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Highly enantioselective addition of phenylethynylzinc to aldehydes using aziridine-functionalized tridentate sulfinyl ligands

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ABSTRACT

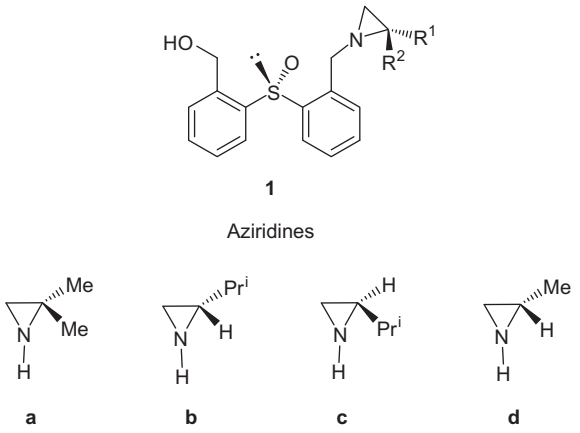
Diastereomerically pure tridentate heteroorganic ligands containing hydroxyl, sulfinyl and aziridine moieties as nucleophilic centers, capable of binding to various organometallic reagents, have been proven to be highly efficient catalysts in the enantioselective addition of phenylethynylzinc to aldehydes to give the desired products in very high yields (up to 95%) and with ee's up to 90%. The influence of the stereogenic centers located on the sulfinyl sulfur atom and in the aziridine moiety on the stereochemical course of the reaction is also discussed.

1. Introduction

Enantioselective carbon–carbon bond formation using organozinc reagents is commonly and widely used in the synthesis of chiral non-racemic compounds and is one of the most successful areas of asymmetric synthesis in recent years.[1,2] The enantioselective alkynylzinc addition to carbonyl compounds[3] is very useful in the preparation of chiral non-racemic propargyl alcohols, which are important building blocks in the synthesis of various biologically active and natural products.[4]

We have recently reported the synthesis of chiral tridentate ligands, bearing hydroxyl, sulfinyl, and amino moieties, with two stereogenic centers located on the sulfinyl sulfur atom and on the carbon atom in the amine moiety.[5] These ligands have proven to be very efficient catalysts for various stereoselective reactions of asymmetric synthesis, namely for nitroaldol (Henry) reactions (those bearing chiral acyclic amine moieties),[6] for enantioselective diethylzinc additions to aldehydes;[7] and enantioselective conjugate Michael additions of diethylzinc to enones[2] (those bearing chiral aziridinyl substituents). Each enantiomer of the product may be obtained using readily available enantiopure diastereomeric ligands.

Taking into account the aforementioned results, we have decided to extend the activity of our tridentate ligands by using them as catalysts for the enantioselective addition of phenylethynylzinc reagents to aldehydes.



Scheme 1. Ligands for the asymmetric addition of phenylethynylzinc to aldehydes.

2. Results and discussion

2.1. Screening of the ligands

Four chiral tridentate ligands containing aziridine moieties were considered, because the best results during the diethylzinc addition to aldehydes and enones were obtained using these chiral catalysts (Scheme 1).

To check the ability of the ligands for catalyzing the enantioselective addition of alkynylzinc reagents to aldehydes, we chose the addition of phenylacetylene and diethylzinc to benzaldehyde as a reference transformation. The reactions were performed under standard conditions (Scheme 2) and the results are shown in Table 1.

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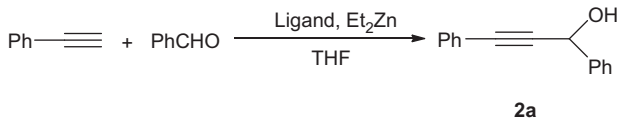


2a

Scheme 2. Screening of ligands **1**.

