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Highly enantioselective Henry reaction catalyzed by chiral tridentate heteroorganic ligands

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ABSTRACT

New tridentate enantiomerically pure heteroatom catalysts, containing hydroxyl, sulfinyl and amino groups, proved to be highly efficient in the enantioselective nitroaldol (Henry) reaction to give the desired adducts in very high yields (up to 90%) and with ees up to 98%. The influence of the stereogenic centres located on the sulfinyl sulfur atom and in the amine moiety is also discussed.

1. Introduction

The nitroaldol (Henry) reaction, particularly its stereoselective version, has recently attracted great attention, as can be seen from the number of recent publications.[1] This is obviously due to the fact that the reaction products, enantiomerically pure (or at least enriched) 2-nitroalcohols, can be easily transformed into valuable chiral building blocks via the appropriate transformations of both the hydroxy and nitro groups. The asymmetric Henry reaction rests upon the aldol-type addition of a nitroalkane to an aldehyde, performed in the presence of metal complexes with chiral ligands. Among the ligands, a variety of chiral amine derivatives have been used, including diamides[2] and those based on chiral diamines, *trans*-1,2-diaminocyclohexane,[3] bis-oxazolines,[4] oxazolidines[5] and aziridines.[6] Although the use of copper diacetate as the metal component seems to be most common, other metal salts have also been applied.[7] Recently, sterically modified salen-chromium complexes have been successfully used as catalysts to give the 2-nitroalcohols with ees of up to 94%.[8]

Over the course of our studies on the application of enzymes in the synthesis of chiral non-racemic heteroorganic compounds,[9] we have recently reported the synthesis of new enantiomerically pure tridentate ligands **3** which possess three different nucleophilic centres capable of binding organometallic reagents: the hydroxyl, sulfinyl and amino moieties. They were prepared via an enzyme-catalyzed desymmetrization of prochiral dihydroxy sulfoxide **1** followed by the relevant chemical transformations comprising the introduction of enantiomeric C-chiral amines (Scheme 1).[10] Although some of them proved to be weak catalysts for the stereoselective addition of diethylzinc to aldehydes,[11] we decided to study their activity in the Henry reaction, hoping that the stereogenic sulfinyl moiety would in this case exert strong stereoinduction.[12]

2. Results and discussion

2.1. Screening of the ligands

To check the ability of the ligands to catalyze the enantioselective nitroaldol reaction, we chose the addition of nitromethane to benzaldehyde as a reference transformation. The reactions were performed under standard conditions, using copper acetate as the metal component (Scheme 2). The results are collected in Table 1.

Inspection of Table 1 shows that both the yields and ees of the product depend strongly on the structure of the ligand. Ligand **3a**, which was a relatively good catalyst,[10] and ligands **3d–f** which were very efficient catalysts[11] in the diethylzinc addition to benzaldehyde turned out to be disappointingly weak in the Henry reaction.[13] On the other hand, ligands **3b** and **3c**, which were inefficient in the diethylzinc addition to benzaldehyde,[10] proved to be almost perfectly enantioselective in the Henry reaction. In contrast to their catalytic activity in the diethylzinc addition, in which the sulfinyl stereogenic centre exerted a strong influence on the stereochemistry of the reaction, the decisive role in the Henry reaction was played by the stereogenic centres located in the amine moieties. This is visible in entries 2 and 3, and 5 and 6 where the use of diastereomeric ligands **3b** and **3c**, and **3e** and **3f**, respectively, having the same absolute configuration at the sulfinyl sulfur atom (*R*) and opposite on the carbon atom in the amine moieties [(*S*) and (*R*), respectively], led to opposite enantiomers of adduct **4a** with almost the same ees.

