Tetrahedron: *Asymmetry* 26 (2015) 148–151

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Aziridinylethers as highly enantioselective ligands for the asymmetric addition of organozinc species to carbonyl compounds

Adam M. Pieczonka, Stanisław Leśniak, Szymon Jarzyński, Michał Rachwalski *

University of Łódź, Department of Organic and Applied Chemistry, Tamka 12, 91-403 Łódź, Poland

ARTICLE INFO

Article history:
Received 24 November 2014
Accepted 10 December 2014

ABSTRACT

In the present paper a straightforward and efficient method for the synthesis of new chiral aziridinylether systems has been described. All of the new compounds have been tested in two stereocontrolled addition reactions of organozinc species to carbonyl compounds. The addition of diethyl- and phenylethynylzinc to aryl and alkyl aldehydes afforded the corresponding chiral products in high chemical yields (up to 90%) and with excellent ee's of approximately 93%.

1. Introduction

Nitrogen-containing chiral ligands are widely applied in asymmetric catalysis,[1,2] due to the coordination ability of the amine function toward metal species, ranging from lithium and magnesium to zinc, copper, early transition metal complexes and also precious metals. Among the various chiral nitrogen-bearing ligands, amine alcohols constitute one of the most applicable and effective groups of catalysts in asymmetric synthesis.[3] It should be stressed that in the literature reports concerning the use of chiral amine-functionalized ligands in asymmetric synthesis, such applications of amine ether derivatives are rarely reported on. In addition to crown ethers with an amino function, which are used in stereocontrolled reactions,[4,5] the application of chiral, small molecules of amine ethers has only been described randomly.[6–9] On the other hand, chiral amine alcohols bearing an aziridine subunit as an amino function have proven to be highly efficient catalysts in asymmetric reactions in the presence of organozinc compounds especially in reactions, such as the addition of diethyl- and phenylethynylzinc to carbonyl compounds.[10–18]

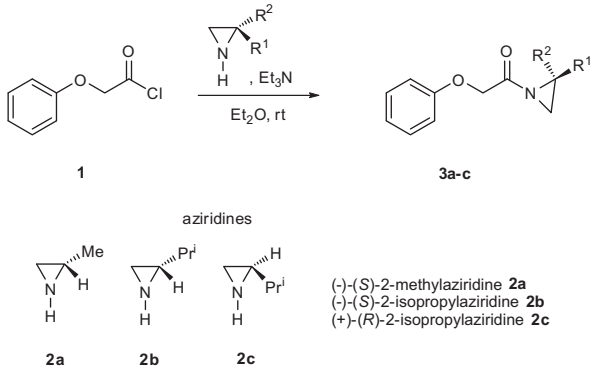
Taking into account all of the aforementioned literature reports we have decided to synthesize a series of new aziridinylether ligands and to check their catalytic activity in the asymmetric addition of organozinc reagents to aldehydes.

2. Results and discussion

2.1. Synthesis of ligands

A straightforward synthesis of the enantiopure ligands was carried out in two steps. For the synthesis of aziridinylethers **4**, an inexpensive and readily available phenoxyacetyl chloride **1** acid was used as the starting material. Thus, chloride **1** was treated with the mixture of triethylamine and chiral aziridines **2a–c** in diethyl ether. The reactions were carried out at 0 °C, which allowed us to obtain the corresponding amides **3a–c** (Scheme 1) in very good chemical yields of approximately 97% (Table 1).

Finally, reduction of amides **3a–c** to the desired aziridinylethers **4** was performed by using triethoxysilane and zinc acetate following the general protocol described by Beller et al.[19] (Scheme 2).



Scheme 1. Synthesis of amides **3a–c**.

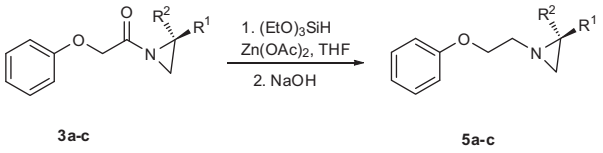
* Corresponding author.
E-mail address: mrach14@wp.pl (M. Rachwalski).

http://dx.doi.org/10.1016/j.tetasy.2014.12.005
0957-4166/

Table 1
Synthesis of amides **3a–c**

Entry	Amide	Yield (%)	$[\alpha]_D^{20}$ [a]
1	**3a**	98	+2.8
2	**3b**	97	−0.6
3	**3c**	98	+0.6

[a] In chloroform (*c* 1).



Scheme 2. Reduction of amides **3a–c** to form ligands **4a–c**.

After aqueous NaOH work-up and purification by standard column chromatography, ligands **4a–c** were obtained as volatile oils. The structures of all of the new chiral catalysts **4a–c** were established by using NMR and mass spectroscopy. Chemical yields and specific rotation values of the final products **4a–c** are summarized in Table 2.

