

RESEARCH ARTICLE OPEN ACCESS

Stable, Reusable Copper-Bispidine Catalysts on Agarose With Diffusion-Limited Turnover: When Immobilization is not Covalent

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Received: 17 June 2026 | **Revised:** 10 September 2026 | **Accepted:** 17 September 2026

Keywords: aziridination | catalyst support | copper-bispidine complexes | epoxy-functionalized agarose

ABSTRACT

In this study, we investigated whether copper(II)-bispidine complexes can be heterogenized on epoxy-functionalized agarose beads to provide reusable heterogeneous catalysts. The ligands employed are rigid *N*-donor systems based on the 3,7-diazabicyclo[3.3.1]nonane scaffold, and the corresponding copper complexes are known to catalyze the aziridination of styrene. To enable covalent attachment to the epoxy groups of the beads, hydroxy-functionalized linkers were introduced into the ligand framework. However, immobilization was found to be dominated by noncovalent interactions. Nevertheless, only minimal copper leaching was observed, and the resulting immobilisates were reused over six consecutive reaction cycles. At high catalyst loadings, comparable yields of 17%–21% were obtained for the different complexes, indicating restricted active-site accessibility within the support. Lowering the catalyst loading markedly improved catalytic performance, resulting in average yields of approximately 40% over six cycles. Under these conditions, immobilization could even enhance the performance of otherwise slowly reacting complexes compared with homogeneous catalysis under air, possibly by restricting oxygen access to the active Cu^I species and alleviating mass-transport limitations associated with high catalyst loadings in heterogeneous systems. Overall, the results demonstrate that catalyst loading, active-site accessibility, and transport within the agarose matrix are key factors governing the performance of immobilized copper(II)-bispidine catalysts.

1 | Introduction

Homogeneous catalysis offers the key advantage that reaction pathways can be investigated spectroscopically, enabling a mechanistic understanding and, consequently, a targeted optimization of the factors that govern efficient catalysis [1]. In particular, ligand environments can be rationally tuned to suppress side reactions, enhance selectivity, and modulate reactivity [2]. Overall, homogeneous catalysts show enhanced reactivity and selectivity in comparison to heterogeneous catalysts

[3, 4]. From a process perspective, however, homogeneous catalysts suffer from practical drawbacks, including the need for catalyst separation and product purification, as well as catalyst loss under continuous operation. In addition, the purification step usually prevents recovery and reuse of the catalysts [4–6]. This has driven strong interest in identifying intermediate concepts that combine the mechanistic tunability of homogeneous systems with the operational benefits of heterogeneous catalysis, such as the immobilization of homogeneous systems on support materials [7–9].

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A central challenge in such hybrid approaches is the identification of a suitable support material and immobilization strategy that match both the molecular catalyst and the intended process conditions [10–12]. Support materials range from porous frameworks to a variety of particles and beads, including metal–organic frameworks (MOFs), magnetic supports, agarose or polymeric beads, and silica [10, 13–15]. Silica and related rigid particulate supports are often attractive because of their pressure stability [16–18]. In porous materials, the homogeneous catalyst may additionally be incorporated within the pore network, although pore size and topology can introduce mass-transport limitations [19–24]. Importantly, the molecular catalyst must often be adapted to the chosen immobilization concept, for instance, by introducing linker groups for covalent immobilization to prevent leaching, which can in turn affect catalytic performance if the anchoring motif perturbs the active site or sterically restricts substrate approach. More generally, immobilization may reduce activity by limiting catalyst mobility and substrate accessibility in the vicinity of the support surface [25]. In addition, metal leaching must be avoided as it would contaminate the resulting reaction solution, and the employed transition-metal complexes should remain stable over extended operation so that immobilization becomes viable for industrial processes [11, 12].

One ligand system that can meet these requirements is the bispidine system, which provides a binding pocket well suited for copper(II) and therefore forms highly stable copper complexes [26]. In our previous studies, we investigated the reaction mechanism of the copper-catalyzed aziridination of styrene using a bispidine ligand [27, 28]. This reaction type is particularly attractive because it enables the formation of C–N bonds and, through selective ring opening of the nitrogen-containing three-membered ring, can introduce stereochemical information. This is of interest both for polymer chemistry and for pharmaceutical transformations [29]. Using the bispidine scaffold, we found that the presence of a secondary amine trans to the tosylimido group substantially increases the turnover frequency (TOF), allowing TOFs of up to 2400 h^{-1} under suitable reaction conditions [28]. The bispidine scaffold is characterized by its high rigidity and strong preorganization, enabling it to stabilize metal centers across a wide range of oxidation states. At the same time, its straightforward and modular synthesis allows the binding pocket to be tuned systematically, and it provides accessible positions for introducing linker functionalities required for catalyst immobilization [30]. We have previously explored the immobilization of a bispidine-based copper catalyst in the Zr-based MOF, NU-1000. Under the reaction conditions investigated, the immobilized system showed copper leaching, highlighting the importance of catalyst retention, support compatibility, and stability in the design of supported molecular catalysts [31]. In this study, we therefore pursue catalyst immobilization via covalent attachment to epoxy-functionalized agarose beads.

2 | Materials and Methods

All chemicals and reagents were purchased from ACROS or Sigma–Aldrich and were used without further purification. Deuterated solvents for nuclear magnetic resonance (NMR) spectroscopy were purchased from Deutero. Epoxy-activated Agarose (7.5% crosslinked, $40\mu\text{m}$ or $50\text{--}150\mu\text{m}$) was purchased from

Cube Biotech. Lucifer Yellow was purchased from Thermo Fisher Scientific. Spectra were processed with Origin 2021b.

Mass spectrometry (MS) experiments were carried out on an X500R from Sciex.

UV/Vis–NIR spectra were recorded on a Genesys 180 spectrometer from Thermo Scientific in UV-transparent 2.5 mL macro cuvettes.

A Tecan spark plate reader with Greiner UV-STAR 96-well plates (UV-Star Half Area 96-well plate, Greiner) was used to determine the loadings of agarose beads.

Attenuated total reflection–Fourier transform infrared spectroscopy (ATR–FTIR) measurements were carried out using a Bruker Optics Tensor 27 spectrometer with room temperature (RT) deuterated triglycinesulfate detector, and a Bruker Optics Platinum ATR accessory (diamond crystal with one reflection) has been applied (Bruker Optics, Ettlingen, Germany). All spectra were recorded at RT using the software Bruker OPUS 7.8. Spectra were recorded from 4497 cm^{-1} to 370 cm^{-1} with a resolution of 2 cm^{-1} against an air background. Thirty-two scans were coadded. The spectra shown were baseline-corrected using the concave rubber band method.

The electrochemical measurements were carried out using a customized 3D-printed cell (see Figure S1). A three-electrode setup consisting of a glassy-carbon working electrode, a platinized titanium wire as counter electrode, and an Ag/AgCl reference electrode (0.01 M Ag^+ , $0.1\text{ M (Bu}_4\text{N)}^+(\text{PF}_6)^-$ in MeCN) was used. The solutions were purged with Ar before the measurements, and the measurement itself was carried out under an argon atmosphere. Scan rates vary for different experiments; in general, scan rates from 1000 to 50 mV/s were used. The redox potentials were reported with respect to Ag/AgCl. As Potentiostat, a Gamry Reference 620+ was used.

Inductively coupled plasma optical emission spectroscopy (ICP–OES) measurements were carried out on an Optima 8300DV from Perkin Elmer. Samples were digested prior to analysis. To this end, 0.25 mL of the samples was treated with 0.375 mL of 30% HCl (Suprapur) and 0.125 mL of 65% HNO_3 (Suprapur), diluted with 2 mL of water, and heated for 1 h in a water bath.

Confocal laser scanning microscopy (CLSM) was done using a Leica TCS SP5 instrument. Immobilisates with $\text{Cu}^{\text{II}}(\text{OTf})_2$ and $[(\text{L}^3)\text{Cu}^{\text{II}}(\text{MeCN})]^{2+}$ for CLSM were prepared using the same protocol as for standard immobilization (see Supporting Information for detailed protocol), except using an incubation time of 1 h . After immobilization, the beads were resuspended in coupling buffer 2. Beads without copper served as controls and were washed 3 times with coupling buffer 2 prior to resuspension in the same buffer. Lucifer Yellow was prepared as a 50 mM stock solution in coupling buffer 2 and diluted to $50\mu\text{M}$. For fluorescence measurements, $18\mu\text{L}$ of bead suspension was mixed with $2\mu\text{L}$ of Lucifer Yellow solution and applied onto a microscope slide, resulting in a final Lucifer Yellow concentration of $5\mu\text{M}$. The beads were imaged using the following laser settings: the 488 nm laser line base power was adjusted to 30%. For imaging, illumination intensity was set to 80% and the smart

gain to 1156 V. Laser scan speed was set to 200 Hz, and a step size of 40 nm using the 63x oil immersion objective was set. The images were digitally zoomed by a factor of 6.86. For image analysis, brightness and contrast were adjusted uniformly across entire images to a range of 0–67 for improved comparability using Fiji/ImageJ.

