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Recyclable Enantioselective Catalysts Based on Copper(II) Complexes of 2-(Pyridine-2-yl)imidazolidine-4-thione: Their Application in Asymmetric Henry Reactions

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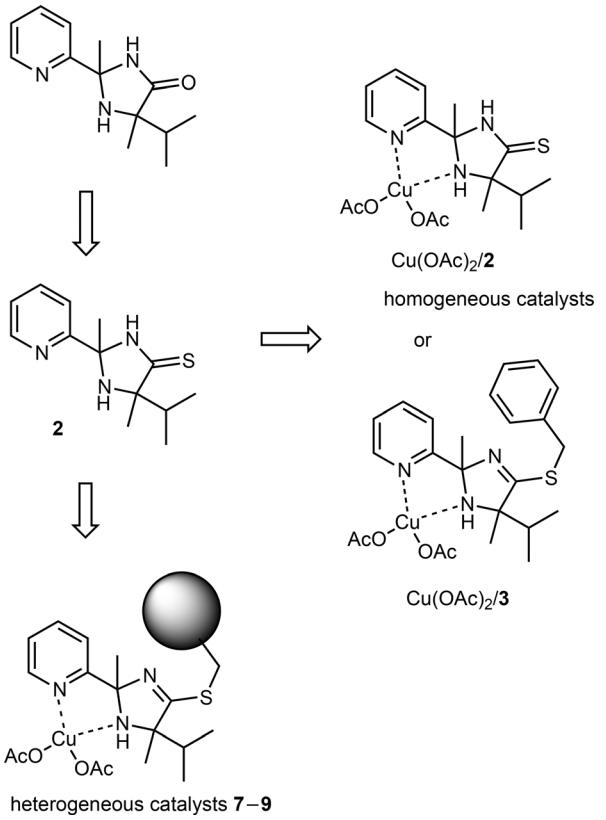
Abstract: This paper describes the preparation of enantioselective catalysts based on derivatives of imidazolidine-4-thione and their subsequent anchoring by means of a sulfur atom on a polymeric carrier. First, we verified the catalytic activity and enantioselectivity in the Henry reaction of the homogeneous variants of the catalysts, i.e., the copper(II) complexes of 2-(pyridine-2-yl)imidazolidine-4-thiones and 4-benzylsufanyl-2-(pyridine-2-yl)imidazolines themselves. It was found that these catalysts exhibit high enantioselectivity (up to 98% *ee*). Subsequently, the imidazolidine-4-thione catalysts were immobilized by anchoring to polymeric carriers based on a copolymer of styrene and 4-vinylbenzyl chloride. These heterogeneous catalysts were analogously tested with regard to their catalytic activity and enantioselectivity in the Henry reaction, and moreover, the possibility of their separation and reuse was studied. It was found that all the prepared immobilized catalysts are highly enantioselective (up to 97% *ee*). Their recycling ability was tested in Henry reaction of 2-methoxybenzaldehyde with nitromethane. It was found that they can be recycled more than ten times without any decrease of their enantioselectivity. Therefore, they present a better means of catalysis than the original copper(II) complexes of imidazolidine-4-ones from both economic as well as ecological points of view. Thus, such immobilized catalysts exhibit high application potential for the asymmetric Henry reaction.

Keywords: asymmetric catalysis; enantioselectivity; heterogeneous catalysis; immobilization; supported catalysts

Introduction

During the last two decades, a considerable number of homogeneous enantioselective catalysts has been developed, with the aim to enable the preparation of various chiral compounds having high optical purity.[1] However, the main disadvantage of these homogeneous catalysts is often a limited possibility of separation and recycling which would be highly desirable with regard to their price and (in many cases) toxicity, i.e., with respect to the economic and ecological aspects of the catalytic process. This problem can generally be solved by modification of homogeneous catalysts into more easily separable forms (e.g., using a release-capture strategy,[2a,b] by employing their insolubility in appropriate solvents[2c–f]) or application of immobilization of the homogeneous catalyst – its anchoring to an easily separable solid carrier. Suitable carriers of homogeneous catalysts include, e.g., polymers soluble in the reaction medium or spherical highly swelling polymers;[2g] furthermore, the group involves different types of inorganic carriers.[2h] However, each of these types of carriers has both more or less serious advantages and disadvantages.[2]

In the case of our original enantioselective catalysts[3] for the asymmetric Henry reaction based on copper(II) complexes of 2-(pyridine-2-yl)imidazolidine-4-one derivatives, we have recently studied their anchoring on three types of carriers: the block copolymer methoxypoly(ethylene glycol)-*b*-poly(L-glutamic acid),[4] the pearl-type swelling copolymer poly-[styrene-*co*-4-vinylbenzyl chloride-*co*-tetra(ethylene glycol)-bis(4-vinylbenzyl) ether)][5] and the magnetic nanoparticles Fe_3O_4@SiO_2.[6] However, in all the cases



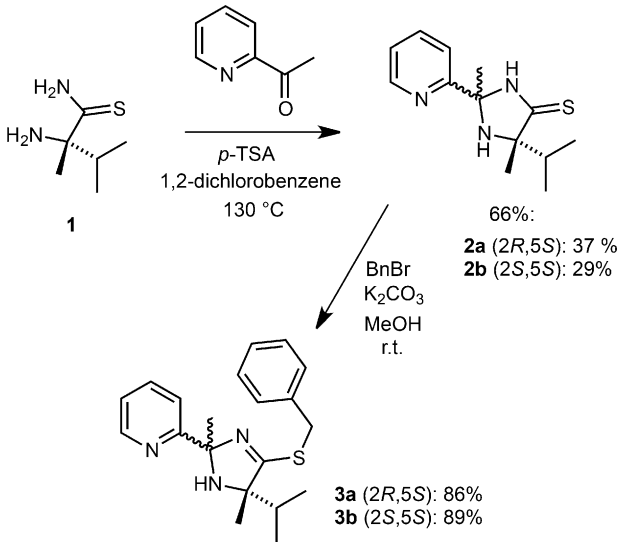
Scheme 1.

we observed a certain decrease in enantioselectivity as well as in catalytic activity of immobilized catalysts as compared with the original homogeneous forms. This fact challenged us to continue in the search leading to an increase of these key parameters of the enantioselective catalyst.

The new strategy of immobilization of 2-(pyridine-2-yl)imidazolidine-4-one derivatives consists in a simple modification of their structure – isolobal replacement of the oxygen atom in imidazolidine-4-one cycle by sulfur – which allows anchoring of the ligand to a polymeric carrier (e.g., Merrified™ resin, JandaJel™ resin, etc.)[7] by means of an alkylation reaction involving formation of a covalent C–S bond (Scheme 1). Thus, the aim of this present research was the verification of the catalytic activity and enantioselectivity of both copper(II) complexes of newly prepared 2-(pyridine-2-yl)imidazolidine-4-thione derivatives and their immobilized forms in the asymmetric Henry reaction and, furthermore, the effect of multiple recycling of the anchored catalysts upon these parameters.

Results and Discussion

The key intermediate in the preparation of the sulfur analogue of chiral 2-(pyridine-2-yl)imidazolidine-4-



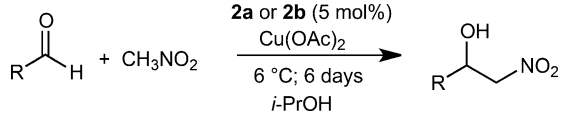
Scheme 2. Synthesis of ligands **2a-b** and **3a-b**.

one ligand **2a** and/or **2b** was (*S*)-2-amino-2,3-dimethylbutanethioamide (**1**). This thioamide was prepared by thionation of the corresponding optically pure amide using the procedure described for preparation of racemic compound **1**.[8b] The subsequent acid-catalyzed condensation of aminothioamide **1** with 2-acetylpyridine gave the required mixture of epimeric imidazolidine-4-thiones **2a** and **2b** with the total yield of 66% (Scheme 2). The separation of individual epimers **2a** and **2b** was carried out by column chromatography; the individual forms were present in the ratio of *ca* 1.3/1.0 (**2a**/**2b**).