Table 1
Screening of ligands **1**

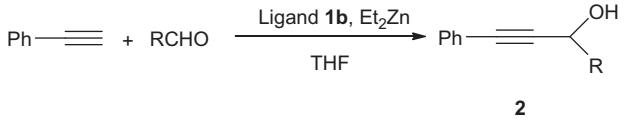
Entry	Ligand (absolute configuration)	Product **2a**			
		Yield (%)	$[\alpha]_D$[a]	ee[b] (%)	Absolute configuration[c]
1	**1a** (R_S)	62	−2.9	57	(*S*)
2	**1b** (R_S,S_C)	96	−5.05	98	(*S*)
3	**1c** (R_S,R_C)	94	+4.9	95	(*R*)
4	**1d** (R_S,S_C)	91	−4.7	92	(*S*)

[a] In chloroform, *c* 1.
[b] Determined using chiral HPLC.
[c] Taken from the literature.[8]

Inspection of Table 1 reveals that the formation of enantiomerically enriched product **2** in the presence of catalyst **1a**, bearing an achiral aziridine moiety, indicates that the stereogenic sulfinyl group exerts a moderate asymmetric induction. Moreover, the reactions promoted by two diastereomeric catalysts **1b** and **1c**, possessing opposite enantiomers of 2-isopropylaziridine, led to the formation of the opposite enantiomers of product **2**. This means that the stereogenic center located in the aziridine moiety exerts a decisive influence on the stereochemistry of the reaction and hence on the absolute configuration of the addition product. The small differences in the ee values of the product may be explained in terms of 'match' and 'mismatch' interactions with the stereogenic sulfinyl center.

2.2. Addition of phenylethynylzinc to various aldehydes in the presence of catalyst 1b

Having obtained the best results with ligands **1b** and **1c**, we then decided to check the scope of the reaction. The title reaction was performed using a series of aldehydes in the presence of ligand **1b** as a catalyst (Scheme 3). The results are collected in Table 2.



2

Scheme 3. The addition of phenylethynylzinc to various aldehydes in the presence of ligand **1b**.

The results clearly indicate that the selected ligand **1b** very efficiently catalyzes the title reaction to give the appropriate propargylic alcohols in high yields with high enantiomeric excesses. Both aryl and alkyl aldehydes are suitable for the reaction. Interestingly, no product of conjugate addition is formed in the case of cinnamaldehyde (Table 2, entry 7). Since both diastereomers of this ligand, **1b** and **1c**, 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 propargylic alcohols.

3. Conclusions

Chiral tridentate ligands, which contain two stereogenic centers, one located on the sulfinyl sulfur atom, and the other on the carbon atom in the aziridine moiety, were found to be very efficient catalysts for the enantioselective addition of phenylacetylenezinc to aldehydes. The stereogenic centers located in the amine moieties exerted a decisive influence on the stereochemistry of the reaction and the absolute configuration of the products. Each enantiomer of the product may be obtained by using easily available diastereomeric ligands.

Table 2
Addition of phenylethynylzinc to aldehydes in the presence of **1b**

Entry	R	Product **2**				
		Symbol	Yield (%)	$[\alpha]_D$[a]	ee[b] (%)	Absolute configuration[c]
1	Ph	**a**	96	−5.05	98	(*S*)
2	2-MeC_6H_4	**b**	93	−11.5	92	(*R*)
3	2-MeOC_6H_4	**c**	96	−8.0	97	(*R*)
4	2-ClC_6H_4	**d**	94	−12.5	95	(*R*)
5	4-BrC_6H_4	**e**	87	+4.05	94	(*R*)
6	*n*-Pr	**f**	95	−3.3	94	(*S*)
7	E-PhCH=CH	**g**	80	−0.95	91	(*R*)

[a] In chloroform, *c* 1.
[b] Determined using chiral HPLC.
[c] Taken from the literature.[8–10]

4. Experimental

4.1. General

Unless otherwise specified, all reagents were purchased from commercial suppliers and used without further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl radical. NMR spectra were recorded on a Bruker instrument at 600 MHz with $CDCl_3$ as 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 or permanganate stain, followed by heating. The enantiomeric excess (ee) values were determined by chiral HPLC (Knauer, Chiralcel OD). Chiral tridentate ligands were obtained using the procedure previously described.[5]

