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Direct asymmetric aldol condensation catalyzed by aziridine semicarbazide zinc(II) complexes



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ABSTRACT

Previously obtained semicarbazides derived from N-triphenylmethyl-aziridine-2-carbohydrazide were explored as ligands in Zn(II) catalyzed diastereo- and enantioselective direct aldol reactions. Complexes of aziridine-semicarbazides with Zn(II) were efficient catalysts in reactions of acetone and hydroxyacetone with NO₂-substituted aromatic aldehydes in the presence of water.

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An important reaction type in modern organic synthesis is the enantioselective carbon-carbon bond formation. Zinc(II) complexes in combination with aziridine ligands are powerful tools in several stereocontrolled reactions such as cycloaddition,¹ nitroaldol (Henry) reactions,² and arylations of aldehydes.³ The aldol condensation is a key tool for the construction of simple βhydroxy carbonyl building blocks, and the ability to control the enantioselectivity of this process is the principal behind the synthesis of many organic and bioorganic systems. Zinc(II) complexes which catalyze the aldol reaction are known in the literature.⁴

On the other hand, aziridine derivatives are versatile ligands, because they can form very strong interactions with Zn(II). More importantly, they are particularly useful in numerous enantioselective carbon-carbon bond-forming reactions such as the addition of diethylzinc and phenylethynylzinc to aldehydes^{5,6} and to enones.

Herein, we report the use of aziridine-2-semicarbazide-type ligands which, in combination with Zn(II), are efficient catalysts in asymmetric aldol reactions. It is worth mentioning that semicarbazide ligands are almost unknown in the field of asymmetric synthesis.

In a series of reports, methods for the synthesis and discussions on the reactivity of diverse carbohydrazide derivatives were described.⁸⁻¹² We also reported a convenient synthesis of semicarbazide ligands starting from N-triphenylmethyl-aziridine-2-carbohydrazide **1**.¹³ Carbohydrazide **1** reacts smoothly with

* Corresponding author. Tel.: +48 426355767. E-mail address: mrach14@wp.pl (M. Rachwalski). isocyanates yielding enantiomerically pure semicarbazides 2, quantitatively (Scheme 1). Compounds 2 were previously tested in asymmetric diethylzinc and phenylethynylzinc additions to aromatic aldehydes proving to be efficient catalysts. In continuation of this research, we decided to test ligands 2 in asymmetric aldol condensations.

The first experiments (Table 1) were performed with p-nitrobenzaldehyde in acetone in the presence of 5 mol % of ligand 2a. After 72 h, only starting materials were isolated. Subsequent experiments were carried out with the addition of 5 mol % of Zn(OTf)₂ (entry 2) and 10% of water (entry 3). Only in the third case we obtained the desired product in 23% yield. The method was modified and a 2.9:0.1 mixture of acetone/water was used to increase the solubility of the ligand and the desired product was obtained in 48% yield and 87% enantiomeric excess.

In the next step, two other ligands (2b, 2c) were tested under the optimized conditions (Table 2, entries 2 and 3). Compound 2c bearing a cyclohexyl ring as the R group (Scheme 1) was the best ligand









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Table 1

Aldol reaction of acetone and p-nitrobenzaldehyde with 5 mol % of 2a under various conditions



Entry	Co-catalyst	Solvent	Yield (%)	ee ^a (%)
1	_	Acetone	0	0
2	$Zn(OTf)_2$	Acetone	0	0
3	$Zn(OTf)_2$	Acetone/H ₂ O 0.9:0.1	23	82
4	Zn(OTf) ₂	Acetone/H ₂ O 2.9:0.1	48	87

^a Determined by HPLC on a Chiralpak OD-H column

Table 2

Aldol reactions of acetone with various aromatic aldehydes using different ligands



Entry	Catalyst	R	Yield (%)	ee ^a (%)
1	2a	4-NO ₂	48	87
2	2b	4-NO ₂	32	84
3	2c	4-NO ₂	58	91
4	2c	4-CF ₃	0	0
5	2c	Н	0	0
6	2c	2-NO ₂	50	61
7	2c	2,4-diNO ₂	67	98

^a Determined by HPLC on a Chiralpak OD-H column.