The absolute configuration at the stereogenic centre in the 2-position of imidazolidine-4-thione derivatives **2a** and **2b** was determined by means of ^{1}H NMR 1D NOESY spectroscopy, when the selective excitation of protons of the methyl group at the positions 2 and/or 5 of the imidazolidine-4-thione cycle either resulted in a positive increase of intensity of signal of the opposite methyl group (2*S*,5*S* – **2b**), or the intensity did not increase (2*R*,5*S* – **2a**). The absolute configuration determined on stereogenic centres of derivatives **2a** and **2b** in this way was in accordance with the earlier findings:[3,9] during chromatographic separation, the derivatives with *trans* arrangement in the imidazolidine-4-one cycle have a higher R_f factor. This phenomenon was observed in the cases of all of the earlier prepared 2-(pyridine-2-yl)imidazolidine-4-ones[3] as well as other chiral imidazolidine-4-one derivatives, e.g., the MacMillan catalysts.[9]

The synthesized imidazolidine-4-thiones **2a** and **2b** were stable to atmospheric oxygen and in aqueous medium. However, it was found that in acid medium the epimerization transformation of **2a** into **2b** and *vice versa* took place. This racemization process was probably connected with acid-catalyzed opening of

Table 1. Survey of experiments on the asymmetric Henry reaction of nitromethane with aldehydes catalyzed by homogeneous catalysts $Cu(OAc)_2$/**2a** and $Cu(OAc)_2$/**2b**.



Entry	R	**2a** Conv.[a] [%] (Yield [%])	*ee*[b] [%]	**2b** Conv.[a] [%] (Yield [%])	*ee*[b] [%]
1	Ph	88 (80)	90	59 (48)	−85
2	2-$CH_3OC_6H_4$	99 (95)	90	82 (76)	−87
3	4-ClC_6H_4	94 (86)	89	53 (50)	−75
4	4-$NO_2C_6H_4$	99 (91)	84	94 (86)	−70
5	4-PhC_6H_4	90 (77)	89	41 (33)	−84
6	*t*-Bu	(98)	97	(58)	−94
7	thien-2-yl	67 (53)	91	28 (15)	−84
8	naphth-2-yl	92 (85)	88	50 (42)	−83
9	$PhCH_2CH_2$	85 (74)	94	43 (31)	−84

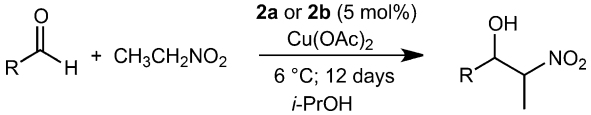
[a] The conversion was determined by ^{1}H NMR of crude product.
[b] The enantiomeric excess was determined by HPLC using a Chiralcel OD-H or Chiralpak AD-H column.

imidazolidine-4-thione cycle giving the corresponding Schiff base and its subsequent recyclization. The described process was not observed in the case of earlier prepared 2-(pyridine-2-yl)imidazolidine-4-one derivatives,[3] but epimerization of the MacMillan catalysts at the 2-position by action of $Yb(OTf)_3$ (1 mol%) in chloroform under reflux (8 h) was observed.[9] For this reason, it was necessary to carry out all handling with ligands **2a** and **2b** in neutral or basic medium, where this epimerization does not take place.

The catalytic activity of the *in situ* prepared copper(II) complexes of 2-(pyridine-2-yl)imidazolidine-4-thiones **2a** and **2b** was studied in the asymmetric Henry reaction. The main aim was verification of their enantioselectivity and comparison with the earlier studied oxygen analogues – copper(II) complexes of 2-(pyridine-2-yl)imidazolidine-4-ones.[3] The set of aldehydes and reaction conditions were chosen with the respect to the possibility of such comparison. Table 1 and Table 2 summarize the attained conversion values and optical yields for the individual aldehydes.

Whereas the catalysis with complex of (2*R*,5*S*)-**2a** gave the corresponding 2-nitroethanols with the *R*-configuration in excess, the application of complex of (2*S*,5*S*)-**2b** gave the products with the *S*-configuration in excess. The *ee* values of products show that the enantioselectivity of copper(II) complex of ligand **2a** is high (88–97% *ee*) and comparable with that of the analogous complex of (2*R*,5*S*)-5-isopropyl-2,5-dimethyl-2-(pyridine-2-yl)imidazolidine-4-one.[3a] Also the conversion values under the given conditions were high (67–99%). Surprisingly, the copper(II) complex of the *cis*-form of the ligand [$Cu(OAc)_2$/**2b**] also exhibited a high enantioselectivity (70–94% *ee*), whereas the oxygen analogue (derivative of imidazolidine-4-one) did not reach such satisfactory results (for benzaldehyde 23% *ee*).[3a] In the case of aromatic aldehydes containing electron-donating groups (experiments 1, 2, 5 and 7) with the application of complex $Cu(OAc)_2$/**2b**, the attained enantioselectivity was higher (84–87% *ee*) than that obtained with aldehydes containing electron-withdrawing groups (experiments 3 and 4; 75% and 70% *ee*, respectively). High *ee* values were attained with aliphatic aldehydes (experiments 6 and 9). The conversions in the case of complex $Cu(OAc)_2$/**2b** were considerably variable (28–94%) and they strongly depended on the reactivity/electrophilicity of the individual aldehyde used. These

Table 2. Survey of experiments on the asymmetric Henry reaction of nitroethane with aldehydes catalyzed by homogeneous catalysts $Cu(OAc)_2$/**2a** and $Cu(OAc)_2$/**2b**.



R	**2a** Conv.[a][%] (Yield [%])	*dr*[a] [%] (*anti*/*syn*)	*ee*[b] [%] (*anti*)	*ee*[b] [%] (*syn*)
Ph	86 (72)	46:54	76	92
2-$CH_3OC_6H_4$	89 (80)	65:35	84	76
	2b Conv.[a] [%] (Yield [%])	*dr*[a] [%] (*anti*/*syn*)	*ee*[b] [%] (*anti*)	*ee*[b] [%] (*syn*)
Ph	97 (88)	48:52	−80	−91
2-$CH_3OC_6H_4$	99 (79)	67:33	−83	−91

[a] The conversion and *dr* were determined by ^{1}H NMR of the crude product.
[b] The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column.

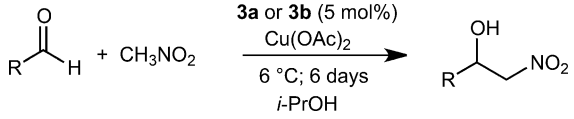
experiments were repeated several times, which confirmed the results stated above.

These results (Table 1 and Table 2) show that the copper(II) complexes of ligands **2a** and **2b** are effective homogeneous enantioselective catalysts for the Henry reaction. Thanks to the finding that they do not undergo racemization during the Henry reaction, it was very promising to prepare their recyclable variant using immobilization by means of anchoring to a solid carrier.

For the purpose of the intended immobilization of ligands **2a** and **2b** by means a C–S bond it was necessary to confirm the presumed regioselectivity of the benzylation reaction at the thiolactam group. It was found that the reaction of one equivalent of ligand **2a** or **2b** and benzyl bromide produced selectively compound **3a** or, respectively, **3b** (Scheme 2), which was confirmed by means of ^{1}H and ^{13}C NMR spectroscopy. The original chemical shift of the carbon atom in thiolactam group C=S ($\delta = 209.1$ ppm) of ligand **2a** was distinctly shifted to the value of 177.6 ppm, which corresponds with the formation of the bond arrangement Bn–S–C=N in ligand **3a**. The preparation of ligands **3a** and **3b** themselves had to be performed in the presence of base, because the hydrogen bromide being formed causes epimerization at the 2-position of the imidazoline cycle. This phenomenon was verified by an experiment in which the addition of several drops of trifluoroacetic acid to a methanolic solution of compound **3a** within 2 days resulted in the formation of a mixture of epimers **3a** and **3b** in the ratio of 3/2; after 10 days this ratio **3a**/**3b** was 8/9. Hence, epimer **3b** seems to be a thermodynamically more suitable form. The individual epimers **3a** and **3b** can again be separated by means of column chromatography [SiO_2/EtOAc:pentane:TEA (2:1:0.06); R_f(**3a**) = 0.66; R_f(**3b**) = 0.50]. The preparation of benzyl derivatives of **3a** and **3b** was studied under both homogeneous (DBU/MeOH; Cs_2CO_3/MeOH) and heterogeneous reaction conditions (K_2CO_3/acetone; K_2CO_3/MeOH). In all the cases, the reaction proceeded with full conversion and without epimerization at the 2-position of the imidazoline cycle.