4.2. General procedure for the asymmetric addition of phenylethynylzinc to aldehydes

To a solution of ligand **1** (0.2 mmol) in THF (5 mL), was added a solution of Et_2Zn (1.4 mL, 1.4 mmol, 1.0 M in hexane) at room temperature under an argon atmosphere. After the mixture was stirred at ambient temperature for 30 min., phenylacetylene (0.154 mL, 1.4 mmol) was added, and stirring continued for another 30 min. The solution was cooled to 0 °C and treated with an aldehyde (1 mmol) and then the resultant mixture stirred for 2 h at 0 °C and overnight at room temperature. After completion of the reaction (TLC), it was quenched by 5% aqueous HCl. The mixture was extracted with ether, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography (silica gel, hexane, and ethyl acetate in gradient) to give the product. The yields, specific rotations, and enantiomeric excess values are shown in Tables 1 and 2.

4.2.1. (*S*)-1,3-Diphenyl-prop-2-yn-1-ol 2a

Yellow liquid; ^{1}H NMR ($CDCl_3$): δ = 2.39 (br s, 1H), 5.67 (s, 1H), 7.33–7.62 (m, 10H). Other spectroscopic data of compound **2a** are in agreement with those reported in the literature.[8]

4.2.2. (*R*)-1-(2-Methylphenyl)-3-phenyl-prop-2-yn-1-ol 2b

Yellowish oil; ^{1}H NMR ($CDCl_3$): δ = 2.27 (br s, 1H), 2.54 (s, 3H), 5.87 (s, 1H), 7.22–7.38 (m, 6H), 7.48–7.52 (m, 2H), 7.75–7.78 (m, 1H). Other spectroscopic data of compound **2b** are in agreement with those reported in the literature.[8]

4.2.3. (*R*)-1-(2-Methoxyphenyl)-3-phenyl-prop-2-yn-1-ol 2c

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 3.12 (br s, 1H), 3.96 (s, 3H), 5.97 (s, 1H), 6.97–7.04 (m, 2H), 7.28–7.39 (m, 4H), 7.50–7.52 (m, 2H), 7.67–7.69 (dd, J = 7.4 Hz, 1H). Other spectroscopic data of compound **2c** are in agreement with those reported in the literature.[8]

4.2.4. (*R*)-1-(2-Chlorophenyl)-3-phenyl-prop-2-yn-1-ol 2d

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 2.41 (br s, 1H), 6.08 (s, 1H), 7.31–7.53 (m, 8H), 7.86–7.88 (m, 1H). Other spectroscopic data of compound **2d** are in agreement with those reported in the literature.[8]

4.2.5. (*R*)-1-(4-Bromophenyl)-3-phenyl-prop-2-yn-1-ol 2e

Yellowish oil; ^{1}H NMR ($CDCl_3$): δ = 2.42 (br s, 1H), 5.68 (s, 1H), 7.29–7.31 (m, 2H), 7.34–7.39 (m, 3H), 7.49–7.57 (m, 4H). Other spectroscopic data of compound **2e** are in agreement with those reported in the literature.[9]

4.2.6. (*S*)-1-Phenyl-hex-1-yn-3-ol 2f

Yellowish oil; ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, J = 7.2 Hz, 3H), 1.52–1.59 (m, 2H), 1.74–1.81 (m, 2H), 2.01 (br s, 1H), 4.61 (t, J = 6.6 Hz, 1H), 7.29–7.32 (m, 3H), 7.42–7.44 (m, 3H). Other spectroscopic data of compound **2f** are in agreement with those reported in the literature.[9]

4.2.7. (*R*)-1,5-Diphenyl-pent-1-en-4-yn-3-ol 2g

Yellow solid; ^{1}H NMR ($CDCl_3$): δ = 2.20 (br s, 1H), 5.29 (d, J = 6.0 Hz, 1H), 6.40 (dd, J = 6.0 Hz, J = 15.6 Hz, 1H), 6.85 (d, J = 15.6 Hz, 1H), 7.26–7.50 (m, 10H). Other spectroscopic data of compound **2g** are in agreement with those reported in the literature.[9]

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