Crystallographic Data were collected from single crystals of $[(L^1)Cu^{II}(OTf)](OTf) \cdot H_2O \cdot MeCN$, $[(L^4)Cu^{II}(MeCN)](OTf)_2 / [(L^4)Cu^{II}(H_2O)](OTf)_2$, and $[(L^2)Cu^{II}(MeCN)(OTf)](OTf) \cdot H_2O$ using a Stoe StadiVari diffractometer equipped with a MetalJet D2 liquid Ga source ($\lambda = 1.34 \text{ \AA}$). Data were corrected for absorption and polarization, and the structure was solved by direct methods using intrinsic phasing (SHELXT [32]) and refined using full-matrix least-squares (SHELXL-2019-3 [33]) within the Olex2-1.5 platform [34]. All nonhydrogen atoms were assigned anisotropic thermal parameters. Organic H atoms were placed in calculated positions. Full crystallographic data and details of the structural determinations for the structures in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 2559438 for $[(L^1)Cu^{II}(OTf)](OTf) \cdot H_2O \cdot MeCN$, CCDC 2559439 for $[(L^4)Cu^{II}(MeCN)](OTf)_2 / [(L^4)Cu^{II}(H_2O)](OTf)_2$, and CCDC 2559437 for $[(L^2)Cu^{II}(MeCN)(OTf)](OTf) \cdot H_2O$. Copies of the data can be obtained free of charge from <https://www.ccdc.cam.ac.uk/structures/>.

Elemental analyses were performed on a CHN-O Vario EL by the staff of the Department of Chemistry at Heidelberg University.

High-performance liquid chromatography (HPLC) measurements for determination of the yield of the aziridination reaction were performed on a Hitachi HPLC Chromaster with a diode array detector. A Phenomenex Gemini 3u C18 column was utilized for separation and kept at 35°C for analysis. The total flow rate was $\dot{V} = 0.6 \text{ mL/min}$. The gradient was initiated at 40/60 MeCN/ H_2O and held for 1 min, followed by a ramp to 65/35 MeCN/ H_2O over 10 min, then returning to 40/60 MeCN/ H_2O within 1 min, and maintaining this for an additional 4 min. The injection volume was $10 \mu\text{L}$, with a prior flush of 1 min with 40/60 MeCN/ H_2O . The autosampler was kept at 10°C . The absorbance measurement of styrene was performed at $\lambda = 210 \text{ nm}$ and for 2-phenyl-1-tosylaziridine at $\lambda = 227 \text{ nm}$ (internal reference value: 380 nm). Retention times were $8.3 \pm 0.3 \text{ min}$ and $9.5 \pm 0.3 \text{ min}$, respectively. Quantification was based on automated peak integration using the instrument's internal software.

NMR spectra were recorded on a 400 MHz Bruker Avance III HD or on a 400 MHz Bruker AvanceCore instrument with the solvent as an internal reference.

2.1 | Aziridination Reactions

For homogeneous batch reactions, 10–20 mg of PhINTs ((N-(p-toluenesulfonyl)imino)phenyliodonane) (20 eq) and 15–35 μL styrene (100 eq) were placed in reaction tubes. The reaction was started by adding a 5 mM solution of the copper complex (1 eq) in MeCN. After vortexing, the reaction was incubated at 25°C and 750 rpm in a thermomixer for 18–19 h, or at least until a clear solution was obtained, to allow the reaction to proceed to completion. The aziridination yields were determined by HPLC

after diluting the reaction mixture 1:1000 with a 1:1 (v/v) solution of MeCN and water. All experiments were performed in triplicate.

For the heterogeneous reaction, the amount of copper complex (1 eq) was determined based on the loading of the beads. Styrene (100 eq) was added to the beads first, followed by PhINTs (20 eq) suspended in 700 μL MeCN. After vortexing, the reaction mixture was incubated at 25°C and 750 rpm for 19–24 h (see Table S7 for detailed reaction time information) on a thermomixer (Eppendorf Thermomixer Comfort). Samples were centrifuged (Eppendorf Centrifuge 5415 R, 2 min, 0.5 rcf), and the supernatant was transferred to new reaction tubes to enable further reaction cycles with the beads. Prior to reuse of the immobilized complex, a washing step with MeCN (1 mL) and another one with water were performed (1 mL). If residual solid PhINTs remained in the reaction mixture, subsequent reactions were carried out assuming minimal impact on catalytic performance. The heterogeneous reaction was repeated 6 times as described, disregarding remaining solid oxidant. The beads were stored in 0.5 mL storage buffer (20 mM sodium acetate with 20% (v/v) ethanol, pH 6.5). Aziridination yields were determined by HPLC analysis of the supernatant. Styrene was quantified from a 1:1000 dilution, while the product 2-phenyl-1-tosylaziridine was analyzed from a 1:100 dilution, both in a 1:1 (v/v) mixture of MeCN and water.

2.2 | Immobilization

For the direct immobilization, maximum complex loading was calculated based on the epoxy group density ($20 \mu\text{mol/mL}$) and the applied particle volume (0.25 mL) of PureCube Epoxy-Activated Agarose beads. Immobilization solutions (40 mM in MeCN and 10 mM for immobilisates with reduced loadings) were prepared accordingly. 0.5 mL of bead suspension was centrifuged (0.5 rcf, 2 min), the supernatant discarded, and the beads washed 4 times with 0.5 mL of double-distilled water, followed by a single wash with 0.5 mL of buffer (100 mM Na_2CO_3 and 500 mM NaCl, pH 8.3). After addition of 0.125 mL of buffer (100 mM Na_2CO_3 and 500 mM NaCl, pH 8.3), the suspension was incubated at 25°C and 750 rpm for 10 min in a thermomixer. Subsequently, 0.125 mL of the complex solution was added, and the mixture was incubated overnight ($\geq 18 \text{ h}$) under the same conditions. The time-dependent immobilization was conducted in the same way, but with variable incubation times (5, 10, 20, 60, and 300 min). After centrifugation, the supernatant was collected for analysis. The loaded beads were washed 5 times with 0.5 mL of double-distilled water, and the respective wash fractions were retained. Quantification of the complex in supernatants and wash fractions was based on absorbance measurements at their characteristic wavelength (see Figures S13–S23 for detailed information, range was between 252 and 258 nm, as well as 620 nm) using UV/Vis spectroscopy. Beads were stored in 0.5 mL of storage buffer at 4°C . Immobilization was performed in triplicate and used in subsequent heterogeneous reactions.

2.3 | Stability Test

To assess the stability of immobilized $[(L^1)Cu^{II}(MeCN)](OTf)_2$ using different immobilization methods, the supernatants of several immobilized samples were analyzed by ICP-OES after completion of the first heterogeneous reaction cycle. Apart from

a single outlier observed for the two-step immobilized samples, all measured losses were $\leq 0.06\%$, indicating negligible leaching of the immobilized complex under the applied reaction conditions. Consequently, we assumed that leaching of the immobilisates can be excluded as a relevant factor in subsequent experiments and did not perform more stability tests in repeated heterogeneous reaction cycles. Detailed results are shown in Table S8 and Figure S29.

2.4 | Immobilization Using Laboratory Automation for the Loading Isotherms

Loading isotherms were determined using a laboratory automation setup, which enabled standardized immobilization of different complexes. The platform consists of a liquid handling station (Opentrons OT-2), a robotic arm (Universal Robots UR5e), a vacuum pump (Vacuubrand MD 4 Vario Select), and a microplate reader (Tecan Spark Multimode Microplate Reader) on a custom-built workbench. The detailed setup is shown in Figure S25.

The UR5e robotic arm transfers liquid reservoirs and well plates between devices and stations throughout the process. The liquid handling station performs pipetting, incubation, and washing of the beads in a 96-well filter plate (Pall Corporation AcroPrep Advance 96 Well 1 mL 0.2 μm Supor) on a heater-shaker module. It also prepares the dilution series in a separate 96-deep well plate (NEST, 96 well deep well plate, square well, 2 mL). Vacuum pumping steps were applied for filtrations and washes using the vacuum pump with a custom vacuum manifold.

An automated workflow was used to determine adsorption isotherms on the BioCAR self-driving laboratory (SDL) platform with Python scripts, which are available in the accompanying repository (<https://doi.org/10.5281/zenodo.20427098>). Before each run, the user equipped the system with fresh labware (e.g., microplates, reagent reservoirs, and pipette tips) and added the required complex solutions and solvents to the reagent reservoirs (NEST, Reservoir Microplates Without Caps, Multi-Well, 12 Channel, 15 mL). The user also manually transfers the bead suspension (washed 3 times with water and resuspended in water) into the filter plate in triplicate (500 μL per well) and fills the rest of the filter plate (500 μL per well) with water. Once the user starts the workflow, the liquid handling station executes a dilution series (shown in Table S5) to procure the desired adsorbate concentrations. Based on the input concentrations (C), the stock concentration (C_{stock}), and the total volume per batch (V_{total}), it calculates (according to Equations (1) and (2)) and mixes the appropriate volumes of diluent (V_{diluent}) and stock solutions (V_{stock}).

$$V_{\text{stock}} = \frac{C}{C_{\text{stock}}} \cdot V_{\text{total}} \quad (1)$$

$$V_{\text{diluent}} = V_{\text{total}} - V_{\text{stock}} \quad (2)$$

For the binding step, 500 μL of each adsorbate solution was dispensed into three wells of the filter plate containing the beads, creating triplicate samples for each concentration. After approximately 30 min, the run pauses with a user prompt. The user manually removed all other labware except the wash reservoir,

refilled the 300 μL tip rackets, emptied the trash, and applied a sealing foil to the filter plate. The foil prevents solvent evaporation during the subsequent 18 h incubation at room temperature and 900 rpm on the heater-shaker module, which starts upon user confirmation. Once the incubation was complete, upon prompt, the user filled a reagent reservoir with water for the following washing steps, emptied the deep well plate in storage, removed the sealing foil, and confirmed that the setup was correct before proceeding.

