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Recyclable catalyst for the asymmetric Henry reaction based on functionalized imidazolidine-4-one-copper(II) complexes supported by a polystyrene copolymer

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ABSTRACT

Imidazolidine-4-one derivatives were anchored by the thiol-ene click reaction to a swellable pearl-like polystyrene copolymer and their complexes with Cu(II) acetate were utilized as recyclable heterogeneous catalysts for the Henry reaction of substituted aldehydes with nitromethane. The corresponding 2-nitroethanols were mostly obtained in high yields (65–99%) and with enantioselectivities of up to 92% ee. After a fivefold recycling of the catalyst, the decrease in enantioselectivity was negligible (Δ 3% ee).

The asymmetric variant of the Henry reaction, between the α-carbon atom of an aliphatic nitro compound and the carbonyl carbon atom, produces up to two stereogenic centers.[1,2] The prepared functionalized 2-nitroethanols represent important synthetic building blocks that have been used in the syntheses of many poly-functionalized compounds, especially pharmaceutical substances.[1i,2c,d] Implementation of this reaction necessitates the presence of a suitable catalyst, frequently represented by Cu(II) complexes based on enantiomerically pure ligands.[1,2] However, a disadvantage of most homogeneous catalysts consists of their difficult separation after reaction completion, which prevents their reuse. In order to facilitate their isolation, purification and allow recycling, a number of efficient homogeneous catalysts have been anchored to an heterogeneous carriers,[3] including those suitable for the asymmetric Henry reaction.[3–5] The key factor for the efficiency of these heterogeneous catalysts has been determined as the high swellability of a pearl-like polymeric carrier,[6,7] which for example include the copolymer of styrene, 4-vinylbenzyl chloride and tetra(ethylene glycol)-bis(4-vinylbenzyl)ether (cross-linker 2%).[5] Previously our group reported an immobilized copper (II) complex of (1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane as an efficient catalyst for the Henry reaction.[5] Unfortunately, this diamine-type catalyst displayed low stability against oxidation which is considered as a general disadvantage for the long-term use of recyclable catalysts. Therefore, we elected to anchor more stable chiral ligands based on previously reported 2-(pyridine-2-yl)imidazolidine-4-one derivatives to the above-mentioned pearl-like styrene copolymer. Thus, the research presented herein describes the preparation and characterization of these heterogeneous catalysts and an examination of their catalytic efficiency and recyclability.

Among the 5-alkyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one derivatives described thus far, ligands based on the 5-isopropyl and 5-*tert*-butyl derivatives represent the most catalytically efficient variants when compared to the corresponding 5-benzyl derivatives.[2a,b,d] For this reason, (2*R*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)-3-(4-vinylbenzyl)imidazolidine-4-one (**3a**) and (2*S*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)-3-(4-vinylbenzyl)-imidazolidine-4-one (**3b**) were prepared (Scheme 1).

The synthesis of isopropyl derivatives **3a** and **3b** began with easily accessible (*S*)-2-amino-2,3-dimethylbutanamide.[2a] Hydrolysis to the hydrochloride of (*S*)-2-amino-2,3-dimethylbutanoic acid was followed by treatment with phosgene to give the corresponding *N*-carboxanhydride, (*S*)-4-isopropyl-4-methyloxazolidine-2,5-dione (**1**). The 4-vinylbenzyl group was next introduced in order to enable anchoring of the imidazolidine-4-one fragment to the polymer by means of a thiol-ene click reaction.[8] Reaction of *N*-carboxanhydride with 4-vinylbenzylamine[9] gave (*S*)-2-amino-2,3-dimethyl-*N*-(4-vinylbenzyl)butanamide (**2**), which underwent acid-catalyzed ring-closure

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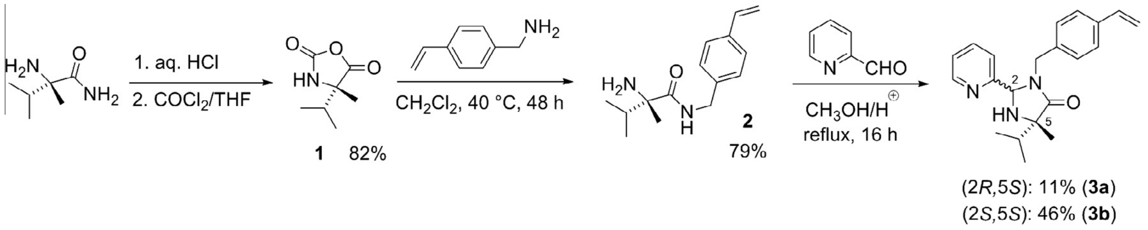


