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Highly efficient conjugate addition of diethylzinc to enones catalyzed by chiral ligands derived from (*S*)-mandelic acid

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ABSTRACT

Diastereomerically pure heteroorganic catalysts built on the chiral scaffold of (*S*)-(+)-mandelic acid and containing secondary hydroxyl and aziridine moieties, have proven to be highly efficient for the enantioselective conjugate diethylzinc addition to chalcone and 2-cyclohexen-1-one to afford the desired chiral adducts in high yields (up to 92%) and with ee's of up to 90%. The influence of the stereogenic center located at the aziridine moiety on the stereochemical outcome is also discussed.

1. Introduction

The synthesis of chiral, enantiomerically pure compounds is an important aspect of synthetic organic chemistry due to the high importance of single chirality in industrial sectors (e.g., pharma and food).[1] As a result, the design and synthesis of appropriate catalysts for asymmetric transformations are crucial in order to create chiral products stereoselectively.

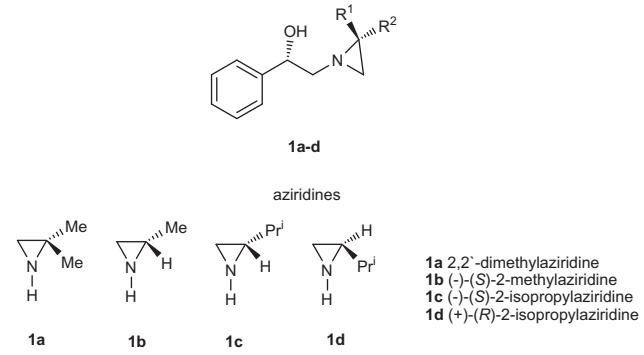
Enantioselective carbon–carbon bond formation using organometallic reagents is one of the most useful synthetic methodologies in recent years.[2] Among the reactions developed, the asymmetric addition of diethylzinc to carbonyl compounds (a 1,2-addition) and to enones (a 1,4-addition) is a model reaction that is commonly used for testing the catalytic activity of newly developed chiral ligands.[3–9]

Previously, we have reported on a highly enantioselective conjugate Michael addition of diethyl zinc to enones catalyzed by tridentate sulfinyl aziridine-containing ligands.[3] These ligands have proven to be versatile catalysts for enantioselective diethyl- and phenylethynylzinc additions to aldehydes.[10,11] More recently, we have described the synthesis of a series of diastereomerically pure aziridine alcohols derived from (*S*)-mandelic acid, and their high catalytic activity in the asymmetric addition of diethylzinc and phenylethynylzinc to aldehydes.[12]

An easy access to both enantiomeric products using isomeric forms of the ligand was demonstrated. As a continuation of our interests in the field of asymmetric synthesis,[13–16] and taking all of the aforementioned results into account, we have decided to extend the scope of the applicability of the ligands[12] derived from (*S*)-mandelic acid by using them as catalysts for the conjugate Michael addition of diethylzinc to enones.

2. Results and discussion

Four ligands prepared as described previously[12] were applied (Scheme 1).



Scheme 1. Ligands for the asymmetric Michael addition of diethyl zinc to enones.

Ligands **1c** and **1d** with aziridinyl groups that originated from both enantiomers of 2-*iso*-propylaziridine **c** and **d** were used to determine the possible match-mismatch effect of both stereogenic centers. Ligand **1a** bearing an achiral aziridine **a** was used to check the influence of the stereogenic center located in the mandelic acid moiety on the stereochemical course of the addition. Since the asymmetric 1,4-addition of diethylzinc to enones requires a metal catalyst,[17–20] nickel acetylacetonate $Ni(acac)_2$ was used and ligands **1a**–**d** were screened for their catalytic activity in the diethylzinc addition to chalcone **2** (Scheme 2) and 2-cyclohexen-1-one **4** (Scheme 3). In order to prove the importance of the metal catalyst,

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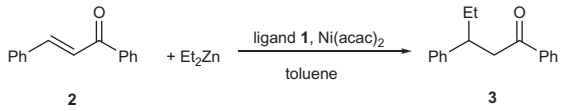
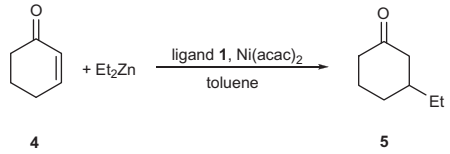


Scheme 2. Asymmetric conjugate Michael addition of diethylzinc to chalcone.



Scheme 3. Asymmetric conjugate Michael addition of diethylzinc to 2-cyclohexen-1-one.

experiments without $Ni(acac)_2$ were also carried out. All of the results are collected in Table 1.

Table 1
Screening of ligands **1a–d**

Entry	Ligand	Product **3**				Product **5**			
		Yield (%)	$[\alpha]_D$[a]	ee[b] (%)	Abs config.	Yield (%)	$[\alpha]_D$[a]	ee[b] (%)	Abs config.[c]
1	**1a**	42	−1.2	46	(*R*)	39	−4.7	44	(*S*)
2	**1b**	90	−2.3	89	(*R*)	88	−9.5	89	(*S*)
3	**1c**	93	−2.3	91	(*R*)	92	−9.6	90	(*S*)
4	**1c**[d]	50	−1.2	53	(*R*)	48	−4.9	46	(*S*)
5	**1d**	91	+2.3	90	(*S*)	90	+9.4	88	(*R*)

[a] In chloroform (*c* 1).
[b] Determined using chiral HPLC.
[c] According to the literature data.[20]
[d] No $Ni(acac)_2$ added.