The supernatants from the binding step were separated from the beads by filtration using an automated vacuum pump and the robotic arm. Therefore, one of the two deep-well plates for supernatant collection was moved from the storage modules to the filtration station. The vacuum manifold was placed on top of the collection plate, and the filter plate was transferred from the heater-shaker module to the filtration module. Phase separation during filtration was achieved using the vacuum pump, which was activated for 60 s at pump speed of 50%, followed by a venting time of 600 s. Then, the filter plate was returned to the heater-shaker module, the vacuum manifold was placed back on the storage bench, and the reservoir was transferred to the liquid handling station. There, 75 μL of the supernatants was transferred from the reservoir plate into a UV 96-well plate (UV-Star Half Area 96-well plate, Greiner). The reservoir was then returned to the storage module next to the vacuum pump.

After the binding step, three identical wash steps were performed. For each wash step, 500 μL water from the reagent reservoir was transferred into the filter plate, followed by an incubation for 2 min at RT and 900 rpm on the heater-shaker module. Absorbance measurements were performed on the microplate reader at the characteristic wavelength of the complex solution (see Figures S22–S23). If absorbance values were outside the calibration range, the respective wells were manually diluted 1:10 or 1:50 with water, and the absorbance measurement was repeated.

For the loading isotherms, a modified BET fit was applied (Equation (3)) [35, 36]. Herein, q is the equilibrium loading, q_m is the monolayer loading capacity, and K is the BET constant related to the affinity of the adsorbate for the adsorbent surface. The relative equilibrium concentration is defined as $x = \frac{C}{C_s}$, where C is the equilibrium concentration of the adsorbate in the supernatant and C_s is its saturation concentration. The parameter n accounts for the maximum number of adsorbate layers that can be formed. The equilibrium concentrations were determined by UV/Vis spectroscopy of the supernatants after binding and washing steps, enabling the quantification of complex adsorption to the beads.

$$q = \frac{q_m K x}{1 - x} \cdot \frac{1 - (n + 1)x^n + nx^{n+1}}{1 + (K - 1)x - Kx^{n+1}} \quad (3)$$

2.5 | Syntheses

Ligand L^3 [37], L^4 [38], L^5 [39], and L^6 [40] as well as piperidone P1 [41] (Dimethyl 1-methyl-4-oxo-2,6-di(pyridin-2-yl)piperidine-3,5-dicarboxylate) and P2 [42] (Dimethyl 4-oxo-2,6-di(pyridin-2-yl)piperidine-3,5-dicarboxylate) and the oxidizing agent PhINTs were prepared as described before [43–45].

General bispidone synthesis. To a suspension of 1 eq piperidone in EtOH, 1.2 eq of the corresponding amine and 2.4 eq of formaldehyde (37% aqueous solution) were added at 50 °C. The reaction mixture was refluxed immediately for 0.5 h. After the mixture was cooled to RT, the solvent was evaporated in vacuo. Remaining traces of water in the residue were removed by dissolving in absolute THF and evaporation until formation of a foam was observed. The crude product was recrystallized from EtOH to obtain the product as colorless crystals, which were dried in vacuo.

L¹ (Dimethyl 7-(2-hydroxyethyl)-9-oxo-2,4-di(pyridin-2-yl)-3,7-diazabicyclo [3.3.1]nonane-1,5-dicarboxylate) Following the general bispidone synthesis, P2 (7.42 g, 19.33 mmol, 1 eq), formaldehyde solution (3.45 mL, 46.39 mmol, 2.4 eq), and aqueous 2-amino-1-ethanol solution (1.39 mL, 23.20 mmol, 1.2 eq) in 100 mL EtOH were refluxed for 0.5 h to obtain the product (4.41 g, 50.2%) as colorless crystals.

¹H NMR (MeOD, 400.13 MHz, 300 K): δ (ppm) = 8.65 (2H, m, H^{py}); 7.84 (2H, td, J =7.7, 1.8 Hz, H^{py}); 7.47 (2H, d, J =7.9, H^{py}); 7.39 (2H, ddd, J =7.6, 4.9, 1.2 Hz, H^{py}); 5.11 (2H, d, J =1.82, N³CH); 3.74 (6H, s, COOCH₃); 3.74 (2H, t, J =5.2 Hz, CH₂CH₂OH); 3.61 (2H, m, CH₂ eq/ax); 2.87 (2H, m, CH₂ eq/ax); 2.50 (2H, t, J =4.8 Hz, CH₂CH₂OH). ¹³C{¹H} NMR (MeOD, 100.62 MHz, 300 K): δ (ppm) = 204.93; 170.34; 157.46; 150.17; 138.75; 125.05; 124.82; 67.03; 63.18; 59.61; 59.40; 59.30; 52.73. ESI-MS (pos., MeCN) m/z : 477.1725 (100%) [L¹ + Na⁺]⁺ (calc: 477.1745), 455.1905 (95%) [L¹ + H⁺]⁺ (calc: 455.1925).

L² (Dimethyl 7-(5-hydroxypentyl)-9-oxo-2,4-di(pyridin-2-yl)-3,7-diazabicyclo [3.3.1]nonan-1,5-dicarboxylate) Following the general bispidone synthesis, P2 (6.25 g, 16.92 mmol, 1 eq), formaldehyde solution (3.02 mL, 40.6 mmol, 2.4 eq), and 5-amino-1-pentanol solution (2.09 g, 20.20 mmol, 1.2 eq) in 150 mL EtOH were refluxed for 0.5 h to obtain the product (5.39 g, 64.2%) as colorless crystals.

¹H NMR: (MeOD, 400.13 MHz, 300 K): δ (ppm) = 8.60 (2H, mf, H^{py}); 7.81 (2H, td, J =7.7, 1.8 Hz, H^{py}); 7.57 (2H, d, 8.0 Hz, H^{py}); 7.34 (2H, ddd, J =7.6, 4.8, 1.2 Hz, H^{py}); 5.11 (2H, d, J =1.75, N³CH); 3.76 (6H, s, CH₃COO); 3.60 (2H, m, N⁷CH₂ eq/ax); 3.51 (2H, t, J =6.7 Hz, CH₂CH₂CH₂CH₂CH₂OH); 2.76 (2H, m, N³CH₂ eq/ax); 2.27 (2H, t, J =6.2 Hz, CH₂CH₂CH₂CH₂CH₂OH); 1.47 (6H, m, CH₂CH₂CH₂CH₂CH₂OH). ¹³C{¹H} NMR: (MeOD, 100.62 MHz, 300 K): δ (ppm) = 204.66, 169.65, 156.81, 148.47, 136.72, 122.94, 65.75, 61.59, 58.32, 56.56, 51.22, 31.95, 26.36, 23.22. ESI-MS (pos., MeCN) m/z : 519.2209 (100%) [L² + Na⁺]⁺ (calc: 519.2214), 497.2394 (89%) [L² + H⁺]⁺ (calc: 497.2395).

General synthesis of the copper(II) complexes. The corresponding ligand and an equimolar amount of Cu^{II}(OTf)₂ were dissolved in acetonitrile or methanol to obtain an intense blue 0.5–2 mM solution. The mixture was stirred for 30 min at RT for complete complexation. The complexes were obtained by ether diffusion as blue crystals in almost quantitative yields (90%–98%).

[Cu^{II}L¹(MeCN)](OTf)₂ Elemental Analysis (C₂₅H₂₆CuF₆N₄O₁₂S₂ x 0.5 H₂O) [%], calc: C, 36.39; H, 3.30; N, 6.79; found, C, 36.60; H, 3.88; N, 6.92. ESI-MS (pos., MeCN) m/z : 267.5622 (100%) [[L¹Cu]²⁺ + H₂O]²⁺ (calc: 267.5622).

[Cu^{II}L²(MeCN)](OTf)₂ Elemental Analysis (C₂₈H₃₂CuF₆N₄O₁₂S₂ x MeCN x 0.5 H₂O) [%], calc: C, 39.67; H, 4.00; N, 7.71; found, C, 39.83; H, 4.38; N, 7.85. ESI-MS (pos., MeCN) m/z : 279.5804 (100%) [L²Cu]²⁺ (calc: 279.5796).

[Cu^{II}L³(H₂O)](OTf)₂ Elemental analysis (C₂₄H₂₆CuF₆N₄O₁₂S₂ x 1.5 H₂O x 0.5 MeCN) [%], calc: C, 35.26; H, 3.61; N, 7.40; found: C, 35.07; H, 3.69; N, 7.45. ESI-MS (pos., MeCN) m/z : 252.5572 (100%) [[L³Cu]²⁺ + H₂O]²⁺ (calc: 252.5569).

[Cu^{II}L⁴(MeCN)](OTf)₂ Elemental Analysis (C₂₆H₂₈CuF₆N₄O₁₂S₂ x H₂O) [%], calc: C, 36.82; H, 3.57; N, 6.61; found, C, 36.55; H, 3.85; N, 6.70. ESI-MS (pos., MeCN) m/z : 274.5698 (100%) [[L⁴Cu]²⁺ + H₂O]²⁺ (calc: 274.5700).

[Cu^{II}L⁵(MeCN)](OTf)₂ Elemental analysis (C₂₄H₂₆CuF₆N₄O₁₂S₂ x 2 H₂O x 0.5 MeCN) [%], calc: C, 34.89; H, 3.69; N, 7.32; found: C, 34.85; H, 3.63; N, 7.35. ESI-MS (pos., MeCN) m/z : 252.5555 (100%) [[L⁵Cu]²⁺ + H₂O]²⁺ (calc: 252.5569).

[Cu^{II}L⁶(MeCN)](OTf)₂ Elemental analysis (C₂₇H₂₉CuF₆N₅O₁₂S₂) [%], calc: C, 38.79; H, 3.52; N, 8.64; found: C, 38.74; H, 3.76; and N, 8.64. ESI-MS (pos., MeOH) m/z : 550.1486 (79%) [Cu^{II}L⁶ + OMe + H₂O]⁺ (calc: 550.1483) and 668.0824 (100%) [Cu^{II}L⁶ + OTf + H₂O]⁺ (calc: 668.0820).

