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Highly efficient conjugate additions of diethylzinc to enones promoted by chiral aziridine alcohols and aziridine ethers

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ABSTRACT

Chiral heteroorganic *N*-trityl aziridine alcohols and aziridine ethers have proven to be highly efficient catalysts in enantioselective conjugate diethylzinc additions to enones, namely chalcone and 2-cyclohexen-1-one providing the desired chiral adducts in high chemical yields (up to 95%) and with ee's up to 93%. The change of the absolute configuration of the stereogenic center located at the aziridine moiety on the stereochemical outcome is also discussed.

1. Introduction

Asymmetric synthesis constitutes one of the main fields in modern organic chemistry.[1–3] The choice of the appropriate chiral catalyst plays a crucial role in the formation of the desired products in good chemical yield and with elevated enantiomeric excess values. Carbon–carbon bond formation in an enantioselective fashion using organometallic reagents is one of the most common and useful synthetic methodologies in stereoselective synthesis.[4–6] Among the reactions applied, the enantioselective addition of diethylzinc to carbonyl compounds (1,2-addition) and to enones (1,4-addition) are the basic model reactions that are commonly used for testing the catalytic activity of newly developed chiral ligands.[7,8]

Previously, we have described a highly enantioselective conjugate Michael addition of diethyl zinc to enones promoted by tridentate sulfinyl aziridine-containing ligands[9] and by diast ereomerically pure aziridine alcohols derived from (*S*)-mandelic acid.[10] More recently, we have reported the synthesis of a series of novel chiral catalysts, *N*-trityl aziridine carbinols,[11] and aziridine ethers,[12] and their high catalytic activity in the asymmetric addition of diethylzinc and phenylethynylzinc to aldehydes. It is worth noting that small-molecule amine ether ligands are scarcely reported in the chemical literature.[13–16]

In continuation of our interests in the field of asymmetric synthesis,[17–21] and taking all of the aforementioned results into account, we decided to extend the scope of the applicability of aziridine alcohols[11] and aziridine ethers[12] using them as chiral catalysts for the conjugate Michael additions of diethylzinc to enones.

2. Results and discussion

Aziridine alcohols **1a–d** and aziridine ethers **2a–c** synthesized as reported previously[11,12] were applied (Fig. 1).

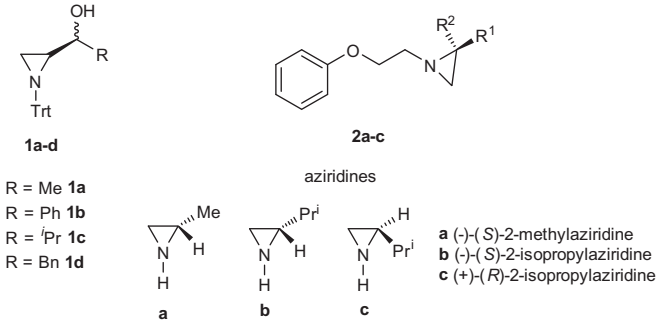

Figure 1. Catalysts for the asymmetric Michael addition of diethyl zinc to enones.

Since the asymmetric 1,4-addition of diethylzinc to α,β-unsaturated carbonyl compounds (enones) requires the application of a metal catalyst,[22–25] nickel acetylacetonate $Ni(acac)_2$ was used and ligands **1a–d** and **2a–c** were tested for their catalytic activity in the asymmetric addition of diethylzinc to chalcone **3** (Scheme 1) and 2-cyclohexen-1-one **5** (Scheme 2). Some experiments in the absence of $Ni(acac)_2$ were also carried out in order to prove the importance of the metal catalyst. All of the results are summarized in Table 1.

From Table 1 it can be seen that all ligands **1a–d** and **2a–c** can catalyze the title Michael addition to deliver chiral adducts in high chemical yields and with high enantiomeric excess values. The use

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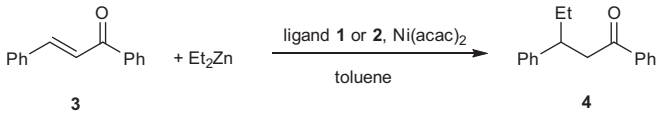
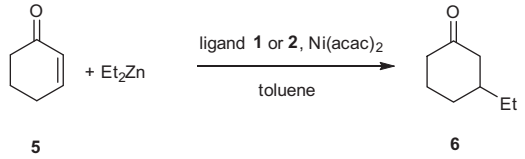
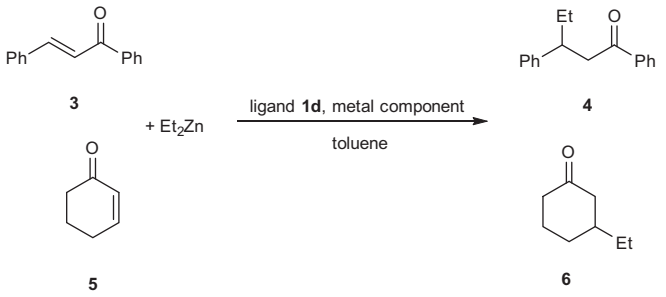


Scheme 1. Asymmetric conjugate Michael addition of diethylzinc to chalcone.