The structure of copper(II) complexes of ligands **3a** and **3b** is closest to the structure of immobilized heterogeneous catalysts **7–9** (Scheme 1). Therefore, they can be considered as a homogeneous variant of the catalysts whose catalytic activity and enantioselectivity can serve as standard for evaluation of these parameters in immobilized heterogeneous catalysts **7–9**. The study was performed with four aldehydes (benzaldehyde, 2-methoxybenzaldehyde, 4-nitrobenzaldehyde and 2,2-dimethylpropanal), the reaction conditions used (the amount of catalyst, solvent, reaction time and temperature) being the same as those in the previous study on the catalytic activity of derivatives **2a** and **2b** in order to enable mutual comparison. Table 3 presents an overview of the results obtained.

Table 3. Survey of experiments on the asymmetric Henry reaction of nitromethane with aldehydes catalyzed by homogeneous catalysts $Cu(OAc)_2$/**3a** and $Cu(OAc)_2$/**3b**.



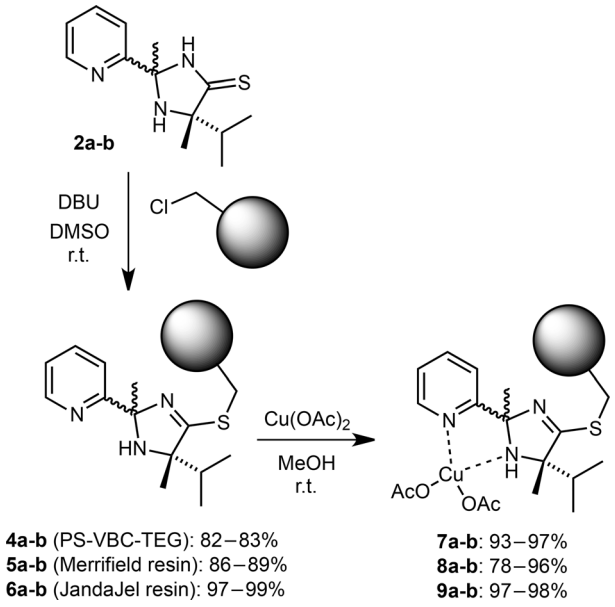
Entry	R	**3a** Conv.[a] [%] (Yield [%])	**3a** *ee*[b] [%]	**3b** Conv.[a] [%] (Yield [%])	**3b** *ee*[b] [%]
1	Ph	98 (91)	85	98 (86)	–84
2	2-$CH_3OC_6H_4$	99 (90)	86	99 (94)	–83
3	4-$NO_2C_6H_4$	99 (89)	82	99 (88)	–78
4	*t*-Bu	(99)	98	(99)	–95

[a] The conversion was determined by ^{1}H NMR of the crude product.

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

From the *ee* values of the individual nitroaldols attained by catalysis with copper(II) complexes of ligands **3a** and **3b** it follows that the enantioselectivity of both forms of catalyst is practically comparable. Comparison of the *ee* values obtained with the complexes of ligands **2a-b** *vs.* **3a-b** shows that in the case of $Cu(OAc)_2$/**3a** the enantioselectivity with aromatic aldehydes slightly decreased, namely by *ca.* 3–5% *ee*. In the case of complex $Cu(OAc)_2$/**3b** the enantioselectivity is comparable with that of complex $Cu(OAc)_2$/**2b**, with exception of 4-nitrobenzaldehyde: here the *ee* value distinctly increased (50% *vs.* 78% *ee*). With respect to the generally high *ee* values, it again can be presumed that during the Henry reaction the epimerization at the 2-position of the imidazoline cycle of compounds **3a** and **3b** does not take place. The attained conversion values were practically quantitative in the case of both derivatives $Cu(OAc)_2$/**3a** and $Cu(OAc)_2$/**3b**, in contrast to the previous catalysts $Cu(OAc)_2$/**2a-b**.

The preparation of immobilized catalysts **7–9** consisted in anchoring of ligands **2a** or **2b** on a polymeric carrier, namely by the reaction of their thiolactam group with the chloromethyl groups of the carrier leading to formation of modified polymers **4–6** (Scheme 3). As polymer carriers we used three types of swelling pearl-type copolymers of styrene and 4-vinylbenzyl chloride, which differed in the type of cross-linking agent and molar amount of chloromethyl groups. In the first case (for **4a-b**) it was a copolymer cross-linked with tetra(ethylene glycol)-bis(4-vinylbenzyl) ether (2%) (ST-VBC-TEG). The size of particles of this pearl-type copolymer was determined by means of DLS (200–800 μm),[7a] and the content of reactive groups $-CH_2Cl$ was 1.56 mmol g^{-1}. The other

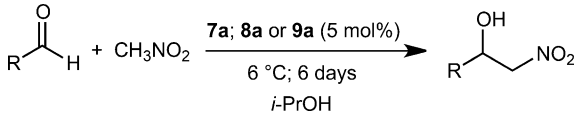


Scheme 3. Synthesis of immobilized catalysts **7–9**.

two copolymers adopted were commercially available, *viz.* the Merrifield™ resin[7b] (for **5a-b**) (which contained 1% divinylbenzene as cross-linking agent, and its chlorine content was 2.75 mmol g^{-1}), and the JandaJel™ resin[7c] (for **6a-b**) with cross-linking agent on the basis of polytetrahydrofuran (2%) and with the chlorine content of 0.48 mmol g^{-1}. An important benefit of all three copolymers is high swelling capacity in polar solvents, which enables an easy penetration of reactants to reactive groups of the copolymer. The anchoring procedure of ligands **2a** and **2b** on copolymer was performed at room temperature in dimethyl sulfoxide in the presence of DBU. When methanol was used as a solvent, the reaction did not proceed with a satisfactory yield (4% conversion, 50 °C, 5 days). Modified polymers **4–6** were characterized by means of elemental analysis and Raman spectroscopy. The content of residual chlorine in compounds **4–6** was under the limit of determination (< 0.03% Cl). Subsequently coordination of copper(II) acetate to immobilized ligands was performed to obtain the heterogeneous catalysts **7–9** (Scheme 3). The copper content was determined by means of atomic absorption spectroscopy.

Furthermore, the immobilized catalysts **7–9** were studied as enantioselective catalysts for the asymmetric Henry reaction (Table 4, Table 5, Table 6 and Table 7). After the reaction, the catalyst was simply separated by means of filtration and reused in the next reaction cycle. From this point of view, Sheldon's filtration test was performed,[10] which involved separation of the heterogeneous catalyst part way through a reaction, followed by continuation of the reaction in the absence of the immobilized catalyst. The result was negative, with the reaction stopping completely after the filtration. The comparison of conversion values (in many cases quantitative) and *ee* values obtained with the individual heterogeneous catalysts **7–9** shows that their catalytic activity and enantioselectivity are very high and not much different within the three types of polymeric carrier. Moreover, it is obvious that the immobilized catalysts **7–9** exhibit practically identical catalytic activity and enantioselectivity as the homogeneous variants of catalysts $Cu(OAc)_2$/**3a** and $Cu(OAc)_2$/**3b** (Table 3). A certain interesting fact is that in many cases the first catalytic cycle gave the products of Henry reaction with significantly lower optical purity. In the first four catalytic cycles of application of catalysts **7–9**, the *ee* value increased and then, in the following catalytic cycles, it remained

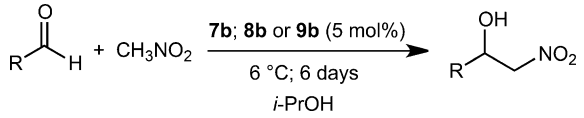
Table 4. Survey of experiments on the asymmetric Henry reaction of nitromethane with aldehydes catalyzed by immobilized catalysts with the *trans* configuration **7a**, **8a** and **9a**.