Scheme 1. Preparation of enantiomerically pure ligands **3a** and **3b**.

with pyridine-2-carbaldehyde to give a diastereomeric mixture of **3a** and **3b** (1:4) which could be separated by column chromatography. The configuration of the newly formed stereogenic center at the 2-position of **3a** and **3b** was determined by ^{1}H NMR NOESY spectroscopy.[10] The pearl-like copolymer ligand carrier was prepared according to literature procedures[5] and functional group interchange of the chlorine for thiol was achieved by the reaction with thiourea and subsequent hydrolysis of the isothiouronium salt.[11] Finally, the ligands were anchored to the modified polymer by means of a thiol-ene click reaction (Scheme 2).[8]

Initially, the thermal variant of the thiol-ene click reaction, initiated by thermal decomposition of azobisisobutyronitrile (AIBN) at reflux in toluene, was examined (Method A).[8a] However, since heating of ligands **3a** and **3b** may be accompanied by racemization, a second variant was also selected for implementation (Method B). This photochemical reaction which proceeded at 25 °C was initiated by the photo-induced decomposition of 2,2-dimethoxy-2-phenylacetophenone (DPAP) using a UV–visible lamp (λ_{max} 365 nm, 40 W).[8b] Subsequently, the modified polymers **4a** and **4b** were transformed by the reaction with cupric acetate to give the corresponding catalyst complex **5a** and **5b** (Scheme 2). The starting mercaptomethyl polystyrene as well as polymers **4a** and **4b** and catalysts **5a** and **5b** were purified by extraction, and after drying, characterized by microanalysis and Raman spectroscopy (Fig. 1).[12] The nitrogen contents in **4a** and **4b** indicated ligand loading on the polymer carrier. The Raman band at 2572 cm^{-1} (S—H stretching vibrations) and bands at 675 and 1251 cm^{-1} (C—S stretching vibrations) typical for the SH group were observed and corresponded to the mercaptomethyl polystyrene (Fig. 1a).[11] A new band at 1703 cm^{-1} (stretching vibration C=O) corresponded to polystyrenes **4a** and **5a** with grafted ligand **3a** (Fig. 1b and c). The band at 2572 cm^{-1} disappeared in the spectrum of **4a** and **5a** showing that ligand **3a** was well anchored to the polystyrene by a covalent bond via a —S— bridge. The new bands at 1410 and 1510 cm^{-1} (COO stretching symmetric and asymmetric vibrations), after coordination of copper(II) acetate, corresponded to the acetate functional group in **5a** (Fig. 1c). The Raman spectra of both **4a** and **4b** were identical as well as the spectra of catalysts **5a** and **5b**.

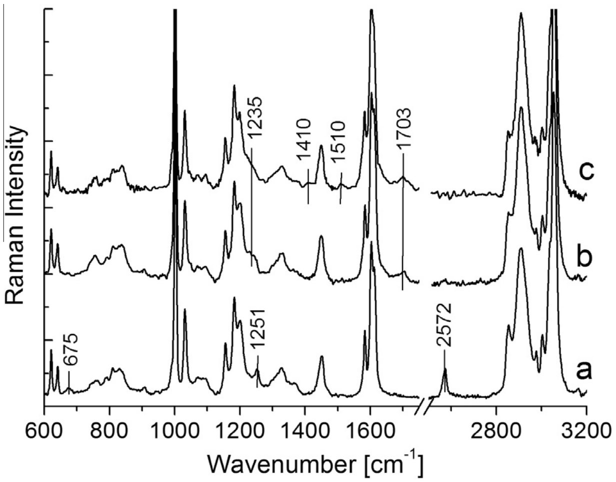
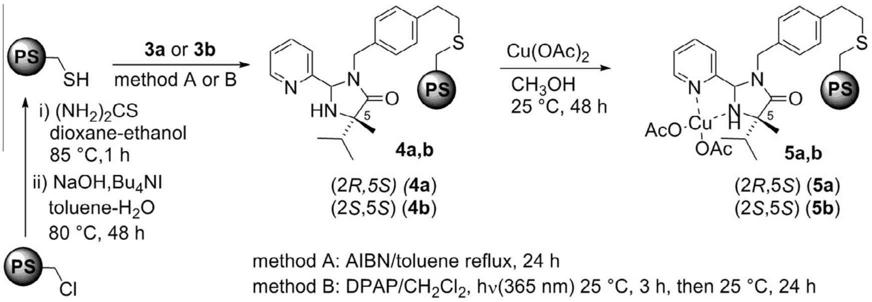