Scheme 2. Asymmetric conjugate Michael addition of diethylzinc to 2-cyclohexen-1-one.



Scheme 3. Screening of various metal components in the Et_2Zn addition to enones **3** and **5**.

of both enantiomeric ligands **2b** and **2c** led to the formation of chiral products **4** and **6** with opposite absolute configurations. The same phenomenon was also observed when using other heteroorganic ligands in asymmetric conjugated additions of diethylzinc to enones.[9,10] Finally, in the absence of a nickel catalyst (Table 1, entries 5 and 8), the 1,4-addition took place, albeit with significantly lower values of chemical yield and enantiomeric excess. This proves that the metal catalyst plays an important role in terms of efficiency and high stereoselectivity of the title reaction, however the crucial factor influencing the stereochemistry of this process constitutes the presence and the configuration of the aziridine ring. It should be noted that the presence of the oxygen atom is necessary as a second complexing center of the catalyst (we did not observe any catalytic effect of non-functionalized enantiomerically pure aziridine in this reaction), while the substituent on the nitrogen atom as well as the chemical character of the oxygen function did not play any important role. This assumption is in full agreement with our previous observations.[11]

With the best results in terms of chemical yield and enantiomeric excess for the reaction catalyzed by ligand **1d** in hand, further studies involving the application of other metal components were performed. Thus, substrates **3** and **5** were subjected to the diethylzinc addition in the presence of the most effective ligand **1d**, using copper(II) acetate, zinc trifluoromethanesulfonate $Zn(OTf)_2$ and tin(II) trifluoromethanesulfonate $Sn(OTf)_2$ (Scheme 3). The results are summarized in Table 2.

From Table 2 it can be seen that all of the metal catalysts tested were less effective in comparison with the previously applied nickel acetylacetonate. Additionally, tin(II) trifluoromethanesulfonate proved to be ineffective in the title addition reaction leading to both products in low chemical yields (22% and 18%, respectively) and with poor ee values (15% and 13%, respectively).

To continue our investigations into the application of aziridine alcohols of type **1** as catalysts in the conjugate Michael addition of diethylzinc to enones, two another ligands **1e** and **1f** (synthesized as described previously[11]) were applied (Fig. 2).

Ligand **1e** was applied in order to check the action of an enantiomerically pure alcohol bearing a primary hydroxyl group at a stereogenic carbon atom, whereas ligand **1f** with an opposite absolute configuration at the aziridine carbon atom was introduced in order to examine the influence of the stereogenic center located in the aziridine subunit on the stereochemical outcome of the title reaction. The results are summarized in Table 3.

These results reveal that ligand **1e** bearing a primary hydroxyl group at a stereogenic carbon atom is prone to catalyze the title reaction to afford the desired products **4** and **6** in good chemical yields and enantiomeric excess values (Table 3, entry 1). More interestingly, the use of ligand **1f** bearing an opposite configuration at the aziridine carbon atom led to products with opposite absolute configurations (in comparison with the use of ligand **1d**). This may suggest that the stereogenic center located at aziridine subunit has a decisive influence on the stereochemical outcome of the addition reaction. This assumption is in agreement with the literature.[9–12]

Finally, in order to check the influence of the ether subunit of ligands type **2** on the chemistry and stereochemistry of the asymmetric diethylzinc addition to enones, three novel catalysts bearing (*S*)-2-isopropylaziridine subunit **2d–f** were synthesized (Fig. 3) according to the literature.[12]

Ligand **2d** derived from 2-benzyloxyacetic acid constitutes an aliphatic ether system, whereas ligands **2e–f** were tested in order to check the presence and character of the substituents in the phenyl ring. All of the results are summarized in Table 4.

Table 1
Screening of ligands **1a–d** and **2a–c**

Entry	Ligand	Product **4**				Product **6**			
		Yield (%)	$[\alpha]_D$[a]	ee[b] (%)	Abs. config.	Yield (%)	$[\alpha]_D$[a]	ee[b] (%)	Abs. config.[c]
1	**1a**	85	−2.1	82	(*R*)	80	−8.4	79	(*S*)
2	**1b**	90	−2.2	86	(*R*)	84	−9.2	86	(*S*)
3	**1c**	93	−2.3	90	(*R*)	88	−9.5	89	(*S*)
4	**1d**	95	−2.4	92	(*R*)	91	−9.9	93	(*S*)
5	**1d**[d]	46	−1.0	40	(*R*)	42	−4.6	43	(*S*)
6	**2a**	83	−2.1	82	(*R*)	81	−8.2	77	(*S*)
7	**2b**	91	−2.3	89	(*R*)	89	−9.6	90	(*S*)
8	**2b**[d]	44	−0.9	38	(*R*)	40	−4.2	39	(*S*)
9	**2c**	87	+2.2	86	(*S*)	86	+9.3	87	(*R*)

[a] In chloroform (*c* 1).
[b] Determined using chiral HPLC.
[c] According to literature data.[25]
[d] No $Ni(acac)_2$ added.