R (cat. cycle)	**7a**		**8a**		**9a**	
	Conv.[a] [%] (Yield [%])	*ee*[b] [%]	Conv.[a] [%] (Yield[%])	*ee*[b] [%]	Conv.[a] [%] (Yield[%])	*ee*[b] [%]
Ph (1st)	98 (88)	75	99 (86)	82	98 (87)	76
Ph (2nd)	95 (83)	79	98 (91)	84	99 (90)	83
Ph (3rd)	96 (89)	79	97 (84)	83	99 (90)	83
4-$NO_2C_6H_4$ (1st)	100 (95)	62	100 (89)	72	100 (91)	60
4-$NO_2C_6H_4$ (2nd)	95 (79)	75	99 (90)	77	100 (87)	72
4-$NO_2C_6H_4$ (3rd)	88 (81)	75	97 (88)	80	99 (90)	72
t-Bu (1st)	(93)	92	(98)	95	(90)	94
t-Bu (2nd)	(97)	93	(91)	96	(86)	95
t-Bu (3rd)	(98)	92	(99)	95	(94)	96

[a] The conversion was determined by ^{1}H NMR of the crude product.
[b] The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column.

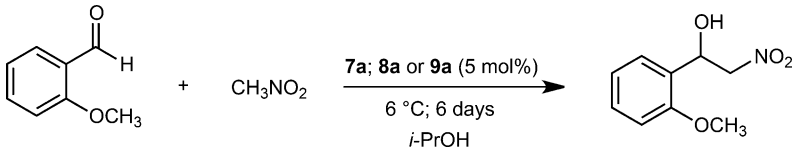
Table 5. Survey of experiments on the asymmetric Henry reaction of nitromethane with aldehydes catalyzed by immobilized catalysts with the *cis* configuration **7b**, **8b** and **9b**.



R (cat. cycle)	**7b** Conv.[a] [%] (Yield [%])	*ee*[b] [%]	**8b** Conv.[a] [%] (Yield [%])	*ee*[b] [%]	**9b** Conv.[a] [%] (Yield [%])	*ee*[b] [%]
Ph (1st)	98 (87)	−83	99 (85)	−85	99 (89)	−85
Ph (2nd)	96 (82)	−86	92 (80)	−85	97 (90)	−88
Ph (3rd)	97 (88)	−86	92 (78)	−88	95 (79)	−89
4-$NO_2C_6H_4$ (1st)	100 (89)	−73	99 (90)	−68	99 (85)	−69
4-$NO_2C_6H_4$ (2nd)	98 (81)	−84	98 (87)	−81	99 (89)	−80
4-$NO_2C_6H_4$ (3rd)	95 (78)	−85	92 (77)	−84	95 (80)	−84
t-Bu (1st)	(95)	−94	(99)	−95	(95)	−96
t-Bu (2nd)	(97)	−94	(99)	−96	(88)	−96
t-Bu (3rd)	(98)	−95	(94)	−94	(95)	−97

[a] The conversion was determined by ^{1}H NMR of the crude product.
[b] The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column.

Table 6. Survey of experiments on the asymmetric Henry reaction of nitromethane with 2-methoxybenzaldehyde catalyzed by immobilized catalysts with the *trans* configuration **7a**, **8a** and **9a**.

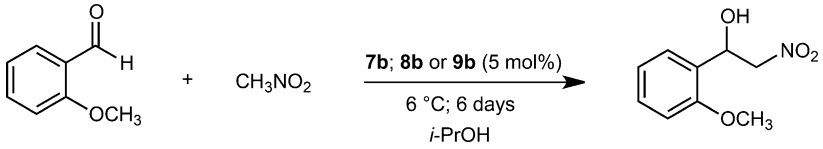


Cat. cycle	**7a** Conv.[a] [%] (Yield [%])	*ee*[b] [%]	**8a** Conv.[a] [%] (Yield [%])	*ee*[b] [%]	**9a** Conv.[a] [%] (Yield [%])	*ee*[b] [%]
1st	98 (91)	69	98 (84)	81	99 (90)	74
2nd	99 (86)	79	98 (90)	82	98 (86)	78
3rd	99 (90)	78	97 (87)	84	99 (89)	78
4th	99 (92)	79	98 (88)	84	99 (87)	80
5th	87 (76)	81	97 (79)	84	99 (91)	80
6th	97 (79)	80				
7th	86 (68)	81				
8th	91 (85)	80				
9th	95 (80)	80				
10th	78 (69)	81				
11th	83 (68)	81				

[a] The conversion was determined by ^{1}H NMR of the crude product.
[b] The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column.

practically constant (Table 6 and Table 7). This phenomenon was observed earlier with other immobilized enantioselective catalysts; however, it was not discussed in detail.[11] The problem mentioned can be solved by activation of the catalysts, which consists in suspending the heterogeneous catalyst in reaction medium throughout a so-called induction period.[11] After separation, the catalyst can be used for the first catalytic cycle, and the *ee* value attained is higher and close to that in subsequent cycles.[11a] This activation of catalyst was tested with derivatives **7a** and **7b** in the Henry reaction of nitromethane with 2-methoxybenzaldehyde. The fresh catalysts **7a** and **7b** were activated by suspending in a medium of *i*-PrOH (1 mL) and nitromethane (0.5 mL) for a period of 2 days at the reaction temperature of 6 °C. After the catalyst separation and subsequent use in the reaction, the first catalytic cycle provided Henry reaction products with 78% *ee* (**7a**) and 82% *ee* (**7b**), which are significantly higher than the values obtained after application of non-activated catalysts **7a** and **7b** (Table 6 and Table 7). These findings can be explained by the hy-

Table 7. Survey of experiments on the asymmetric Henry reaction of nitromethane with 2-methoxybenzaldehyde catalyzed by immobilized catalysts with the *cis* configuration **7b**, **8b** and **9b**.



Cat. cycle	**7b**		**8b**		**9b**	
	Conv.[a] [%] (Yield [%])	*ee*[b] [%]	Conv.[a] [%] (Yield [%])	*ee*[b] [%]	Conv.[a] [%] (Yield [%])	*ee*[b] [%]
1	97 (84)	−74	96 (80)	−83	99 (91)	−85
2	99 (90)	−83	98 (89)	−86	99 (88)	−90
3	98 (88)	−83	97 (82)	−88	99 (89)	−90
4	98 (81)	−85	97 (90)	−90	98 (85)	−89
5	95 (82)	−87	97 (85)	−89	97 (89)	−90
6	98 (90)	−86				
7	95 (79)	−86				
8	88 (75)	−86				
9	88 (78)	−86				
10	85 (72)	−87				
11	93 (85)	−87				

[a] The conversion was determined by ^{1}H NMR of the crude product.
[b] The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column.

pothesis that the non-activated catalysts can contain copper bounded not only to the chiral ligand, but also by non-specific coordination to the polymer carrier. The problem especially occurred in the case of immobilized catalysts **7a-b** and **9a-b** based on copolymer of styrene/4-chloromethylstyrene cross-linked by tetra(ethylene glycol) (for **7a-b**) or, respectively, polytetrahydrofuran (for **9a-b**). These types of cross-linkers could be possible ligands for coordination of copper ion, therefore removing unreacted copper(II) acetate from the polymer matrix of crude catalysts **7a-b** and **9a-b** by washing with methanol (using a Soxhlet extractor, 24 h) was not probably sufficient. On the other hand, in the case of the catalysts **8a-b** derived from Merrifield resin (cross-linker is divinylbenzene), there were less problems with the first catalytic cycle (see Table 4, Table 5, Table 6 and Table 7), which can be caused by the absence of the non-chiral copper complexes in their polymer matrixes. From this point of view, the catalysts **8a-b** can be considered as better candidates for the application in asymmetric syntheses. The high recycling potential of catalysts **7–9** is obvious from Figure 1, which displays no decrease of enantioselectivity even after ten recycling procedures (derivatives **7a-b**). Starting from the seventh cycle, the conversions were not completely quantitative; nevertheless they reached still high values (78–95%). This mild decrease was probably caused by loss of catalyst during recycling (filtration, decantation), which could be prevented by modification of the reaction procedure involving the "tea bag" method of catalysis. Generally, the enantioselectivity and catalytic activity of the immobilized catalysts **7–9** can be considered as comparable to the best of the previously described[2] recyclable forms of catalysts (~90% *ee*) for the Henry reaction. However, the main advantage of catalysts **7–9** compared with the above-mentioned catalytic forms consists in their easy separation (solid material) by