3 | Results

The secondary amine trans to the tosylimido moiety renders the bispidine complex L³ (an overview of the ligands used, including their numbering and complex geometries, is given in Figure 1) a potent catalyst for the aziridination of styrene. To enable immobilization on epoxy-functionalized agarose beads (see Scheme 1), a hydroxy linker group was introduced at N⁷. For this purpose, two bispidine ligands were synthesized: one bearing an ethanol linker and another bearing a pentanol linker. The syntheses were carried out according to adapted literature procedures using the corresponding amines in the second double Mannich reaction to achieve the second ring closure and construct the bispidine backbone. After obtaining the ligands, the corresponding copper complexes were prepared by reaction with equimolar amounts of Cu^{II}(OTf)₂.

Crystals suitable for single-crystal X-ray diffraction were obtained from MeCN/Et₂O solutions. The crystal structures of the complexes with L¹, L², and L⁴ are shown in Figure 2, all relevant bond lengths for all complexes used in this study are given in Table 1 (crystallographic data are displayed in Table S1). In all obtained structures, hydration of the C⁹ ketone moiety to the corresponding geminal diol was observed. This behavior is well documented for bispidine-based copper complexes and is commonly attributed to the pronounced tendency of the C⁹ carbonyl group to undergo hydration under aqueous, protic, or strongly hydrogen-bonding conditions [48–50]. For both complexes with ligand L¹ or L⁴, the ethanol residue coordinates, so the ligand acts as pentadentate ligand.

The newly reported structures display six-coordinate geometries, with acetonitrile, water, or a triflate counterion occupying an

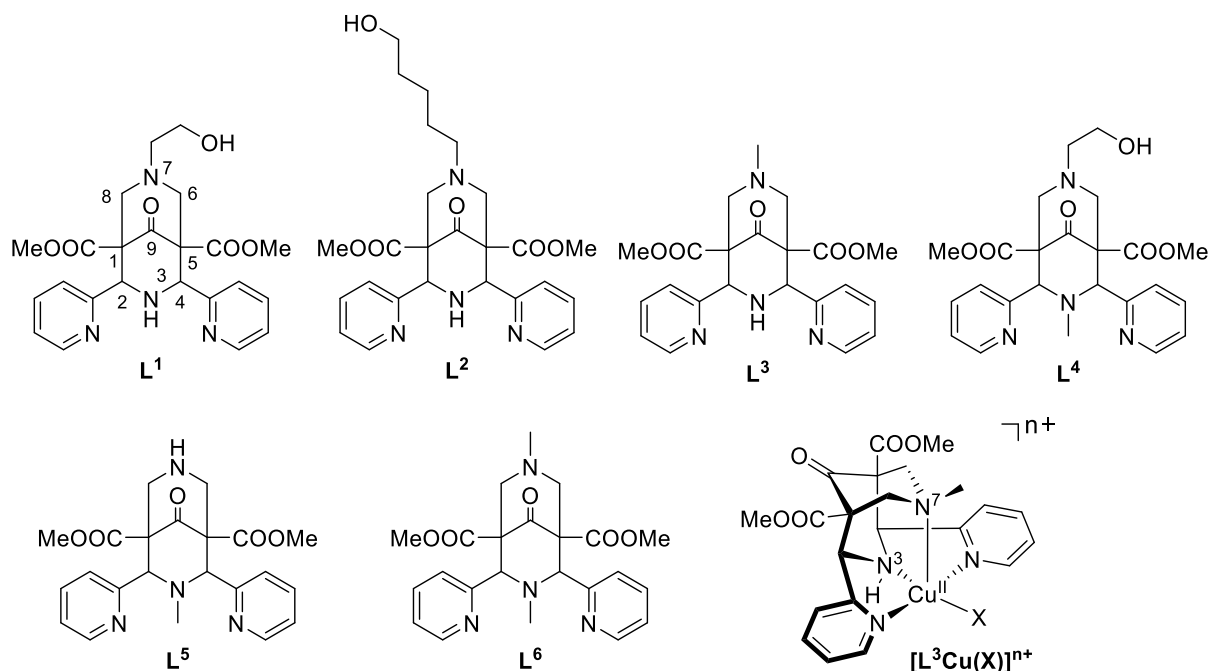
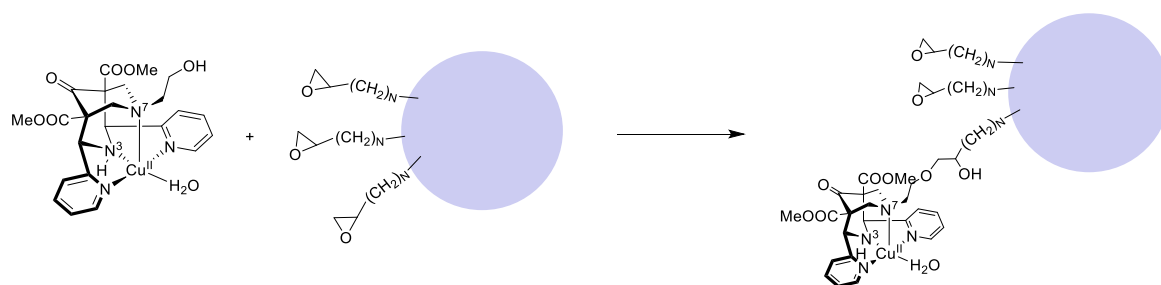


FIGURE 1 | Used ligands in this manuscript. Atom numbering is exemplarily shown on L^1 , and the complexation geometry is shown with L^3 , with X being either a solvent molecule or counter ion.



SCHEME 1 | Covalent immobilization strategy for copper(II)-bispidine complexes on epoxy-functionalized agarose beads, illustrated using $[(L^1)Cu^{II}(H_2O)]^{2+}$.

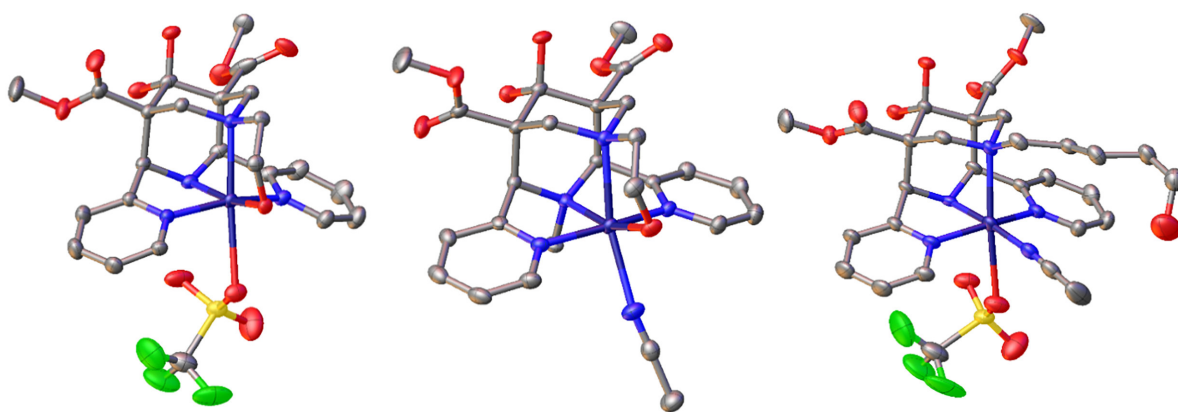


FIGURE 2 | Olex2 plot of the crystal structure analysis of $[(L^1)Cu^{II}(OTf)]^+$ (left), $[(L^4)Cu^{II}(MeCN)]^{2+}$ (middle), and $[(L^2)Cu^{II}(MeCN)(OTf)]^+$ (right). Non-coordinating counter ions, H-atoms and lattice solvent molecules are omitted for clarity, ellipsoids are shown at 50% probability level. Color code: blue: N, red: O, dark blue: Cu, gray: C, yellow: S, green: F.

additional coordination site besides the tetradentate or pentadentate ligand framework. In these complexes, the elongation is observed along the Cu–N⁷ axis, but elongation along the other

axes is also possible, as illustrated, for example, by the structural data of $[(L^3)Cu^{II}(MeCN)]^{2+}$ [51–53]. This behavior is consistent with the characteristic Jahn–Teller distortion of six-coordinate

TABLE 1 | Selected bond lengths and angles of the crystal structures of $[(L^m)Cu^{II}(X)(Y)]^{n+}$ (X denotes the equatorially coordinated ligand or coligand, Y denotes the coligand in the axial plane). Distances are given in (Å) and angles in (°).

Bond length (Å)	$[(L^1)Cu^{II}(OTf)]^{+a,b}$	$[(L^2)Cu^{II}(MeCN)]^{2+a,b}$	$[(L^3)Cu^{II}(MeCN)]^{2+}$ [31]	$[(L^3)Cu^{II}(Cl)]^{+}$ [46]	$[(L^4)Cu^{II}(MeCN)]^{2+a,c}$	$[(L^5)Cu^{II}(MeCN)]^{2+}$ [27] ^a	$[(L^6)Cu^{II}(MeCN)]^{2+}$ [47] ^d
Cu–N ³	1.982 (2)	1.995 (5)	2.272 (6)	2.007 (2)	2.0349 (16)	2.018 (3)	2.022 (2)
Cu–N ⁷	2.264 (2)	2.361 (4)	1.964 (6)	2.358 (2)	2.3542 (17)	2.242 (3)	2.353 (2)
Cu–py	2.0115 (18)/ 1.9919 (15)	2.008 (3)/ 2.012 (3)	2.022 (6)/ 2.024 (6)	2.013 (2)/ 2.009 (2)	1.994 (2)/ 1.990 (2)	2.005 (4)/ 2.006 (4)	1.994 (2)/ 2.003 (2)
Cu–X	1.9831 (18)	1.976 (5)	1.991 (6)	2.228 (6)	2.07123 (15)	1.953 (4)	1.972 (2)
Cu–Y	2.620 (2)	2.605 (4)	—	—	2.274 (2)	—	2.757 (2)
Py1–Cu–py2	3.932 (2)	3.959 (4)	3.964	4.022	3.942 (3)	4.011	3.997
N3–Cu–X	3.938 (3)	3.969 (7)	3.943	4.235	4.056 (2)	3.971	3.994
angle (°)							
N3–Cu–N7	83.91 (8)	82.16 (16)	84.7 (2)	81.25 (6)	83.28 (6)	84.92 (12)	83.26 (2)

^aHydrolyzed at C⁶ (C=O) → C(OH)₂.