2.2. Henry reaction with various aldehydes in the presence of catalyst 3c

Having obtained promising results with ligands **3b** and **3c**, we then decided to check the scope of the reaction. The title reaction

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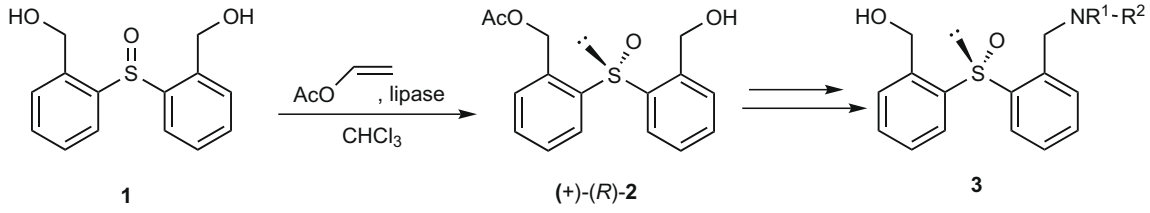
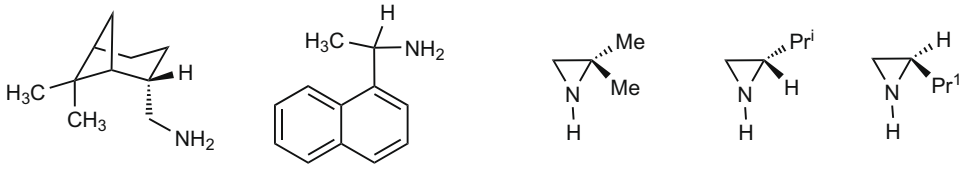


Amines



a) (–)-*cis*-myrtanylamine

b) (–)-(*S*)-1-(1'-naphthyl)ethylamine

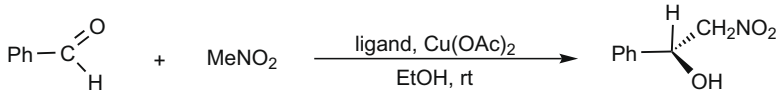
c) (+)-(*R*)-1-(1'-naphthyl)ethylamine

d) 2,2-dimethylaziridine

e) (–)-(*S*)-2-isopropylaziridine

f) (+)-(*R*)-2-isopropylaziridine

Scheme 1. Synthesis of tridentate ligands.



Scheme 2. Screening of ligands **3**.

Table 1
Screening of ligands **3**

Entry	Ligand	Adduct **4a**			
		Yield (%)	$[\alpha]_D$[a]	ee (%)[b]	Absolute configuration
1	**3a**	30	−10	48	(*R*)
2	**3b**	90	+22	98	(*S*)
3	**3c**	87	−22	98	(*R*)
4	**3d**	40	−5	24	(*R*)
5	**3e**	81	−3.5	15	(*R*)
6	**3f**	85	+4.1	20	(*S*)

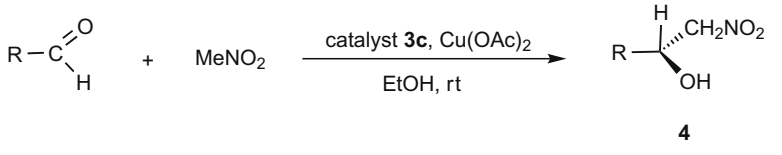
[a] In chloroform (*c* 1).
[b] Determined using chiral HPLC.

was performed using a series of aldehydes in the presence of ligand **3c** as a catalyst (Scheme 3). The results are collected in Table 2.

The results clearly indicate that the selected ligand **3c** efficiently catalyzes the title reaction to give the appropriate products in high yields and with high enantiomeric excesses. Both aryl and alkyl aldehydes are suitable for the reaction while the absolute configurations of the resulting adducts are the same in each case. Since both diastereomers of this ligand, that is, **3b** and **3c**, are available, and each of them leads to the formation of the opposite enantiomer of the product (Table 1, entries 2 and 3), this approach constitutes an easy access to the desired sterically defined 2-nitroalcohols.