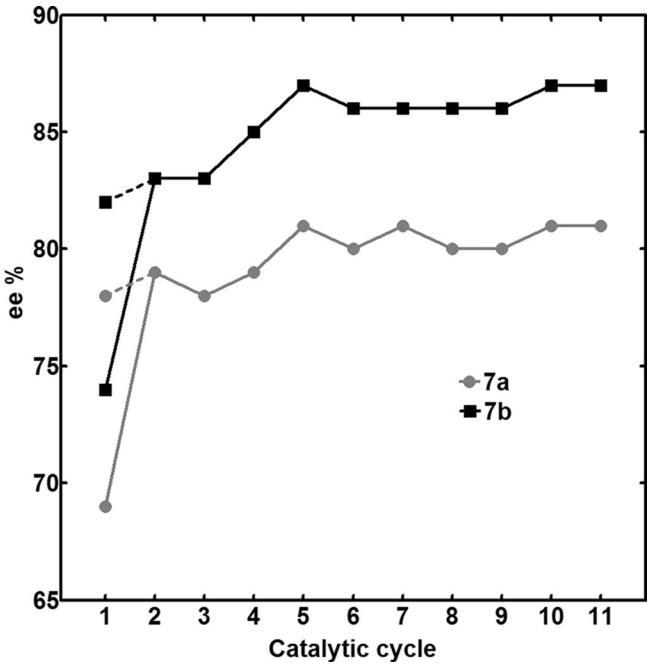


Figure 1. Dependence of attained *ee* of 1-(2-methoxyphenyl)-2-nitroethanol on catalytic cycle with the use of catalysts **7a** and **7b** (the *ee* values are taken from Table 6 and Table 7). The first cycles were also carried out with pre-activation of the catalysts (dashed lines).

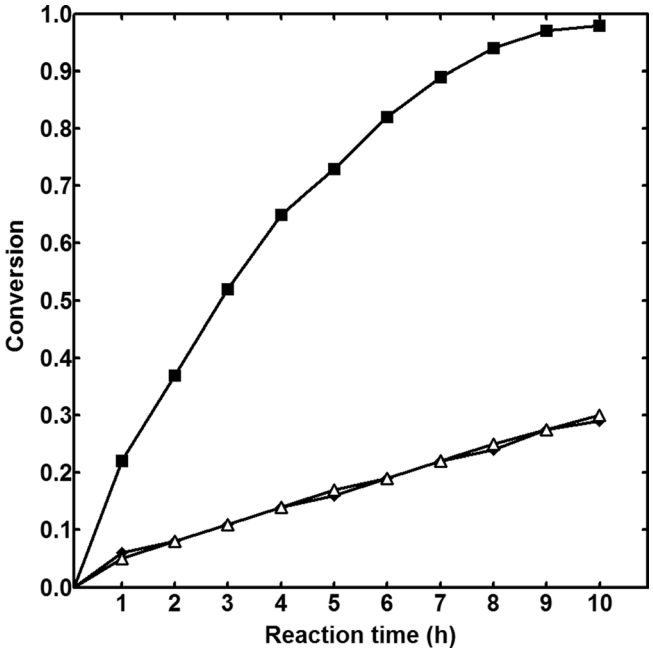
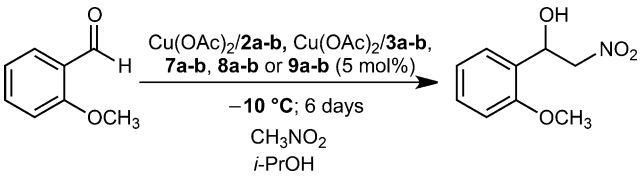


Figure 2. The time dependence (h) of conversion for reaction of $MeNO_2$ with 2-methoxybenzaldehyde catalyzed by 5 mol% of homogeneous catalysts $Cu(OAc)_2$/**2a** (△); $Cu(OAc)_2$/**3a** (◆) and heterogeneous catalyst **9a** (■) at 6 °C.

Table 8. Survey of experiments on the asymmetric Henry reaction of nitromethane with 2-methoxybenzaldehyde with application of catalysts $Cu(OAc)_2$/**2a-b**, $Cu(OAc)_2$/**3a-b**, **7a-b** and **9a-b** at a temperature of −10 °C.



Catalyst	Conv.[a] [%] (Yield [%])	*ee*[b] [%]
$Cu(OAc)_2$/**2a**	49 (44)	93
$Cu(OAc)_2$/**2b**	34 (25)	−89
$Cu(OAc)_2$/**3a**	83 (70)	88
$Cu(OAc)_2$/**3b**	89 (75)	−91
7a	99 (89)	83
7b	99 (86)	−91
8a	72 (65)	89
8b	89 (79)	−91
9a	99 (90)	86
9b	99 (88)	−90

[a] The conversion was determined by ^{1}H NMR of the crude product.

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

simple filtration, instead of precipitation of the soluble form[2a–f] which can be connected with possible contamination of the Henry reaction products with catalyst.

Table 3, Table 4, Table 5, Table 6 and Table 7 show that heterogeneous catalysts **7–9** exhibit a higher catalytic activity than homogeneous catalysts $Cu(OAc)_2$/**2a-b** (Table 1). This fact was confirmed by means of a kinetic study describing the dependence of conversion on reaction time and performed in reaction of nitromethane with 2-methoxybenzaldehyde catalyzed by $Cu(OAc)_2$/**2a**; $Cu(OAc)_2$/**3a** or **9a** (Figure 2). The dependence shows that with application of immobilized heterogeneous catalyst **9**, the conversion is almost quantitative (99%) at the temperature of 6 °C within 10 h. On the other hand, both types of homogeneous catalysts $Cu(OAc)_2$/**2a** and $Cu(OAc)_2$/**3a** identically gave after the same time a conversion of only *ca.* 30% (after 30 h, the conversion was *ca.* 70%), which corresponds to reaction half-life $\tau_{1/2}$ ~16 h. This phenomenon can be probably explained by possible particular formation of dimeric/oligomeric adducts[12] of homogeneous catalysts $Cu(OAc)_2$/**2a-b** and $Cu(OAc)_2$/**3a-b**, which are catalytically inactive.[13] In the case of heterogeneous catalysts **7–9** the formation of these dimeric/oligomeric adducts is prohibited, which led to their enhanced catalytic activity. The attempts included in Table 4, Table 5, Table 6 and Table 7 were done with a reaction time of 6 days for overall comparison and evaluation of both homogeneous and heterogeneous forms of the catalysts, although the Henry reactions were completed early in the case of heterogeneous catalysts.

With regard to the confirmed higher catalytic activity of heterogeneous catalysts **7–9**, in the subsequent study, we tested their enantioselectivity in the Henry reaction at the temperature of −10 °C (Table 8). From the *ee* values found (~90%) it is obvious that the enantioselectivity of catalysts $Cu(OAc)_2$/**3a-b** and **7–9** increased (under these reaction conditions) up to the level comparable with that of the homogeneous catalyst $Cu(OAc)_2$/**2a-b** (Table 1), and/or with the earlier prepared catalyst based on 2-(pyridine-2-yl)imidazolidine-4-one.[3a] The conversion values at this lower temperature remained very high (72–99%). From the above-given facts it follows that the homogeneous catalyst $Cu(OAc)_2$/**2a** provides high conversion values and *ee* in the products of the Henry reaction at the temperature of 6 °C, whereas with application of heterogeneous forms of catalysts (**7–9**) is favourable to lower the temperature (to −10 °C), where these nitroaldols can be prepared in comparable optical purity and yield.