^bCoordinated OTf[−] in axial position.

^cIn the unit cell, there are two complexes, each with either MeCN or water coordinated axially. The values given in the table refer to the complex with axially coordinated MeCN.

^dCoordinated CClO₄[−] in axial position.

copper(II) centers in pseudo-octahedral environments, although the direction of elongation may depend on the precise ligand field and overall coordination environment.

In addition to the solid-state structures, the solution properties of the copper(II) complexes were also investigated. All obtained values are summarized in Table 2, and the corresponding spectra are shown in Figure S5. Previous studies on Cu^{II/I}-bispidine complexes have demonstrated that the structures in solution closely correspond to those observed in the solid state, with the exception that the coligand present in the crystal structure is substituted by a solvent molecule in solution [55, 56]. In MeCN, the absorption spectra displayed the characteristic transition of copper(II)-bispidine complexes at around 650 nm, assigned to excitation from a d π orbital, which indicates that no significant structural changes occur upon dissolution in this case [27]. The absence of the weak band around 900 nm in solution is consistent with the crystallographic data, which show six-coordinate pseudo-octahedral copper(II) centers. This suggests that the coordination environment observed in the solid state is largely retained in solution.

After the absorption spectra had been examined, the redox potentials in MeCN were determined (see Figures S2–S4). Here, too, the trends already observed in previous studies were confirmed. Complexes with tetradentate ligands bearing a secondary amine at N³ are characterized by relatively high redox potentials of about −400 mV versus FcH/FcH⁺, which correspond to approximately −300 mV versus Ag/AgCl. Complexes with tetradentate ligands lacking a secondary amine are around 100 mV more negative. Complexes with pentadentate ligands also lie at lower potentials, which is well reflected in the present data; for example, the complex with L⁴ shows a redox potential of −437 mV versus Ag/AgCl [27]. However, the potential is shifted to more positive values compared to a pentadentate complex bearing an additional pyridine donor. The coordinating hydroxy group is less effective in donating electron density to the copper center, leading to an increase in the redox potential of approximately 140 mV [28]. This trend is also evident for the complex with L¹, which, due to its pentacoordinate coordination environment and the presence of an additional secondary amine, exhibits a slightly more positive redox potential of −384 mV versus Ag/AgCl. A similar behavior is observed for the complex with L², where the presence of the secondary amine leads to a somewhat higher redox potential compared to the complex with L⁶, which is likewise tetradentate but lacks the secondary amine and instead bears a different substitution at N⁷.

3.1 | Homogeneous Catalysis

After the complexes had been characterized, their activity in the catalytic aziridination of styrene using PhINTs ((N-(p-toluenesulfonyl)imino)phenyliodinane) as an oxidant was investigated. This reaction has been well studied for bispidine systems and serves as a model reaction [27]. All complexes used in this work show activity in the homogeneous reaction (see Table 3). It is known that tetradentate ligands lacking a secondary amine at N³ tend to exhibit lower TOF values and yields, as do pentadentate systems [27, 28]. This trend is also observed here: the complex with L⁴ shows only a yield of approximately 27%.

TABLE 2 | Absorption maxima (1 mM [Cu^{II}], MeCN, air) and redox potentials of various complexes. For CV measurements, a three-electrode setup with a glassy-carbon working electrode, a platinized titanium wire as counter electrode, and an Ag/AgCl reference electrode (0.01 M Ag⁺ 0.1 M (Bu₄N)⁺(PF₆)⁻ in MeCN, purged with Ar) was used.

Complex	λ (nm) [ϵ (mol ⁻¹ L ⁻¹)] MeCN	E ^{1/2} (mV) versus Ag/ AgCl MeCN	E ^{1/2} (mV) versus FcH/FcH ⁺ MeCN
[(L ¹)Cu ^{II} (MeCN)](OTf) ₂	679 [106]	-384	
[(L ²)Cu ^{II} (MeCN)](OTf) ₂	621 [124]	-401	
[(L ³)Cu ^{II} (MeCN)](OTf) ₂ [27]	691 [131] 913 [32]	-308 ^a	-395
[(L ⁴)Cu ^{II} (MeCN)](OTf) ₂	676 [95]	-437	
[(L ⁵)Cu ^{II} (MeCN)](OTf) ₂ [27]	637 [110] 977 [24]	-429 ^a	-516
[(L ⁶)Cu ^{II} (MeCN)](OTf) ₂ [27]	626 [107] 899 [26]	-417 ^a	-504

^aValues were calculated using conversion constants from [54] using 0.01 M Ag concentration.

In contrast, the complexes with L¹ and L² gave yields of 60% and 68%, respectively. These values are comparable to the yields of 65% of [(L³)Cu^{II}(MeCN)](OTf)₂ and show that the introduced substituents have little influence on the homogeneous reaction [28]. On this basis, the immobilization of the complexes was carried out in the next step.

3.2 | Immobilization and Heterogeneous Catalysis

Before evaluating the performance of the complexes as heterogeneous catalysts, the loading of the support material was investigated. The loading isotherms of [(L¹)Cu^{II}(MeCN)](OTf)₂ and [(L²)Cu^{II}(MeCN)](OTf)₂ are shown in Figure 3. The loading isotherms were evaluated using a modified BET fit to estimate the maximum monolayer loading of the respective system; the complete fit parameters are provided in Figure S26 [35]. Due to the high uncertainties of individual fit parameters, however, the obtained values are not discussed in detail here. Contrary to expectations, neither isotherm shows a clear plateau at higher incubation concentrations. Although an apparent plateau was observed in the intermediate concentration range, the loading continued to increase across the full concentration range investigated. This indicates that the loading behavior is not fully described by a simple monolayer-type model. In addition to the intended covalent immobilization of the support, further processes may contribute to the overall loading, including nonspecific adsorption, pore filling, aggregation, or the formation of additional layers through weaker intermolecular interactions. The formation of multiple layers on a support material has previously been observed for a bispidine complex bearing acidic groups at the backbone [31]. The increased scattering observed at higher concentrations further supports the conclusion that overlapping adsorption processes and surface heterogeneity contribute to the loading behavior. The particularly pronounced difference in loading between the two complexes observed in the low-loading region of the isotherm is likely related to the different denticities of the ligands. While [(L¹)Cu^{II}(MeCN)](OTf)₂ has a pentadentate ligand, the hydroxy group in [(L²)Cu^{II}(MeCN)](OTf)₂ remains accessible and may therefore contribute more effectively to covalent attachment and/or noncovalent interactions with the

agarose support. Nevertheless, the isotherms clearly demonstrate successful loading of the support material with the copper(II)-bispidine complexes.

After determining the loading isotherms, immobilized materials were prepared for heterogeneous batch reactions. The loading results are summarized in Table 3. The immobilization conditions used here were selected such that the amount of complex corresponded to the available epoxy group content of the agarose support, thereby targeting the highest achievable monolayer catalyst loadings. In addition to direct immobilization of the preformed complex, a two-step immobilization strategy was investigated, in which the ligand was first immobilized on the support and subsequently complexed with copper(II). Although higher overall loadings were obtained with this two-step approach, the resulting materials were less well defined, as the coordination environment of copper(II) could not be unambiguously assigned and nonspecifically retained copper species could not be excluded (see Table S4). In addition to the complexes based on L¹ and L², the complexes with ligands L³-L⁶ were included as control samples. Since epoxy groups are readily attacked by nucleophiles and the complexes with ligands L¹ and L² used here contain both a hydroxy group and an amine group capable of undergoing ring-opening reactions, different combinations were examined in order to better assess the underlying effects. Among these, [(L⁶)Cu^{II}(MeCN)](OTf)₂, which does not contain a nucleophilic group, was included as a reference complex. As shown, similar loadings in the range of 41%–51% were achieved for all complexes investigated. Most notably, [(L⁶)Cu^{II}(MeCN)](OTf)₂, which does not contain a nucleophilic group, exhibited the highest loading, whereas [(L⁵)Cu^{II}(MeCN)](OTf)₂ showed the lowest loading. The high loading obtained for [(L⁶)Cu^{II}(MeCN)](OTf)₂ supports the interpretation of the loading isotherms that immobilization in this system is not necessarily based on covalent attachment but rather arises from other interactions with the agarose network [13]. Time-dependent immobilization experiments were additionally carried out for complexes [(L³)Cu^{II}(MeCN)](OTf)₂ and [(L⁴)Cu^{II}(MeCN)](OTf)₂ to further investigate the role of the nucleophile (see Table S6). Immobilization proceeded rapidly for both systems, and no clear dependence on whether an amine or hydroxy group was present could be observed. This indicates that differences in covalent

TABLE 3 | Loading of immobilisates, yields and standard deviation of the heterogeneous reactions in the catalytic conversion of styrene to the corresponding aziridine (cat:ox:substrate 1:20:100 in MeCN, RT, 19–24 h) in six consecutive reactions, as well as yields and standard deviation of the homogenous reactions in the catalytic conversion of styrene to the corresponding aziridine (cat:ox:substrate 1:20:100, 5 mM copper(II) complex in MeCN, RT, 18–19 h) under air. All experiments were carried out in triplicates, and values are reported as mean $\pm$ standard deviation ($n = 3$).

