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Zinc(II) mediated asymmetric aldol condensation catalyzed by chiral aziridine ligands

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ABSTRACT

Exploration of chiral aziridine ethers and aziridine alcohols as ligands for the Zn(II) catalyzed enantioselective direct aldol condensations reaction is described. The reaction of acetone with NO_2-substituted aromatic aldehydes in the presence of water gave the desired adducts in moderate chemical yields (40–70%) and good to excellent enantiomeric excesses (80–98% ee).

The aldol condensation reaction is one of the most common tools in modern organic synthesis for the preparation of carbon–carbon bonds.[1–5] While the aldol condensation reaction is traditionally carried out using anhydrous solvents it can also be performed in an aqueous environment. However, this area of research is underdeveloped and remains the current interest of a number of different research groups.[6–12] On the other hand, small organic molecules, for example, amino acid derivatives[13,14] have been successfully used as ligands, which can act as previously studied enzymatic catalysts (mimicking of type II aldolases[14]), and thus promote aldol reactions originally catalyzed by the enzymes.

In a series of Letters we have described the application of various zinc(II) complexes with aziridine ligands in several stereoselective reactions; such as the addition of diethylzinc and phenylethynylzinc to aldehydes[15–21] and enones.[22] Furthermore, chiral aziridine ligands[23] have been successfully applied to the asymmetric aldol condensation reaction in the presence of Zn(II) salts.[24]

As a continuation of our research interests, we decided to examine the catalytic activity of previously synthesized aziridine alcohols[20] and aziridine ethers[21] in the asymmetric aldol reaction.

Chiral *N*-trityl aziridine alcohols **1** and aziridine ethers **2** were synthesized as previously described.[20,21] Catalysts of type **1** were obtained from *N*-trityl aziridine-2-carboxylic acid ester via the corresponding Weinreb amide and subsequent reaction with various Grignard reagents leading to aziridinyl ketones which upon reduction gave the desired *N*-trityl aziridine alcohols **1a–e** as 59:41 mixtures of diastereoisomers.[20]

Aziridine ethers were prepared from phenoxyacetyl chloride, which upon treatment with a series of the corresponding secondary aziridines and subsequent reduction of the tertiary amide, gave optically pure (*S*)-**2a**, (*S*)-**2b**, (*R*)-**2b**[21] (Scheme 1).

Having a series of chiral aziridine catalysts **1a–e** and **2a**,**b** in hand, we examined their catalytic activity in the stereocontrolled asymmetric aldol condensation of acetone and 4-nitrobenzaldehyde in the presence of 5 mol % catalyst and 5 mol % $Zn(OTf)_2$ in acetone/water (2.9/0.1) (Scheme 2).[24,25]

The reaction time was optimized for 72 h, after which the reaction products were isolated via column chromatography.

As shown in Table 1, aziridine alcohol ligands **1a–e** exhibited similar catalytic activities leading to the corresponding adduct in yields ranging from 40% to 54% and enantiomeric excesses in the range of 90–93%. Chiral aziridine ethers **2a**,**b** also possessed comparable catalytic efficacy with (*S*)-**2b** (bearing a (*S*)-2-isopropylaziridine moiety) emerging as the best ligand to afford the corresponding aldol adduct in 60% yield and 93% ee (Table 1, entry 7).

The most effective ligand (*S*)-**2b** was also tested as a chiral catalyst in the aldol condensation of acetone with 2-nitro- and 2,4-dinitrobenzaldehyde (Table 1, entries 9 and 10). In both cases, the yields of the corresponding adducts were higher than with 4-nitrobenzaldehyde (72%), however the values of enantiomeric

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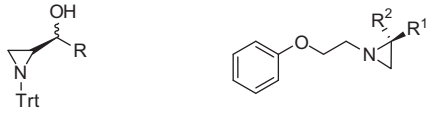
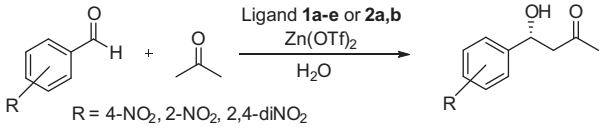


1 2

R = Me (**1a**) R = Bn (**1d**)
R = Ph (**1b**) R = H (**1e**)
R = ^{i}Pr (**1c**)

R^1 = Me, R^2 = H ((*S*)-**2a**)
R^1 = *i*Pr, R^2 = H ((*S*)-**2b**)
R^1 = H, R^2 = *i*Pr ((*R*)-**2b**)

Scheme 1. Chiral aziridine ligands **1a**–**e** and **2a**,**b**.



Scheme 2. Asymmetric aldol reaction catalyzed by chiral aziridine ligands **1a**–**e** and **2a**,**b**.

Table 1
Aldol reaction of acetone with various aromatic aldehydes and ligands

Entry	Catalyst	R	Yield (%)[a]	ee[b] (%)	Abs conf.[c]
1	**1a**	4-NO_2	50	93	*R*[27]
2	**1b**	4-NO_2	40	92	*R*[27]
3	**1c**	4-NO_2	48	91	*R*[27]
4	**1d**	4-NO_2	52	90	*R*[27]
5	**1e**	4-NO_2	54	93	*R*[27]
6	**2a**	4-NO_2	40	88	*R*[27]
7	**2b**	4-NO_2	60	93	*R*[27]
8	**2c**	4-NO_2	44	90	*S*[27]
9	**2b**	2-NO_2	72	47	*R*[28]
10	**2b**	2,4-DiNO_2	72	98	*R*[29]

[a] Reaction conditions: acetone (2.9 mL), H_2O (0.1 mL), catalyst (0.025 mmol), Zn $(OTf)_2$ (0.025 mmol), aldehyde (1 mmol), 72 h, rt).
[b] Determined by HPLC using a Chiralpak OD-H column.
[c] Taken from the literature[27–29] (on the basis of optical rotations signs and retention times in HPLC chromatograms).

excess were variable—47% for the reaction of 2-nitrobenzaldehyde (Table 1, entry 9) and 98% for the reaction of 2,4-dinitrobenzaldehyde (Table 1, entry 10). The use of aziridine carbinols **1a**–**e** led to adducts with (*R*)-absolute configuration. The use of both enantiomers of aziridine ethers (*S*)-**2b** and (*R*)-**2b** gave the opposite enantiomers of adducts (entries 7 and 8) which was in accordance with our previous findings.[26]

We presume that aziridine ligands **1a**–**e** and **2a**,**b** in combination with the Zn(II) salt creates an active catalyst which acts as a Lewis acid through the generation of a zinc enolate (also mimicking the mode of action of type II aldolase).[14,29–32]

It is worth mentioning that the application of chiral, small amine–ether molecules as catalysts, have only been described sporadically in the literature.[21,33–36]

The scope of the substrates was limited to nitro-substituted aldehydes due the fact that such compounds exhibit the highest activity in this reaction[12,14] (especially 2-nitrosubstituted ones as explained by Maycock and Ventura[37]). Previous experiments conducted in our group using benzaldehydes without the nitro functional group in the reaction with acetone as well as aliphatic aldehydes in the reaction with cyclohexanone[14] gave no products or proceeded with low chemical yields and ee values around 10%.

In conclusion we have reported that aziridine-ether ligands in combination with $Zn(OTf)_2$ in the presence of water constitutes an efficient catalytic system for the aldol reaction of acetone with nitrobenzaldehydes furnishing products with up to 98% ee.

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