Conclusions

In summary, it can be stated that the copper(II) complexes of synthesized 2-(pyridine-2-yl)imidazolidine-4-thiones **2a-b** and their benzyl derivatives **3a-b** are effi-

cient homogeneous enantioselective catalysts of the Henry reaction (up to 98% *ee*). Moreover, the immobilized forms of these catalysts **7–9** exhibit a comparable catalytic activity and enantioselectivity and can be recycled more than ten times without any decrease in the enantioselectivity. Their high enantioselectivity classifies them as the best so far known enantioselective recyclable catalysts for the Henry reaction.[2d] Two further reactions performed in the case of the synthesis of immobilized catalysts **7–9**, namely the thionation of the starting (*S*)-2-amino-2,3-dimethylbutaneamide giving (*S*)-2-amino-2,3-dimethylbutanethioamide (**1**) (72%) and anchoring of ligands **2a-b** on polymeric carriers (82–99%), led to a lowering of the total yield of this synthetic procedure as compared with the yield of the synthesis of the original catalyst based on 2-(pyridine-2-yl)imidazolidine-4-one derivative.[3a] On the other hand, the immobilized catalysts **7–9** can be recovered and reused more than ten times and thus they are more advantageous not only economically, but their application is also more environment-friendly. The synthesized polymeric catalysts **7–9** possess a high application potential for the asymmetric Henry reaction.

Experimental Section

General Information

If not otherwise stated, the starting chemicals and solvents were obtained from Sigma–Aldrich or Acros Organic and used without further purification. (*S*)-Amino-2,3-dimethylbutanamide was prepared according to a previously described procedure.[8] ^{1}H NMR spectra were recorded on a Bruker Avance 400 instrument or Bruker Avance 500 instrument. Chemical shifts δ were referenced to the residual peak of the $CDCl_3$ (7.26 ppm) or MeOD-d_4 (3.31 ppm). The ^{13}C NMR spectra were calibrated with respect to the middle signal in the triplet of $CDCl_3$ (77.23 ppm) or quintet of MeOD-d_4 (49.00 ppm). The Raman spectra were measured at room temperature using an FT-IR spectrophotometer IFS 55 provided with a Raman FRA-106 accessory (Bruker) for the back scattering method. The YAG:Nd^{3+} laser line (1064 nm) was used for excitation. The resolution was 2 cm^{-1} and the laser power was 50 mW. The FT-Raman data are presented in cm^{-1} (vw, very weak; w, weak; m, medium; s, strong; sh, shoulder). The microanalyses were performed on an apparatus from FISONS Instruments, EA 1108 CHNS. The determination of Cu was carried out with an Avanta P double beam atomic absorption spectrometer (GBC Scientific Equipment Pty. Ltd., Australia) in the flame atomization mode. Microwave digestion of samples was carried out in the Speedwave MWS-3+ (Berghof, Germany) microwave system with the maximum total output of the microwave generator 1450 W. Quantification of Cu concentrations was performed by establishing a calibration curve by linear regression. The optical rotation was measured on a Perkin–Elmer 341 instrument; the concentration *c* was given in g/100 mL. High-resolution mass spectra were measured on the Thermo Fisher Scientific MALDI LTQ Orbitrap instrument. HPLC analyses were performed on Watrex HPLC instrument with UV-Vis DAD (200–800 nm) SYKAM 3240 and with chiral Daicel columns: Chiralcel OD-H, Chiralpak AS-H and Chiralpak AD-H (250 mm × 4.6 mm).

Synthesis of Ligands 2 and 3

(*S*)-Amino-2,3-dimethylbutanethioamide (1): A mixture of (*S*)-2-amino-2,3-dimethylbutanamide[8] (8.7 g, 67 mmol) and P_4S_{10} (17.4 g, 40 mmol) was refluxed in dry dioxane (200 mL) for 10 h and then was stirred at room temperature for 72 h. Dioxane was removed under reduced pressure, the oily residue was diluted with cold aqueous NH_3 (10%, 120 mL) and the mixture was extracted with CH_2Cl_2 (4× 50 mL). Organic extracts were combined and dried and the solvent was distilled off. The crude product was purified by recrystallization from cyclohexane/EtOAc (5/1) to obtain **1** as a white crystalline solid **1**; yield: 7.1 g (72%); mp 87–90 °C; $[\alpha]_D^{25}$: −74.7 (*c* 0.99, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.47 (bs, 1H, $CSNH_2$), 8.11 (bs, 1H, $CSNH_2$), 2.69 (sp, ^3J = 6.8 Hz, 1H, CH), 1.41 (s, 3H, CH_3), 1.32 (bs, 2H, NH_2), 0.92 (d, ^3J = 6.8 Hz, 3H, *i*-Pr), 0.77 (d, ^3J = 6.8 Hz, 3H, *i*-Pr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 215.7, 65.8, 35.8, 29.3, 17.3, 16.3; elemental analysis for $C_6H_{14}N_2S$ (146.25) calcd.: C 49.28, H 9.65, N 19.15, S 21.92; found: C 49.45, H 9.39, N 19.17, S 22.04; HR-MS (ESI): *m/z* = 147.09511 $[M+H]^+$, calcd. 147.09505 $[M+H]^+$.

5-Isopropyl-2,5-dimethyl-2-(pyridine-2-yl)imidazolidine-4-thione (2a and 2b): A solution of thioamide **1** (370 mg, 2.5 mmol), 2-acetylpyridine (480 mg, 4 mmol) and *p*-TSA·H_2O (4.8 mg, 0.25 mmol) in 1,2-dichlorobenzene (4 mL) was stirred at 130 °C for 2 h. After evaporation of the solvent under reduced pressure the obtained yellow oil was treated with CH_2Cl_2 (6 mL) and a saturated aqueous solution of Na_2CO_3 (6 mL). The organic layer was dried over Na_2SO_4 and solvent was evaporated. The mixture of diastereomers was separated by column chromatography [SiO_2/EtOAc/hexane (1/1), (v/v)].

(2*R*,5*S*)-5-Isopropyl-2,5-dimethyl-2-(pyridine-2-yl)imidazolidine-4-thione (2a): yield: 37%; colorless oil; R_f 0.46; $[\alpha]_D^{25}$: −84.4 (*c* 0.8, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.61 (bs, 1H, CONH), 8.52 (m, 1H, Py), 7.72 (m, 1H, Py), 7.66 (m, 1H, Py), 7.18 (m, 1H, Py), 2.61 (bs, 1H, NH), 2.32 (sp, ^3J = 6.8 Hz, 1H, CH), 1.71 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.02 (d, ^3J = 6.8 Hz, 3H, *i*-Pr), 1.00 (d, ^3J = 6.8 Hz, 3H, *i*-Pr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 209.1, 163.4, 149.3, 137.3, 123.1, 119.5, 82.2, 77.7, 35.6, 30.3, 27.2, 18.2, 16.9; elemental analysis for $C_{13}H_{19}N_3S$ (249.38) calcd.: C 62.61, H 7.68, N 16.85, S 12.86; found: C 62.44, H 7.81, N 16.73, S 12.71; HR-MS (ESI): *m/z* = 250.13729 $[M+H]^+$, calcd. 250.13722 $[M+H]^+$.

(2*S*,5*S*)-5-Isopropyl-2,5-dimethyl-2-(pyridine-2-yl)imidazolidine-4-thione (2b): yield: 29%; white crystalline solid; mp 128–130 °C; R_f 0.30; $[\alpha]_D^{25}$: +19.3 (*c* 0.9, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.13 (bs, 1H, CONH), 8.51 (m, 1H, Py), 7.73–7.66 (m, 2H, Py), 7.19 (m, 1H, Py), 2.43 (bs, 1H, NH), 2.10 (sp, ^3J = 6.8 Hz, 1H, CH), 1.75 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 0.97 (d, ^3J = 6.8 Hz, 3H, *i*-Pr), 0.53 (d, ^3J = 6.8 Hz, 3H, *i*-Pr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 207.9, 162.7, 148.9, 137.1, 122.9, 119.3, 81.9, 77.1, 36.3, 32.6, 28.9,

18.3, 16.8; elemental analysis for $C_{13}H_{19}N_3S$ (249.38) calcd.: C 62.61, H 7.68, N 16.85, S 12.86; found: C 62.97, H 7.68, N 16.73, S 12.62; HR-MS (ESI): $m/z = 250.13691$ $[M+H]^+$, calcd. 250.13722 $[M+H]^+$.