Metric	$[(L^1)Cu^{II}(MeCN)]$ (OTf) ₂	$[(L^2)Cu^{II}(MeCN)]$ (OTf) ₂	$[(L^3)Cu^{II}(MeCN)]$ (OTf) ₂	$[(L^3)Cu^{II}(Cl_2)]$	$[(L^4)Cu^{II}(MeCN)]$ (OTf) ₂	$[(L^5)Cu^{II}(MeCN)]$ (OTf) ₂	$[(L^6)Cu^{II}(MeCN)]$ (OTf) ₂	$Cu^{II}(OTf)_2$
Loading (mg/g)	176.1 $\pm$ 16.0	168.5 $\pm$ 7.0	163.5 $\pm$ 6.1	—	182.1 $\pm$ 8.6	143.9 $\pm$ 6.8	179.6 $\pm$ 4.8	148.0 $\pm$ 0.2
Loading (%)	49.0 $\pm$ 4.5	44.7 $\pm$ 1.9	47.3 $\pm$ 1.8	—	49.9 $\pm$ 2.4	41.7 $\pm$ 2.0	51.2 $\pm$ 1.4	93.1 $\pm$ 0.1
Yield heterogeneous (%)	20.8 $\pm$ 6.8	17.4 $\pm$ 5.2	19.9 $\pm$ 6.0	—	17.7 $\pm$ 4.7	20.7 $\pm$ 5.1	19.5 $\pm$ 5.0	14.0 $\pm$ 4.6
Yield homogeneous (%)	59.9 $\pm$ 12.1	68.4 $\pm$ 1.8	64.9 $\pm$ 4.3	53.4 $\pm$ 0.5 [31]	26.8 $\pm$ 3.5	21.5 $\pm$ 7.2	12.7 $\pm$ 5.2	98.0 $\pm$ 6.9

reaction rates with the support functionalities are unlikely to be the sole factor controlling the loading. Overall, these results further support the hypothesis that noncovalent interactions play an important role in the immobilization process.

The immobilized materials were subsequently employed in heterogeneous reactions for the conversion of styrene. The same immobilisates were used in six consecutive reaction cycles. Each reaction cycle was carried out for approximately 19–24 h to determine the endpoint yield. At these reaction times, no substantial further increase in product concentration was observed (see Figure S27). This approach minimizes the impact of kinetic differences between the catalyst systems when comparing aziridination product yields. After the first reaction cycle, the reaction solution of samples with $[(L^1)Cu^{II}(MeCN)](OTf)_2$ was analyzed by ICP-OES for copper leaching. As all samples investigated here exhibited leaching $\leq 0.06\%$ (see Table S8), the immobilized materials were reused, and catalyst leaching was considered negligible. The average yield across all cycles is also reported in Table 3, whereas the results of the individual reaction cycles are shown in Figure 4. Inspection of the reaction cycles reveals a clear trend: the first reaction cycle affords the highest yield, after which the yield declines and, for most complexes, levels off at approximately 15%–20%. This is likewise reflected in the mean yields, with all complexes giving values between 17% and 21%, again showing only little variation, as already observed for the loadings. A decrease in catalytic performance after immobilization of the homogeneous system is not uncommon as attachment to a support material may hinder substrate access or reduce the accessibility of vacant coordination sites at the copper center. Chloride-containing buffers were also employed. The presence of chloride anions has been reported to interfere with copper-catalyzed aziridination as chloride can remain coordinated to the active site and thereby alter the reaction pathway [57]. However, our previous results indicate that this effect becomes less pronounced when the reaction is performed under air since hydroxy or aqua ligands preferentially coordinate to the copper center under these conditions [31]. The near-uniformity of the results is nevertheless unexpected since different ligands were employed that had been specifically designed to enhance reactivity and increase yields. If the complexes were immobilized predominantly via covalent attachment, the loss of activity, and thus the similarity of the results, might be rationalized by binding through the secondary amine at N³, which is known to cause a significant decrease in activity, turning it into a tertiary amine. However, the loading results, in particular, the high loadings obtained for complexes lacking a nucleophilic group, indicate that covalent immobilization is unlikely to be the dominant process in this system and that noncovalent interactions with the agarose matrix may instead be largely responsible for the immobilization. This interpretation was further supported by a control experiment in which the epoxy groups of the agarose support were blocked prior to immobilization with $[(L^3)Cu^{II}(MeCN)](OTf)_2$ so that covalent binding of the complex is suppressed (Table S3). Although this treatment resulted in a lower overall loading of 37%, the catalytic performance over six consecutive reaction cycles remained comparable to that of the corresponding unblocked material, which gave an average yield of $18.8\% \pm 4.3\%$. An alternative explanation for the similar catalytic performance could be a convergence of the different complexes to similar copper species during immobilization. Although this possibility cannot be fully

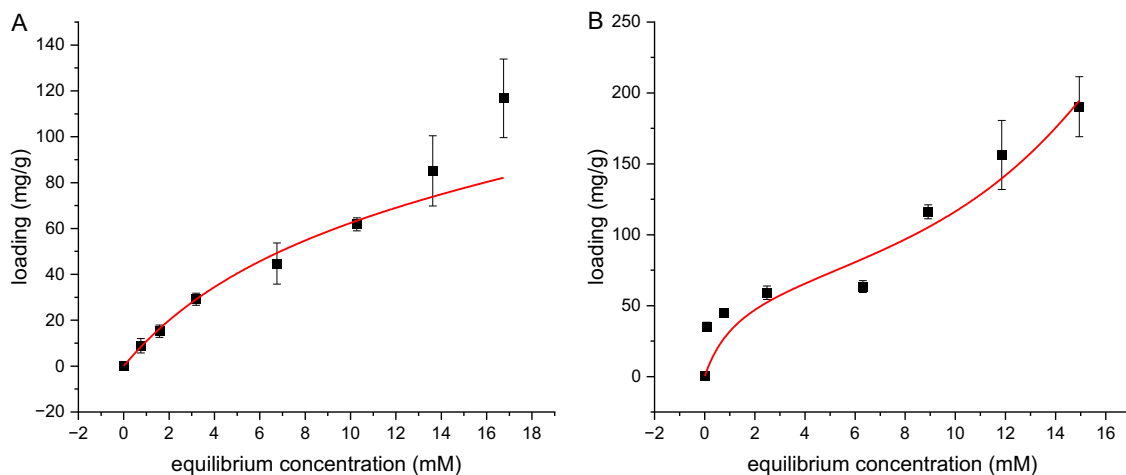


FIGURE 3 | Loading isotherms of A: $[(L^1)Cu^{II}(MeCN)](OTf)_2$ and B: $[(L^2)Cu^{II}(MeCN)](OTf)_2$ in water. Note: Bead size for loading isotherm with $[(L^1)Cu^{II}(MeCN)](OTf)_2$ was 50–150 μm . Error bars represent the standard deviation of three independent measurements ($n = 3$).

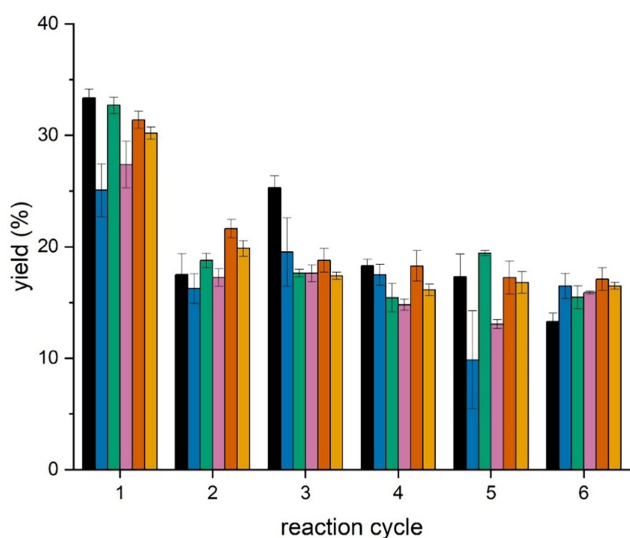


FIGURE 4 | Overview of yields in heterogeneous reactions with various copper complexes across six reaction cycles: black: $[(L^1)Cu^{II}(MeCN)](OTf)_2$, blue: $[(L^2)Cu^{II}(MeCN)](OTf)_2$, green: $[(L^3)Cu^{II}(MeCN)](OTf)_2$, purple: $[(L^4)Cu^{II}(MeCN)](OTf)_2$, red: $[(L^5)Cu^{II}(MeCN)](OTf)_2$, yellow: $[(L^6)Cu^{II}(MeCN)](OTf)_2$. Loadings of immobilisates can be taken from Table 3. Error bars represent the standard deviation of three independent measurements ($n = 3$).

excluded, the lower activity of ligand-free immobilized $Cu^{II}(OTf)_2$ despite its substantially higher loading argues against complete conversion of all systems into an identical simple copper species. Nevertheless, direct spectroscopic characterization would be required to establish the coordination environment of the immobilized copper centers conclusively. In addition to interactions between the complexes and the support, retention of substrate or product within the agarose matrix could in principle also contribute to the near-uniform product yields observed for the different immobilized catalysts. A catalyst-free control containing epoxy-activated agarose and styrene indeed showed substantial styrene depletion (Figure S28), demonstrating that interactions of the reaction components with the support cannot be neglected. If irreversible product retention at a finite number of adsorption sites was the dominant factor, progressive saturation of these sites

might be expected to result in increased product recovery during repeated use of the same immobilized material. Such an increase was not observed over six consecutive cycles. However, other effects, including reversible partitioning, substrate adsorption, or changes in mass transport associated with occupation of the agarose matrix, cannot be excluded. The present data therefore argue against a simple progressive saturation model but do not allow support-related retention effects to be ruled out.