3. Conclusions

The chiral tridentate ligands, which contain two stereogenic centres, one located on the sulfinyl sulfur atom, and the other on the carbon atom in the amine moiety, were found to be very efficient catalysts for the enantioselective nitroaldol (Henry) reaction performed with aryl and alkyl aldehydes in the presence of copper acetate. The stereogenic centres located in the amine moieties exerted a decisive influence on the stereochemistry of the reaction and the absolute configuration of the products. Each enantiomer



Scheme 3. Nitroaldol reaction with various aldehydes.

Table 2
Nitroaldol reaction with various aldehydes

Entry	R	Adduct **4**				
		Symbol	Yield (%)	$[\alpha]_D$[a]	ee[b] (%)	Absolute configuration
1	Ph	**a**	87	−22.0	98	(*R*)
2	2-$MeOC_6H_4$	**b**	90	−45.5	95	(*R*)
3	2-$NO_2C_6H_4$	**c**	87	+228.0	90	(*R*)
4	2-ClC_6H_4	**d**	86	−50.4	87	(*R*)
5	$Ph(CH_2)_2$	**e**	78	+14.2	85	(*R*)
6	*n*-Bu	**f**	85	−9.0	90	(*R*)

[a] In chloroform (*c* 1).
[b] Determined using chiral HPLC.

of the product may be obtained by using easily available diastereomeric ligands.

4. Experimental

4.1. General

The enzymes were purchased from AMANO or FLUKA. The NMR spectra were recorded on a Bruker instrument at 200 MHz with $CDCl_3$ and CD_3OD as solvents. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter (*c* 1). Column chromatography was carried out using Merck 60 silica gel. TLC was performed on Merck 60 F_{254} silica gel plates. The enantiomeric excess (ee) values were determined by chiral HPLC (Varian Pro Star 210, Chiralpak AS).

4.2. Synthesis of tridentate ligands 3a–f

All enantiomerically pure ligands **3a–f** were prepared using a methodology described previously.[10,11]

4.3. Copper acetate—catalyzed Henry reaction of nitromethane with aldehydes—general procedure

Ligand **3** (0.055 mmol) and $Cu(OAc)_2$ monohydrate (10 mg, 0.05 mmol) were placed in a round-bottomed flask. Ethanol (1.5 mL) was added and the mixture was stirred for 1 h. After that, nitromethane (0.54 mL, 10 mmol) and the corresponding aldehyde (1 mmol) were added. After stirring for 48 h the volatile components were evaporated and the crude product was purified by column chromatography (chloroform).

4.3.1. (*R*)-1-Phenyl-2-nitroethanol 4a

Colourless oil yield = 87%. Enantiomeric excess was determined by HPLC with a Chiralpak AS column (85:15 hexane/isopropanol, 0.8 mL/min, 215 nm); major enantiomer t_R = 12.1 min, minor enantiomer t_R = 14.2 min; ee = 98%; $[\alpha]_D$ = −22.0 (*c* 1.00, $CHCl_3$). All spectroscopic data of compound **4a** are in good agreement with those reported the in literature.[4]

4.3.2. (*R*)-1-(2-Methoxyphenyl)-2-nitroethanol 4b

Yellow oil, yield = 90%.Enantiomeric excess was determined by HPLC with a Chiralpak AS column (90:10 hexane/isopropanol, 0.8 mL/min, 215 nm); major enantiomer t_R = 14.6 min, minor enantiomer t_R = 17 min; ee = 95% $[\alpha]_D$ = −45.5 (*c* 1.00, $CHCl_3$). All spectroscopic data of compound **4b** are in good agreement with those reported in the literature.[4]

4.3.3. (*R*)-1-(2-Nitrophenyl)-2-nitroethanol 4c

Dark solid, yield = 87%. Enantiomeric excess was determined by HPLC with a Chiralpak AS column (90:10 hexane/isopropanol, 0.8 mL/min, 215 nm); major enantiomer t_R = 17.6 min, minor enantiomer t_R = 19.2 min; ee = 90%; $[\alpha]_D$ = +228.0 (*c* 1.00, $CHCl_3$). All spectroscopic data of compound **4c** are in good agreement with those reported in the literature.[4]