4-Benzylsulfanyl-5-isopropyl-2,5-dimethyl-2-(pyridine-2-yl)imidazoline (3a and 3b): To a suspension of ligand **2a** or **2b** (175 mg, 0.7 mmol) and K_2CO_3 (200 mg, 1.45 mmol) in MeOH (3 mL) was added benzyl bromide (86 μL, 0.72 mmol) and mixture was stirred at room temperature for 2 days. Then, the reaction mixture was filtered and the solvent was evaporated under reduced pressure.

(2*R*,5*S*)-4-Benzylsulfanyl-5-isopropyl-2,5-dimethyl-2-(pyridine-2-yl)imidazoline (3a): yield: 86%; yellow oil; $[\alpha]_D^{25}$: −53.5 (*c* 1.0, MeOH); ^{1}H NMR (MeOD-d_4, 400 MHz): $\delta =$ 8.47 (m, 1H, Py), 7.68 (m, 1H, Py), 7.46 (m, 1H, Py), 7.39 (m, 2H, Ph), 7.28–7.21 (m, 4H, Py+Ph), 4.40–4.31 (2× d, $^2J = 13.6$ Hz, 2H, CH_2), 1.77 (sp, $^3J = 6.8$ Hz, 1H, CH), 1.64 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.96 (d, $^3J = 6.8$ Hz, 3H, *i*-Pr), 0.92 (d, $^3J = 6.8$ Hz, 3H, *i*-Pr); ^{13}C NMR (MeOD-d_4, 100 MHz): $\delta = 177.6$, 166.3, 149.2, 139.0, 138.2, 130.0, 129.4, 128.2, 123.5, 121.7, 93.4, 78.1, 35.7, 35.6, 31.5, 26.1, 18.7, 17.0; elemental analysis for $C_{20}H_{25}N_3S$ (339.5) calcd.: C 70.76, H 7.42, N 12.36, S 9.44; found: C 70.68, H 7.64, N 12.27, S 9.19; HR-MS (ESI): $m/z = 340.18398$ $[M+H]^+$, calcd. 340.18419 $[M+H]^+$.

(2*S*,5*S*)-4-Benzylsulfanyl-5-isopropyl-2,5-dimethyl-2-(pyridine-2-yl)imidazoline (3b): yield: 89%; yellow oil; $[\alpha]_D^{25}$: +31.7 (*c* 2.4, MeOH); ^{1}H NMR (MeOD-d_4, 400 MHz): $\delta =$ 8.50 (m, 1H, Py), 7.75 (m, 1H, Py), 7.68 (m, 1H, Py), 7.38 (m, 2H, Ph), 7.29–7.22 (m, 4H, Py+Ph), 4.39–4.30 (2× d, $^2J = 13.2$ Hz, 2H, CH_2), 1.78 (sp, $^3J = 6.8$ Hz, 1H, CH), 1.65 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 0.94 (d, $^3J = 6.8$ Hz, 3H, *i*-Pr), 0.46 (d, $^3J = 6.8$ Hz, 3H, *i*-Pr); ^{13}C NMR (MeOD-d_4, 100 MHz): $\delta = 176.9$, 164.7, 148.9, 139.0, 138.2, 130.1, 129.3, 128.2, 123.6, 122.4; 94.0, 78.2, 36.2, 35.8, 32.6, 27.6, 18.2, 17.3; elemental analysis for $C_{20}H_{25}N_3S$ (339.5) calcd.: C 70.76, H 7.42, N 12.36, S 9.44; found: C 70.58, H 7.31, N 12.39, S 9.21; HR-MS (ESI): $m/z = 340.18490$ $[M+H]^+$, calcd. 340.18419 $[M+H]^+$.

General Procedure for Immobilization of Ligands 2a and 2b

To a solution of ligand **2a** or **2b** (250 mg, 1 mmol), DBU (0.3 mL, 2 mmol) and NaI (4.5 mg, 0.03 mmol) in dry DMSO (5 mL) was added a pearl-type chloromethylated polystyrene support (0.66 mmol, calculated from Cl content) and was stirred at room temperature for 5 days. After filtration and washing with methanol (5× 5 mL), the catalyst was extracted in a Soxhlet extractor with methanol for 24 h and then dried under vacuum.

Compound 4a: Prepared from swelling pearl-like copolymer styrene-(4-vinylbenzyl chloride) cross-linked by means of tetra(ethylene glycol)-bis(4-vinylbenzyl) ether (2%)[7a] and ligand **2a**. Yield: 83%; elemental analysis found: C 79.07, H 7.63, N 3.72, S 2.75; FT-Raman: $\nu = 217$ (vw), 406 (vw), 576 (vw), 621 (w), 642 (w), 682 (vw), 747 (sh), 760 (vw), 790 (sh), 811 (sh), 837 (vw), 907 (vw), 928 (vw), 963 (vw), 1002 (s), 1030 (w), 1046 (w), 1090 (vw), 1155 (w), 1183 (w), 1201 (w), 1240 (vw), 1292 (sh), 1327 (vw), 1369 (sh), 1448 (w), 1584 (m), 1602 (m), 1611 (sh), 2852 (sh), 2872 (sh), 2904 (sh), 2914 (sh), 2924 (m), 2975 (w), 3001 (vw), 3036 (sh), 3054 (m).

Compound 4b: Prepared from swelling pearl-like copolymer styrene-(4-vinylbenzyl chloride) cross-linked by means of tetra(ethylene glycol)-bis(4-vinylbenzyl) ether (2%)[7a] and ligand **2b**. Yield: 82%; elemental analysis found: C 80.63, H 7.48, N 3.65, S 2.69; FT-Raman: $\nu = 220$ (sh), 234 (w), 272 (vw), 407 (vw), 576 (vw), 621 (w), 642 (w), 674 (vw), 747 (sh), 758 (vw), 767 (sh), 790 (sh), 814 (sh), 833 (vw), 1002 (s), 1030 (w), 1046 (w), 1090 (vw), 1155 (w), 1183 (w), 1201 (w), 1240 (vw), 1299 (sh), 1327 (vw), 1369 (sh), 1448 (w), 1583 (m), 1602 (m), 1611 (sh), 2853 (sh), 2912 (sh), 2924 (m), 2975 (w), 3001 (vw), 3036 (sh), 3054 cm^{-1} (s).

Compound 5a: Prepared from Merrifield^{TM} resin (2.5–4.0 mmol g^{-1} Cl, cross-linker 1%, 50–100 mesh) and ligand **2a**. Yield: 86%; elemental analysis found: C 77.22, H 7.63, N 6.61, S 3.92; FT-Raman: $\nu = 218$ (vw), 407 (vw), 576 (vw), 621 (w), 642 (w), 679 (vw), 709 (vw), 755 (vw), 790 (sh), 807 (sh), 836 (vw), 1002 (s), 1031 (w), 1046 (vw), 1088 (vw), 1112 vw), 1155 (vw), 1183 (w), 1203 (w), 1240 (w), 1296 (sh), 1311 (sh), 1326 (vw), 1363 (sh), 1448 (w), 1528 (vw), 1569 (sh), 1583 (w), 1602 (m), 1611 (m), 2857 (sh), 2910 (sh), 2925 (s), 2978 (m), 3000 (w), 3033 (sh), 3053 cm^{-1} (s).