A particularly noteworthy result is obtained for $[(L^6)Cu^{II}(MeCN)](OTf)_2$, which is the only complex that, contrary to the expected trend upon immobilization, exhibits a higher yield than under homogeneous conditions, increasing from 13% to 20%. Under homogeneous conditions, $[(L^6)Cu^{II}(MeCN)](OTf)_2$ is a very slowly reacting complex, displaying a TOF of $1.3\ h^{-1}$ under argon with a resulting yield of 35% [27]. As the reactions in the present study were carried out under air, the active copper(I) species may be readily reoxidized to copper(II), and this effect may be particularly pronounced for such a slowly turning-over system. The improved performance of the immobilized material is therefore consistent with restricted oxygen transport within the agarose matrix, which may reduce reoxidation of the active species [58]. However, such diffusional limitations would also affect the transport of substrate and oxidant. The similar yields obtained for the different immobilized copper complexes may therefore reflect a mass-transfer-limited regime in which differences in intrinsic catalyst reactivity are partly masked. A detailed kinetic analysis would be required to establish this mechanism conclusively, but the substantially slower increase in product yield observed for the immobilized catalyst $[(L^1)Cu^{II}(MeCN)](OTf)_2$ compared with the homogeneous reaction is consistent with reduced accessibility of the active sites and mass-transfer limitations within the agarose matrix (see Figure S27).

As incubation concentrations corresponding to the available epoxy group content were found to be particularly favorable for achieving high loadings, the influence of catalyst loading was investigated in more detail. Additional immobilizations were therefore performed using complex concentration of 10 mM. This resulted in loadings of $16.7\% \pm 0.7\%$ for $[(L^1)Cu^{II}(MeCN)](OTf)_2$ and $18.0\% \pm 0.8\%$ for $[(L^4)Cu^{II}(MeCN)](OTf)_2$. As described above, these immobilisates were used for six consecutive catalytic

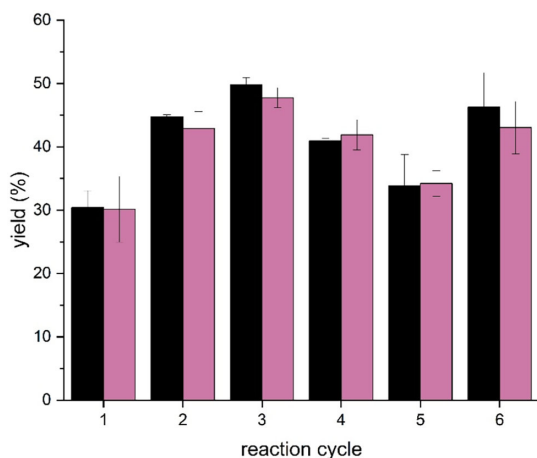


FIGURE 5 | Overview of yields in heterogenous reactions with: $[(L^1)Cu^{II}(MeCN)](OTf)_2$ (black) and $[(L^4)Cu^{II}(MeCN)](OTf)_2$ (purple) across six reaction cycles. Loadings were $16.7 \pm 0.7\%$ for $[(L^1)Cu^{II}(MeCN)](OTf)_2$ and $18.0 \pm 0.8\%$ for $[(L^4)Cu^{II}(MeCN)](OTf)_2$ (cat:ox:substrate 1:20:100, MeCN, RT, 19–24h under air), error bars represent the standard deviation of three independent measurements ($n = 3$).

reaction cycles, and the corresponding results are shown in Figure 5. Mean yields of $41.0 \pm 7.4\%$ and $40.0 \pm 6.5\%$ were obtained for $[(L^1)Cu^{II}(MeCN)](OTf)_2$ and $[(L^4)Cu^{II}(MeCN)](OTf)_2$,

respectively. These values are approximately twice as high as the mean yields obtained for the corresponding highly loaded immobilisates ($20.8 \pm 6.8\%$ and $17.7 \pm 4.7\%$). The increase in yield observed upon reducing the complex concentration used for immobilization may arise from several effects. First, at lower complex concentrations, the relative contribution of selective covalent attachment to the epoxy functionalities of the support may increase, resulting in a larger fraction of the immobilized complexes being present in a catalytically accessible form. Second, nonspecific interactions with the agarose matrix may become more pronounced at higher complex concentrations. Such interactions, for example, between the copper(II) center and functional groups of the support, could alter the coordination environment or orientation of the complex and thereby hinder substrate access to the copper center. In addition, high local complex densities may lead to accumulation or spatial crowding of the immobilized complexes within the porous network, further limiting the steric or diffusional accessibility of individual active sites. Lower catalyst loadings may therefore result in a more favorable spatial distribution and more efficient utilization of the available catalytic centers. Notably, the product yield also remained comparatively stable over six consecutive reaction cycles at the lower loading, whereas the highly loaded materials showed a pronounced decrease after the first cycle. This shows that catalyst density and active site accessibility strongly influence the performance of the immobilized system.

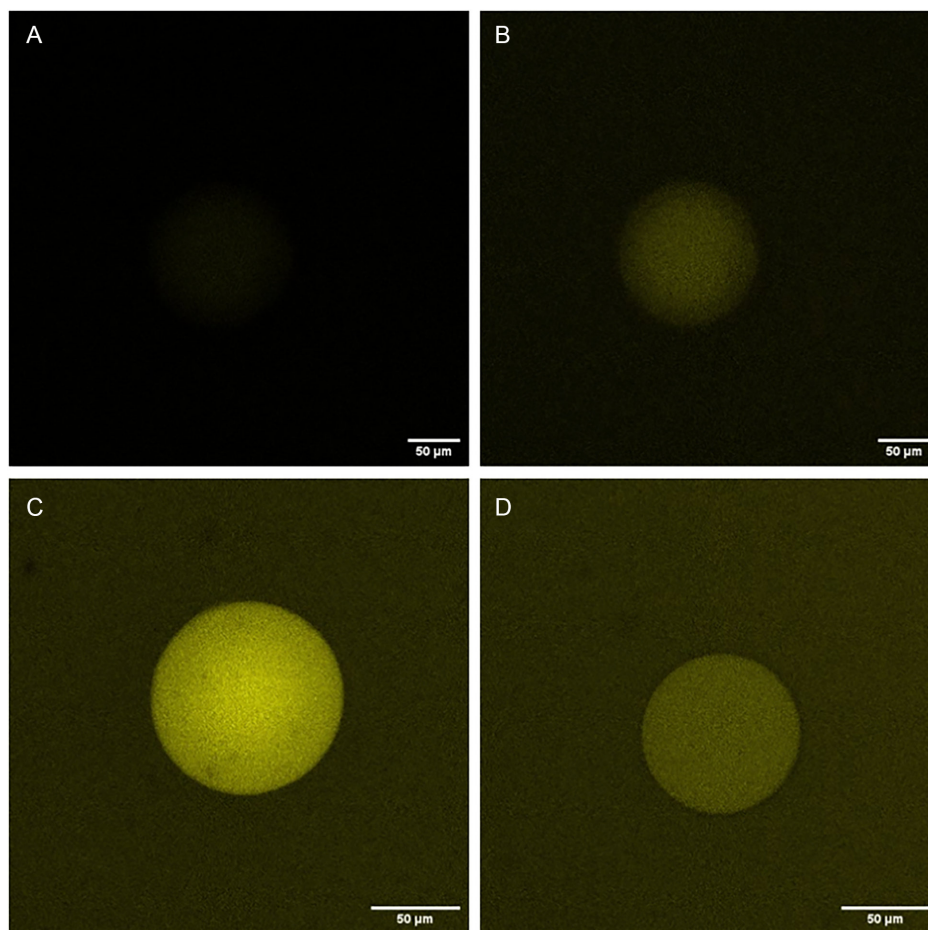


FIGURE 6 | Confocal laser scanning microscopy with A: pure agarose beads; B: agarose beads with Lucifer Yellow ($5 \mu M$) and preloaded agarose beads with C: $Cu^{II}(OTf)_2$ ($q_m = 158.3 \text{ mg/g}$, $q = 99.6\%$) and Lucifer Yellow ($5 \mu M$); D: $[(L^3)Cu^{II}(MeCN)](OTf)_2$ ($q_m = 136.7 \text{ mg/g}$, $q = 39.6\%$) and Lucifer Yellow ($5 \mu M$).

Remarkably, $[(L^1)Cu^{II}(MeCN)](OTf)_2$ and $[(L^4)Cu^{II}(MeCN)](OTf)_2$ exhibited very similar product yields at both high and low catalyst loadings, despite differences observed for the corresponding homogeneous catalysts. Even more strikingly, the effect previously observed for $[(L^6)Cu^{II}(MeCN)](OTf)_2$ is now also apparent for $[(L^4)Cu^{II}(MeCN)](OTf)_2$: under the lower loading conditions, the heterogeneous reaction afforded a higher yield than the corresponding homogeneous reaction performed under air ($40.0\% \pm 6.5\%$ vs. $26.8\% \pm 3.5\%$). This behavior may arise, as stated above, from restricted oxygen transport within the agarose matrix, thereby decreasing reoxidation of the catalytically active copper(I) by reducing local oxygen availability. The same transport restrictions are expected to affect the diffusion of substrate and reagents to the active sites, reflected again in the observed similar yields for $[(L^1)Cu^{II}(MeCN)](OTf)_2$ and $[(L^4)Cu^{II}(MeCN)](OTf)_2$ in the heterogeneous reaction. It cannot be excluded that a further optimization of catalyst loading could improve the utilization efficiency of the immobilized copper centers. However, an optimum loading is expected since at sufficiently low catalyst densities the number of available active sites will become limiting. The loading applied within the low-loading regime of the S-shaped adsorption isotherm therefore appears to provide a more favorable balance between catalyst accessibility and active site density, although additional loading levels would be required to identify the catalytic optimum.