4.3.4. (*R*)-1-(2-Chlorophenyl)-2-nitroethanol 4d

Colourless oil yield = 86%. Enantiomeric excess was determined by HPLC with a Chiralpak AS column (97:3 hexane/isopropanol, 0.8 mL/min, 215 nm); major enantiomer t_R = 53.0 min, minor enantiomer t_R = 57.2 min; ee = 87%; $[\alpha]_D$ = −50.4 (*c* 1.00, $CHCl_3$).

All spectroscopic data of compound **4d** are in good agreement with those reported in the literature.[4]

4.3.5. (*R*)-1-Nitro-4-phenylbutan-2-ol 4e

White solid yield = 78%. Enantiomeric excess was determined by HPLC with a Chiralpak AS column (87:13 hexane/isopropanol, 0.8 mL/min, 215 nm); major enantiomer t_R = 21.4 min, minor enantiomer t_R = 20.1 min; ee = 85%; $[\alpha]_D$ = +14.2 (*c* 1.00, $CHCl_3$). All spectroscopic data of compound **4e** are in good agreement with those reported in the literature.[4]

4.3.6. (*R*)-1-Nitrohexan-2-ol 4f

Colourless oil yield = 85%. Enantiomeric excess was determined by HPLC with a Chiralpak AS column (98:2 hexane/isopropanol, 0.8 mL/min, 215 nm); major enantiomer t_R = 34.2 min, minor enantiomer t_R = 46.1 min; ee = 90%; $[\alpha]_D$ = −9.0 (*c* 1.00, $CHCl_3$). All spectroscopic data of compound **4f** are in good agreement with those reported in the literature.[4]

Acknowledgement

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References

1. For recent reviews see: (a) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561–2574; (b) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326; (c) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442–5444.
2. Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, *49*, 272–276.
3. Kowalczyk, R.; Sidorowicz, Ł.; Skarżewski, J. *Tetrahedron: Asymmetry* **2008**, *19*, 2310–2315, and references therein.
4. Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693.
5. Liu, S.; Wolf, C. *Org. Lett.* **2008**, *10*, 1831–1834.
6. Bulut, A.; Aslan, A.; Dogan, O. *J. Org. Chem.* **2008**, *73*, 7373–7375.
7. Arai, T.; Takashita, R.; Endo, Y.; Watanabe, M.; Yanagisawa, A. *J. Org. Chem.* **2008**, *73*, 4903–4906, and references therein.
8. Kowalczyk, R.; Kwiatkowski, P.; Skarżewski, J.; Jurczak, J. *J. Org. Chem.* **2009**, *74*, 753–756.
9. Kiełbasiński, P.; Mikołajczyk, M. In *Future Directions in Biocatalysis*; Matsuda, T., Ed.; Elsevier, 2007; pp 159–203.
10. Rachwalski, M.; Kwiatkowska, M.; Drabowicz, J.; Kłos, M.; Wieczorek, W. M.; Szyrej, M.; Sieroń, L.; Kiełbasiński, P. *Tetrahedron: Asymmetry* **2008**, *19*, 2096–2101.
11. In contrast to ligands **3a**–**c**,[10] ligands **3d**–**f** turned out to be efficient catalysts for the diethylzinc addition to benzaldehyde; for their synthesis and application see Leśniak, S.; Rachwalski, M.; Sznajder, E.; Kiełbasiński, P., submitted for publication.
12. Mikołajczyk, M.; Drabowicz, J.; Kiełbasiński, P. *Chiral Sulfur Reagents: Application in Asymmetric and Stereoselective Synthesis*; CRC Press: Boca Raton, 1997.
13. Ferrocenyl(hydroxymethyl)aziridines were recently found to be good catalysts for the Henry reaction. However, instead of copper acetate, diethylzinc was used as the metal component: see Ref. 6.