Figure 1. Raman spectra of the mercapto-polystyrene (a); polymer **4a** (b) and catalyst **5a** (c).

The synthesized catalysts were then tested in the Henry reaction of nitromethane with various aldehydes in ethanol at 10 °C (Table 1).

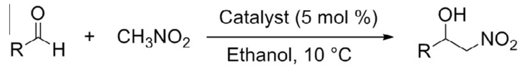
First, we examined the catalytic activity of soluble complexes of cupric acetate with ligands **3a,b** which were prepared in situ. The complex using ligand (2*R*,5*S*)-**3a** gave the corresponding 2-nitroethanols with the (*R*) configuration, whereas (2*S*,5*S*)-**3b** gave products with an (*S*) configuration.[1] The results given in Table 1 (entries 1–8) showed that introduction of the 4-vinylbenzyl group onto the 3-position of the imidazolidine skeleton led to an approximate fourfold decrease of the reaction rate in comparison to the previously reported non-functionalized ligand.[2a] On the other hand, imidazolidine-4-one (2*S*,5*S*)-**3b** bearing the 4-vinylbenzyl group proceeded with high enantioselectivity (80–85% ee), in comparison to the previously studied non-substituted (2*S*,5*S*)-derivative (25–27% ee);[2a] therefore **3b** can be also considered for immobilization.



Scheme 2. Preparation of catalysts **5a** and **5b**.

Table 1

Henry reaction of nitromethane with various aldehydes catalyzed by Cu(II) complexes of **3a**,**b** and polymeric catalysts **5a**,**b** prepared by method A or B



Entry	R	Catalyst	Time (days)	Conv[a]/Yield[b] (%)	ee[c,e] (%)
1	Ph	**3a**/Cu(OAc)$_2$	6	92 (78)	89
2	Ph	**3b**/Cu(OAc)$_2$	6	65 (59)	−85
3	2-CH$_3$OPh	**3a**/Cu(OAc)$_2$	6	96 (81)	88
4	2-CH$_3$OPh	**3b**/Cu(OAc)$_2$	6	98 (80)	−80
5	4-NO$_2$Ph	**3a**/Cu(OAc)$_2$	5	>99 (82)	81
6	4-NO$_2$Ph	**3b**/Cu(OAc)$_2$	6	98 (78)	−81
7	*t*-Bu	**3a**/Cu(OAc)$_2$	3	86[d]	96
8	*t*-Bu	**3b**/Cu(OAc)$_2$	6	64[d]	−82
9	2-CH$_3$OPh	**5a** (A)	6	35 (28)	80
10	2-CH$_3$OPh	**5a** (B)	6	59 (49)	76
11	2-CH$_3$OPh	**5b** (A)	6	48 (33)	−42
12	2-CH$_3$OPh	**5b** (B)	5	99 (91)	−47
13	4-NO$_2$Ph	**5a** (B)	5	>99 (87)	51
14	4-NO$_2$Ph	**5b** (B)	6	99 (80)	−29
15	*t*-Bu	**5a** (B)	6	95[d]	92
16	*t*-Bu	**5b** (B)	6	66[d]	−69

[a] Values of conversions were estimated by ^{1}H NMR spectroscopy.

[b] The yields of isolated products after chromatographic purification are in parentheses.

[c] The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column.[2a]

[d] Only the chemical yields (not conversions) were determined due to the volatility of pivaloyl aldehyde.