3.3 | Determination of Loading in Pores

Since the previous experiments indicated that immobilization most likely occurs primarily through noncovalent interactions, CLSM and ATR-FTIR measurements were performed to further investigate the copper-dependent probe distribution within the agarose beads and the nature of their interaction with the support material. For CLSM, preloaded agarose beads containing either $Cu^{II}(OTf)_2$ or $[(L^3)Cu^{II}(MeCN)]^{2+}$ were used, and Lucifer Yellow (LY) was subsequently pipetted onto the beads as fluorescence probe. The corresponding images are shown in Figure 6. The fluorescence intensity distributions across the bead cross-sections are shown in Figures S30 and S31; the original data files are available via the DOI provided in the

Supporting Information. In the absence of copper species, only weak LY fluorescence was observed within the beads (Figure 6B). In contrast, copper-containing beads showed markedly increased fluorescence across the bead volume, indicating that the presence of copper species strongly affects the uptake or retention of LY within the porous agarose matrix. The effect was observed for both $Cu^{II}(OTf)_2$ and $[(L^3)Cu^{II}(MeCN)]^{2+}$, with the highest fluorescence intensity observed for the free copper salt. This behavior appears at first sight counterintuitive since copper(II)-induced quenching of LY fluorescence is well documented. However, fluorescence quenching depends strongly on the local proximity, coordination environment, and spatial arrangement of the metal center and the fluorophore [59–62]. While copper(II)-induced turn-on fluorescence is known for selected fluorophore systems, no such effect has, to the best of our knowledge, been described for LY; therefore, the increased bead fluorescence observed here is more likely attributable to matrix-mediated uptake or retention effects rather than intrinsic fluorescence enhancement by copper(II) [63–67]. At neutral or basic pH, LY is negatively charged and can therefore interact electrostatically with copper ions, particularly with the solvated copper cations derived from the copper salt. This may enhance retention of the fluorescent dye within the bead volume and, despite the quenching effect of Cu^{II} ions, lead to an overall increase in bead fluorescence. In Figure 6B, where only LY was used, retention of LY within the bead is low, and the bead is only faintly visible. Thus, the CLSM experiments support the conclusion that the porous agarose network is accessible throughout their internal volume and that copper species affect probe distribution within the pore network. To further assess whether the interaction between the immobilized complex and the support involves covalent binding or predominantly adsorptive retention, ATR-FTIR spectra were recorded.

ATR-FTIR measurements were used in order to monitor changes in the epoxy vibrations after the immobilization of complexes $[(L^3)Cu^{II}(H_2O)](OTf)_2$ and $[(L^4)Cu^{II}(H_2O)](OTf)_2$. The recorded spectra are shown in Figure 7 (full spectra are given in the Supporting Information, Figures S32–39). In particular, two regions of the ATR-FTIR spectrum are of interest. The first is located around 3050 cm^{-1} , where the C–H stretching vibration of the oxirane group can be observed.

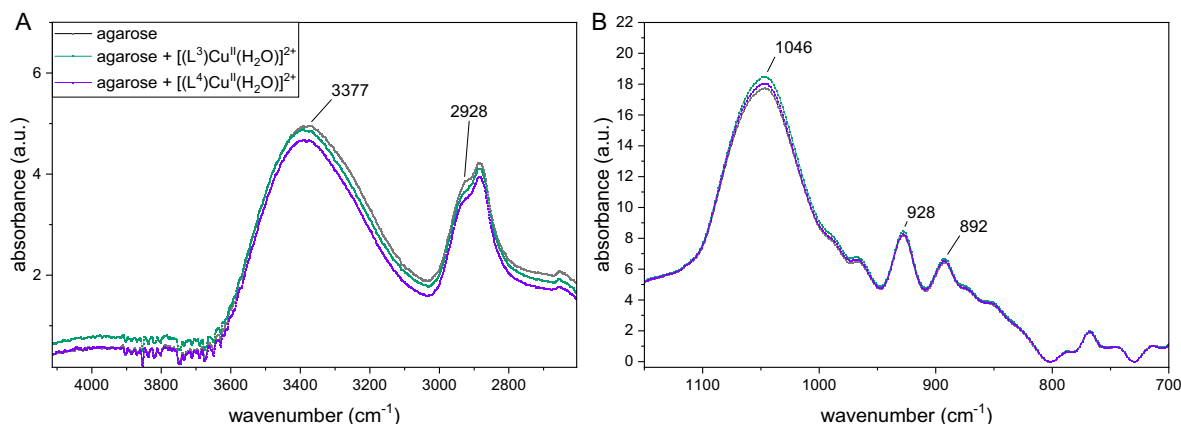


FIGURE 7 | ATR-FTIR spectra of untreated agarose (gray) and samples loaded with 43.7% $[(L^3)Cu^{II}(MeCN)](OTf)_2$ ($q_m = 151.1\text{ mg/g}$, green) and 52.9% $[(L^4)Cu^{II}(MeCN)](OTf)_2$ ($q_m = 193.2\text{ mg/g}$, purple). Shown are different spectral sections: A: the oxirane C–H stretching region around 3050 cm^{-1} and B: the region containing symmetric and asymmetric C–O–C stretching modes of the oxirane ring around 900 cm^{-1} , as well as ether C–O–C stretching vibrations between 1030 and 1100 cm^{-1} . A baseline correction was applied by setting the absorbance at 4497 cm^{-1} to zero.

The second lies in the region around 900 cm^{-1} , where characteristic vibrations of the oxirane ring are found, including both symmetric and asymmetric C—O—C stretching modes [68–70]. Additionally, vibrations corresponding to the C—O—C stretching mode of ethers can be found between 1030 and 1100 cm^{-1} [71]. However, no significant spectral changes were observed after immobilization of the complexes. Only the shoulder at 2928 cm^{-1} appears to be slightly less intense after immobilization, whereas the characteristic oxirane bands in the region around 900 cm^{-1} remain largely unchanged. Considering the substantial loading of the support material, the persistence of these oxirane-related bands indicates that extensive consumption of epoxy groups is unlikely to account for the overall immobilization. These results therefore suggest that covalent reaction with the epoxy functionalities, if present, contributes only to a minor extent to the total loading, while other interactions with the porous agarose network appear to play a major role.

4 | Conclusion

In conclusion, copper(II)-bispidine complexes can be immobilized on agarose beads to provide reusable heterogeneous catalysts with negligible copper leaching. The presented results, however, demonstrate that immobilization is not dominated by covalent attachment but by uptake into the porous agarose network. At high catalyst loadings, the different immobilized complexes exhibited comparable catalytic performances, consistent with limited active-site accessibility that partly mask the intrinsic reactivity differences observed for the corresponding homogeneous catalysts. Importantly, lowering the catalyst loading substantially improved catalytic performance, resulting in average yields of up to 40% over six consecutive reaction cycles. For slowly reacting complexes, immobilization could even lead to higher yields than under homogeneous conditions under air, despite the transport limitations generally associated with immobilized systems, an effect that may be related to restricted oxygen access to the active Cu^{I} species within the support. These findings identify catalyst loading, active site accessibility, and transport within the support as key parameters governing catalytic performance and show that, under suitable conditions, immobilization can create a beneficial local reaction environment. Overall, this study therefore establishes agarose-supported copper-bispidine complexes as stable and reusable catalyst systems and provides design principles for the further development of related immobilized catalysts.

Author Contributions

The first draft of the manuscript was written by Katharina Bleher and Nadjana Schneider, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Conceptualization (Katharina Bleher), Investigation (Nadjana Schneider, Sebastian Putz, Sebastian Fleer, Stefan Heißler, Jonas Braun, Eric Gottwald, André Tschöpe, and Katharina Bleher), Visualization (Nadjana Schneider, Katharina Bleher), Validation (Nadjana Schneider, Katharina Bleher), Methodology (Nadjana Schneider, Sebastian Putz, Katharina Bleher), Formal Analysis (Nadjana Schneider, Katharina Bleher), Software (Sebastian Putz), Supervision (Katharina Bleher).

Acknowledgments

The authors thank Matthias Franzreb for the access to their laboratories. Furthermore, the authors thank Marita Heinle from KIT for performing the ICP-OES analyses, Peter Comba for providing the opportunity to perform EA measurements, and Christopher Anson for his help with crystallography. Moreover, the authors would like to thank Juliane Diehm, Thomas Josephy and Matthias Franzreb for the fruitful discussions. This work was partly carried out with the support of the Karlsruhe Nano Micro Facility (KNMFi, www.knmf.kit.edu), an Open Access Research Infrastructure within the Karlsruhe High Technology Hub at the Karlsruhe Institute of Technology (KIT – The University in the Helmholtz Association, www.kit.edu). During the preparation of this manuscript, the authors used ChatGPT (GPT-5.4 Thinking and GPT-5.6 Sol) to improve the clarity, readability, grammar, and language quality of the text. These tools were used solely for language refinement (e.g., wording, sentence structure, and prepositions). The authors carefully reviewed and edited the output as necessary and take full responsibility for the content of the publication.

Open Access funding enabled and organized by Projekt DEAL.

Funding

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.