Table 3

Aldol reactions of hydroxyacetone with aromatic aldehydes

	R R	+ 0 –	R	
Entry	R	Yield (%)	dr ^a (anti:syn)	ee ^a (%) anti:syn
1 2 3	4-NO ₂ 2-NO ₂ 2,4-diNO ₂	80 82 98	80:20 64:36 86:14	16:29 3:16 nd ^b

^a Determined by HPLC on a Chiralpak OD-H column.

^b Not determined.

in the aldol reaction of acetone with *p*-nitrobenzaldehyde, so we decided to test it in reactions with other aromatic aldehydes. Four other aldehydes (Table 2, entries 4–7) were tested, but products were only obtained in the reactions with nitro-substituted compounds. The best result was achieved with 2,4-dinitrobenzal-dehyde and the corresponding adduct was isolated in 67% yield and 98% enantiomeric excess.

As these ligands were found to be efficient catalysts in Zn(II)mediated aldol reactions of acetone, we decided to extend our research using hydroxyacetone as the carbonyl component (Table 3). As the catalyst we used 5 mol % of compound **2c** and 5 mol % of Zn(OTf)₂ in a mixture of hydroxyacetone/water (2.9:0.1). All experiments were performed at room temperature with nitro-substituted aryl aldehydes. The yields were better than those obtained in the case of acetone. The best diastereomeric ratio (86:14) was achieved in the case of 2,4-dinitrobenzaldehyde, but we were unable to determine the enantiomeric excess of the isolated product by HPLC.

The diastero- and enantioselectivity of the presented reactions is in agreement with the literature, where an *anti*-selective process is the most common.^{14,15} However, a number of *syn*-selective direct asymmetric aldol additions have also been reported.4,16 The application of Lewis acidic metal complexes (mimicking the mode of action of type II aldolases) in solvents containing water is still difficult.¹⁷ Zinc can act as an efficient Lewis acid, even in the presence of water, ^{18,19} so we assumed that our ligands in combination with Zn(II) can create zinc-containing catalysts, which act through the generation of a zinc enolate, as similarly described in the literature.^{4,14–20} It should be mentioned that our ligands contain, with the exception of an aziridinvl nitrogen atom which should primarily coordinate a metal atom (strong effective complexation of a zinc cation was described earlier $^{21-23}$), five other potential chelating centers. The proposal of any tentative mechanistic model which could explain the interactions between the substrate and catalysts seems to be rather premature and speculative at this stage of our studies.

In summary, little is known about the use of semicarbazide derivatives as chiral catalysts in asymmetric synthesis. Compounds having an aziridine ring and semicarbazide moiety proved to be very effective ligands in Zn(II)-catalyzed aldol reactions of acetone with nitrobenzaldehydes yielding products with up to 98% ee.²⁴ The same catalytic system in reaction with hydroxyacetone afforded adducts in moderate diastereoselectivity and poor enantioselectivity. These ligands are interesting for further research in the field of asymmetric catalysis.

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24. General procedure for the aldol reactions of acetone and hydroxyacetone with aldehydes: The ketone (2.9 ml) and H_2O (0.1 ml) were added to a vial containing the catalyst (0.025 mmol) and $Zn(OTf)_2$ (0.025 mmol). After vigorous stirring at rt for 15 min the aldehyde was added. The resulting mixture was stirred at rt and monitored by TLC. Following completion, the solvent was evaporated and the aldol product (*anti/syn* mixture) was purified by flash column chromatography (hexane/EtOAc). Spectroscopic data of all

products were in agreement with published data.⁴ 3,4-Dihydroxy-4-(2,4-dinitrophenyl)-butan-2-one (Table 3, entry 3).¹H NMR (*major*): 7.99–7.98 (m, 1H); 7.88–7.86 (m, 1H); 7.51–7.48 (m, 1H); 5.53 (d, J = 2.4 Hz, 1H); 4.44 (d, J = 2.4 Hz, 1H); 4.25 (br s, 1H), 3.59 (br s, 1H); 2.16 (s, 3H); ¹H NMR (*minor*): 8.11–8.09 (m, 1H); 7.81–7.79 (m, 1H); 7.73–7.67 (m, 1H); 5.89 (br s, 1H); 4.55 (d, J = 2.4 Hz, 1H); 3.85 (br s, 1H); 2.18 (s, 3H). HRMS (CI): m/z [M+H]⁺ calcd for C₁₀H₁₁N₂O₇: 271.0561; found 271.0563.