Table 1 shows some noteworthy findings. First, the formation of enantiomerically enriched products **3** and **5** in the presence of catalyst **1a**, containing an achiral 2,2-dimethylaziridine, indicates that the stereogenic center located in the aziridine moiety has a decisive influence on the stereochemistry of the reaction. Second, the use of both diastereomeric ligands **1c** and **1d** led to the formation of chiral products **3** and **5** with opposite absolute configurations. The small differences in their ee values may be explained in terms of 'match' and 'mismatch' interactions with the stereogenic center located in the mandelic acid moiety. The same tendency was previously observed using other heteroorganic ligands in asymmetric conjugate additions of diethylzinc to enones.[3] Finally, in the absence of a nickel catalyst (entry 4), the 1,4-addition took place, although chemical yield and enantiomeric excess of **3** and **5** were significantly lower. As a result, the use of a metal catalyst is crucial for both the efficiency and high stereoselectivity of the title reaction. Additionally, the high chemical yield and enantiomeric excess of the product of the nickel-catalyzed addition of diethylzinc to 2-cyclohexen-1-one [(*S*)-*trans* enone] were somewhat unexpected due to the usually accepted mechanism and previous literature findings[18] that only (*S*)-*cis* enones were good substrates for the title reaction. However, this unusual phenomenon was observed in our previous studies on the nickel-catalyzed addition of diethylzinc to (*S*)-*cis* and (*S*)-*trans* enones using chiral heteroorganic aziridine alcohols.[3] This fact might be based on the extraordinary ability of aziridines to form complexes with various zinc species,[21–23] leading to the desired chiral product **5** probably via another mechanistic pathway than reported earlier.[18] Further mechanistic studies into this process will be undertaken.

3. Conclusion

The chiral bidentate ligands of type **1** derived from (*S*)-(+)-mandelic acid containing two stereogenic centers were found to be highly effective catalysts for the enantioselective conjugate Michael additions of diethylzinc to enones (chalcone and 2-cyclohexen-1-one, respectively). The stereogenic centers located at the azirdine moieties had a decisive influence on the stereochemistry of the reactions. It should be noted that each enantiomer of the designed product should be available by the use of the respective diastereomeric ligands.

4. Experimental

4.1. General

Unless otherwise specified, all reagents were purchased from commercial suppliers and used without further purification. Toluene was distilled from sodium benzophenone ketyl radical. ^1H NMR spectra were recorded on a Bruker instrument at 600 MHz with $CDCl_3$ as the solvent and relative to TMS as the internal standard. Data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter with a sodium lamp at room temperature (*c* 1). Column chromatography was carried out using Merck 60 silica gel. TLC was performed on Merck 60 F_{254} silica gel plates. Visualization was accomplished with UV light (254 nm) or using iodine vapor. The enantiomeric excess (ee) values were determined by chiral HPLC (Knauer, Chiralcel AS). Aziridines **a–d** were prepared according to the literature.[24] Chiral bidentate ligands were synthesized using the procedure previously described.[12]

4.2. General protocol for the conjugate Michael addition of diethylzinc to α,β-unsaturated enones using the chiral bidentate ligands and $Ni(acac)_2$

A solution of $Ni(acac)_2$ (0.018 g, 0.07 mmol) and chiral ligand **1a–d** (0.11 mmol) in 5 mL of freshly distilled toluene was stirred under a nitrogen atmosphere at room temperature for 1 h. After this time, the corresponding substrate (1 mmol) was added, the mixture was cooled to −20 °C, and a solution of diethylzinc in hexane (1.0 M) (1.65 mL, 1.65 mmol) was added. The mixture was stirred at −20 °C for 1 h and at room temperature overnight. After complete conversion (TLC), the reaction mixture was poured into 20 mL of 1 M HCl and extracted three times with diethyl ether. The combined organic phases were washed with brine and dried over anhydrous magnesium sulfate. Filtration and evaporation yielded the crude products **3** and **5**. After purification via column chromatography on silica gel using hexane and ethyl acetate in gradient as an eluent, pure products **3** and **5** were obtained. Chemical yields, enantiomeric excesses (determined by chiral HPLC), and specific rotation values are shown in Table 1.

4.2.1. (*R*)-(−)-1,3-Diphenyl-pentan-1-one 3

Colorless solid; ^1H NMR ($CDCl_3$): δ = 0.75 (t, *J* = 7.3 Hz, 3H), 1.56–1.60 (m, 1H), 1.71–1.74 (m, 1H), 3.16–3.22 (m, 3H), 7.10–7.34 (m, 5H), 7.35–7.38 (m, 2H), 7.44–7.47 (m, 1H), 7.82–7.83 (m, 2H). Other spectroscopic data of compound **3** are in agreement with the literature.[20]

4.2.2. (*S*)-(−)-3-Ethylcyclohexanone 4

Colorless liquid; ^1H NMR ($CDCl_3$): δ = 0.93 (t, *J* = 7.2 Hz, 3H), 1.28–1.41 (m, 3H), 1.67–1.74 (m, 2H), 1.94–2.39 (m, 6H). Other

spectroscopic data of compound **5** are in agreement with the literature.[20]

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