed reactors, which necessitates a membrane that bears the danger of obstruction. Moreover, the application of the highly ferromagnetic nanomagnets is clearly superior when compared to catalysts immobilized on the magnetite@silica particles, since virtually no leaching occurs with the former under continuous-flow conditions.

Conclusion

In summary, the results obtained indicate that carbon coated cobalt particles might serve as a promising and versatile alternative to well-established SPION

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(24) Selectivity factors are most accurately determined by measuring conversion via NMR and the enantioselectivity via HPLC of product and starting material of the crude[22,23] according to $C = \mathrm{ee}_{sm}/(\mathrm{ee}_{sm} + \mathrm{ee}_{pr})$. $S = \ln[1 - C(1 + \mathrm{ee}_{pr})]/\ln[1 - C(1 - \mathrm{ee}_{pr})] = \ln[(1 - C)(1 - \mathrm{ee}_{sm})]/\ln[(1 - C)(1 + \mathrm{ee}_{sm})]$. Due to the possibility of traces of magnetic nanoparticles in the crude, analyzing the crude by this methods is prohibitive. We have thereore determined the selectivity factors from the enantiomeric excess of the monobenzoylated product **3** and its *isolated yield* (instead of using *conversion C*) as precedented by Matsumura[13] for this process. This approach is less accurate, leaving the major error by underestimating the conversion C. Therefore, the selectivity factors reported by us are a lower estimate. For further discussion, see also Mazet, C.; Roseblade, S.; Köhler, V.; Pfaltz, A. *Org. Lett.* **2006**, *8*, 1879.

particles due to the superior ferromagnetism of the pure metal core. The high saturation magnetization, along with the impermeability, chemical inertness, and thermal stability of the carbon coating, qualifies the nanopowder as an excellent scaffold for recyclable catalysts.

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Supporting Information Available: Additional information on the methods and characterization of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.