Compound 5b: Prepared from Merrifield^{TM} resin (2.5–4.0 mmol g^{-1} Cl, cross-linker 1%, 50–100 mesh) and ligand **2b**. Yield: 89%; elemental analysis found: C 76.93, H 8.04, N 6.28, S 3.61; FT-Raman: $\nu = 219$ (vw), 409 (vw), 585 (vw), 621 (w), 642 (w), 671 (vw), 717 (vw), 747 (sh), 760 (vw), 790 (sh), 807 (sh), 830 (vw), 1002 (s), 1031 (w), 1046 (vw), 1088 (vw), 1155 (vw), 1183 (w), 1201 (w), 1240 (w), 1296 (sh), 1327 (vw), 1363 (sh), 1448 (w), 1528 (vw), 1583 (w), 1602 (s), 1611 (s), 2857 (sh), 2910 (sh), 2925 (s), 2978 (m), 3000 (w), 3033 (sh), 3053 cm^{-1} (s).

Compound 6a: Prepared from JandaJel^{TM} resin (0.45–0.70 mmol g^{-1} Cl, cross-linker 2%, 50–100 mesh) and ligand **2a**. Yield: 99%; elemental analysis found: C 83.51, H 7.98, N 2.77, S 1.48; FT-Raman: $\nu = 217$ (vw), 402 (vw), 621 (w), 642 (vw), 760 (vw), 796 (vw), 810 (sh), 840 (sh), 907 (vw), 966 (w), 1002 (s), 1030 (w), 1046 (sh), 1084 (vw), 1155 (w), 1183 (w), 1201 (vw), 1240 (m), 1297 (sh), 1325 (vw), 1367 (sh), 1450 (w), 1584 (w), 1602 (m), 1611 (sh), 2855(sh), 2910 (m), 2977 (w), 3000 (w), 3038 (sh), 3053 (s), 3162 cm^{-1} (vw).

Compound 6b: Prepared from JandaJel^{TM} resin (0.45–0.70 mmol g^{-1} Cl, cross-linker 2%, 50–100 mesh) and ligand **2b**. Yield: 97%; elemental analysis found: C 84.07, H 7.83, N 3.01, S 1.71; FT-Raman: 217 (vw), 406 (vw), 621 (w), 642 (vw), 760 (vw), 796 (vw), 810 (sh), 837 (sh), 907 (vw), 966 (w), 1002 (s), 1030 (w), 1046 (sh), 1084 (vw), 1155 (w), 1183 (w), 1201 (vw), 1240 (m), 1297 (sh), 1325 (vw), 1367 (sh), 1450 (w), 1584 (w), 1602 (m), 1611 (sh), 2855(sh), 2910 (m), 2977 (w), 3000 (w), 3038 (sh), 3053 (s), 3162 cm^{-1} (vw).

General Procedure for Preparation of Heterogeneous Catalysts 7–9

The suspension of polymer **4–6** (300 mg) in a solution of copper(II) acetate (91 mg, 0.5 mmol) in methanol (12 mL) was stirred for 24 h at room temperature. After filtration and washing with methanol (5× 20 mL), the catalyst was extracted in a Soxhlet extractor with methanol for 24 h and then dried under vacuum.

Catalyst 7a: Yield: 97%; elemental analysis found: C 70.37, H 6.89, N 3.19, S 2.33, Cu 4.86; FT-Raman: ν = 508 (vw), 576 (vw), 621 (vw), 639 (vw), 673 (vw), 709 (vw), 790 (sh), 807 (sh), 829 (vw), 925 (vw), 1000 (s), 1027 (m), 1046 (sh), 1092 (vw), 1154 (vw), 1183 (w), 1201 (sh), 1240 (w), 1327 (vw), 1364 (sh), 1448 (w), 1583 (sh), 1602 (m), 2857(sh), 2907 (sh), 2926 (m), 2977 (w), 3003 (w), 3039 (sh), 3055 cm^{-1} (m).

Catalyst 7b: Yield: 93%; elemental analysis: found C 72.89, H 7.01, N 3.54, S 2.46, Cu 4.83; FT-Raman: ν = 221 (vw), 508 (vw), 576 (vw), 621 (vw), 639 (vw), 673 (vw), 709 (vw), 790 (sh), 807 (sh), 829 (vw), 925 (vw), 1000 (s), 1027 (w), 1046 (sh), 1095 (vw), 1154 (vw), 1183 (w), 1201 (sh), 1240 (w), 1327 (vw), 1364 (sh), 1448 (w), 1583 (sh), 1602 (m), 2857(sh), 2907 (sh), 2926 (m), 2980 (w), 3000 (w), 3039 (sh), 3055 cm^{-1} (m).

Catalyst 8a: Yield: 78%; elemental analysis found: C 68.41, H 7.04, N 4.93, S 2.97, Cu 6.12; FT-Raman: ν = 215 (vw), 239 (sh), 400 (vw), 621 (w), 642 (w), 680 (vw), 703 (vw), 759 (vw), 788 (sh), 806)vw), 837 (vw), 1001 (s), 1031 (w), 1043 (w), 1087 (vw), 1156 (vw), 1183 (w), 1199 (sh), 1245 (vw), 1317 (vw), 1447 (vw), 1583 (sh), 1605 (m), 2864(sh), 2926 (s), 2974 (m), 3002 (sh), 3054 cm^{-1} (s).

Catalyst 8b: Yield: 96%; elemental analysis found: C 70.12, H 7.54, N 4.76, S 2.89, Cu 5.39; FT-Raman: ν = 220 (sh), 236 (vw), 397 (vw), 549 (vw), 574 (vw), 622 (w), 641 (w), 677 (vw), 707 (vw), 756 (vw), 801 (sh), 832 (vw), 1001 (s), 1044 (sh), 1083 (vw), 1156 (vw), 1183 (w), 1199 (sh), 1243 (sh), 1312 (vw), 1447 (vw), 1583 (sh), 1605 (m), 2864(sh), 2926 (s), 2974 (m), 3002 (sh), 3054 cm^{-1} (s).

Catalyst 9a: Yield: 97%; elemental analysis found: C 79.80, H 7.77, N 2.25, S 1.25, Cu 2.47; FT-Raman: ν = 216 (vw), 576 (vw), 607 (vw), 620 (vw), 640 (vw), 754 (vw), 796 (vw), 832 (vw), 1001 (s), 1030 (w), 1080 (sh), 1154 (vw), 1183 (w), 1193 (sh), 1244 (vw), 1325 (vw), 1372 (sh), 1448 (w), 1562 (sh), 1583 (sh), 1602 (m), 2853 (sh), 2913 (sh), 2923 (m), 2974 (w), 3000 (w), 3035 (sh), 3053 cm^{-1} (s).

Catalyst 9b: Yield: 98%; elemental analysis found: C 80.23, H 7.56, N 2.40, S 1.36, Cu 2.56; FT-Raman: ν = 183 (sh), 214 (sh), 239 (m), 607 (vw), 623 (vw), 642 (vw), 754 (vw), 794 (vw), 831 (vw), 1001 (s), 1030 (w), 1086 (sh), 1154 (vw), 1182 (w), 1193 (sh), 1244 (vw), 1325 (vw), 1372 (sh), 1448 (w), 1562 (sh), 1583 (sh), 1602 (m), 2853 (sh), 2912 (m), 2923 (sh), 2974 (w), 3000 (w), 3035 (sh), 3053 cm^{-1} (m).

General Procedure for the Asymmetric Henry Reaction[5]

A mixture of ligand **2a**, **2b**, **3a** or **3b** (27.5 μmol) and $Cu(OAc)_2$ (4.5 mg, 25 μmol) or polymeric catalyst **7–9** (5 mol%) and nitroalkane (0.5 mL, 9–10 mmol) in dry isopropyl alcohol (1 mL) was stirred for 1 h at room temperature. Then the mixture was cooled to 6 °C or −10 °C and aldehyde (0.5 mmol) was added. The mixture was stirred for a period of 6 or 12 days. The catalyst was removed by flash chromatography (homogeneous catalyst) or by filtration (heterogeneous catalyst) and washed with EtOAc (3 × 5 mL). After evaporation of solvents under reduced pressure, the crude product was purified by column chromatography (EtOAc/hexane; 1/3 (v/v). The enantiomeric excess was determined by HPLC. The characterization data for all enantiomers of the nitro alcohols were in accordance with data published previously.[3a]

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