[e] The absolute configurations of prepared 2-nitroethanols were determined by comparison to literature HPLC data.

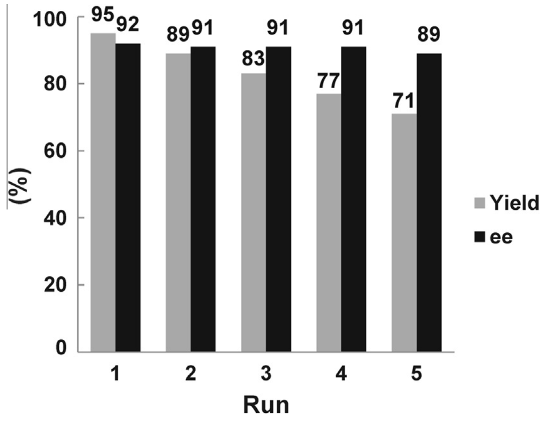


Figure 2. Recoverability of catalyst **5a** (up to 5 times) in the catalytic enantioselective Henry reaction of MeNO$_2$ with *t*-BuCHO.

Furthermore, we studied the catalytic activities of the heterogeneous polymer supported catalysts **5a**,**b** (entries 9–16). In comparison to the corresponding homogeneous catalysts, it was found that in all cases, the enantioselectivity was decreased. On the other hand, in most cases a decrease in conversion due to the presence of the polymeric matrix was not observed. The largest difference in enantioselectivity was observed between the homogeneous complex of ligand **3b** and heterogeneous catalyst **5b** (B) for the reaction of 4-nitrobenzaldehyde (entries 6 and 14). This decrease could most likely be ascribed to the interaction of the electron-deficient benzene ring of 4-nitrobenzaldehyde with the electron-rich polymeric matrix which helped overcome the energetically less advantageous transition states leading to the opposite enantiomer. The smallest difference (Δ 4% ee) was found for the reaction of pivaloyl aldehyde with nitromethane catalyzed by complex **3b** and catalyst **5b** (B) (entries 7 and 15). Moreover, we compared the enantioselectivity differences of the catalysts prepared by anchoring ligands using the thermal method **5a**,**b** (A) (Method A) and the photochemical method **5a**,**b** (B) (Method B). The observed difference in product enantiomeric purity in the case of the reaction of 2-methoxybenzaldehyde catalyzed with **5b** (A) and **5b** (B) was only minor (Δ 4–5% ee) (entries 9 vs 10 and 11 vs 12). This finding indicated that thermal exposition of the ligand did not cause partial racemization, and that it was stable under the conditions examined.

Finally, we also tested the possibility of recycling using catalyst **5a** for the model reaction of pivaloyl aldehyde with nitromethane (Fig. 2). After five reaction cycles only a small reduction of enantioselectivity (92–89% ee) was observed. However, the decrease in yield was more significant, decreasing from 95% to 71%, and was interpreted, as in the previous case,[3c] as being due to catalyst mass loss during recycling.

In conclusion, newly prepared (2*R*,5*S*)- (**3a**) and (2*S*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)-3-(4-vinylbenzyl)imidazolidine-4-one (**3b**) were successfully anchored via the thiol-ene click reaction to mercaptomethyl polystyrene to give recyclable heterogeneous enantioselective catalysts **5a**,**b**. The application of these catalysts **5a**,**b** to the Henry reaction resulted in some cases to a decrease of enantioselectivity, which is commonly observed after immobilization of enantioselective catalysts.[3] The use of reagents on a polymeric carrier matrix did not practically affect the observed catalytic activity and the conversions obtained with supported catalysts **5a**,**b** were comparable to the conversions afforded by the analogous homogeneous catalysts **3a**,**b**. Fivefold recycling of the heterogeneous catalyst caused a significant decrease in yield (Δ 25%), but only a minor decrease of enantioselectivity was observed. The newly synthesized 4-vinylbenzyl ligands have high potential for the preparation of mechanically robust monolithic columns for a flow reactor. The synthesized ligands and catalysts possess a potential for application in the Henry reaction.

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Supplementary data

Supplementary data (the synthetic procedures, NMR spectra and HPLC data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.112.

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