2.2. Screening of the ligands

In order to test the catalytic activity of the novel ligands **4a–c** in the asymmetric addition of organozinc reagents to aldehydes, the reactions of diethylzinc and phenylethynylzinc with benzaldehyde were chosen as the model transformations (Scheme 3). The results are collected in Table 3.

From Table 3 it can be seen that all ligands **4a–c** are prone to catalyze the selected model transformations to give the desired chiral products **5a** and **6a** in high chemical yields and with excellent enantiomeric excess (up to 95%). Moreover, the use of enantiomeric ligands **4b** and **4c** bearing moieties of both enantiomeric 2-isopropylaziridine led to the formation of each enantiomer of adducts **5a** and **6a** (Table 2, entries 2 and 3). Thus, each enantiomer of the product may be obtained by using easily available enantiomeric ligands. The absolute configurations of the stereogenic centers of **5a** and **6a** were attributed to the literature reports.[10,20]

2.3. Asymmetric addition of diethylzinc and phenylethynylzinc to various aldehydes catalyzed by ligand 4b

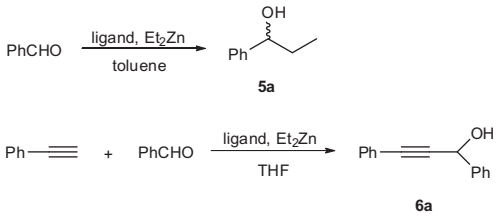
With the new ligands in hand, we decided to determine the scope of the catalytic activity of the most active ligand **4b** in the aforementioned asymmetric addition reactions using a series of aldehydes (Scheme 4). The results are summarized in Table 4.

All of the results obtained clearly indicate that the selected ligand **4b** could be considered as a highly efficient catalyst for the asymmetric additions of diethylzinc and phenylethynylzinc to aldehydes, leading to the formation of the desired alcohols in high chemical yields and with high ee's.

Table 2
Synthesis of catalysts **4a–c**

Entry	Compound	Yield (%)	$[\alpha]_D^{20}$ [a]
1	**4a**	89	+4.0
2	**4b**	92	−0.3
3	**4c**	90	+0.3

[a] In chloroform (*c* 1).



Scheme 3. Asymmetric addition of diethyl- and phenylethynylzinc to benzaldehyde.

3. Conclusion

Chiral ether-derived catalysts bearing one stereogenic center located at the carbon atom of the aziridine moiety were found to be efficient catalysts for the enantioselective addition of diethylzinc and phenylethynylzinc to various aldehydes. The use of enantiomeric ligands gave easy access to both enantiomeric addition products.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance III instrument at 600 MHz using the solvent signals as reference. Chemical shifts (δ) are given in ppm and coupling constants J in Hz. The assignments of the signals in ^{13}C NMR spectra were made on the basis of HMQC experiments. HR-MS: Bruker Esquire LC spectrometers. Optical rotations were determined 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). The enantiomeric excess values were determined by chiral HPLC (Knauer, Chiralcel OD).

4.2. Starting materials

All solvents and reagents are commercially available and were used as received. The enantiomerically pure aziridines **2a–c** were prepared according to the literature.[23]

4.3. Synthesis of amides 3a–c

In a round-bottomed flask, aziridine **2** (1 mmol), triethylamine (1 mmol), and diethyl ether (10 mL) were placed. The mixture was cooled to 0 °C using an ice bath and chloride **1** (1 mmol) in THF was added dropwise. After 30 min of stirring at room temperature, the precipitate was filtered off and the filtrate was concentrated on a rotary evaporator to yield the corresponding amides **3a–c**.

Amide **3a** (colorless oil, 187 mg, 98%), ^{1}H NMR ($CDCl_3$): δ = 1.34 (d, J = 5.5 Hz, 3H), 2.02 (d, J = 3.6 Hz, 1H), 2.45 (d, J = 5.8 Hz, 1H), 2.61–2.63 (m, 1H), 4.67 (d, J = 16.0 Hz, 1H), 4.71 (d, J = 16.0 Hz, 1H), 6.92–6.99 (m, 3H), 7.28–7.30 (m, 2H).

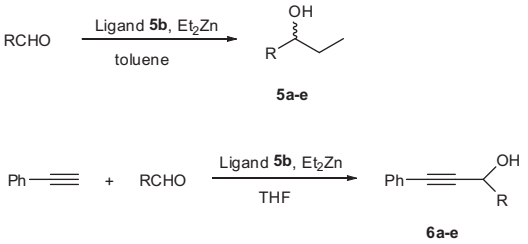
Amide **3b** (colorless oil, 212 mg, 97%), ^{1}H NMR ($CDCl_3$): δ = 0.96 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 1.65–1.70 (m, 1H), 2.12 (d, J = 3.7 Hz, 1H), 2.39–2.42 (m, 1H), 2.45 (d, J = 6.1 Hz, 1H), 4.71 (d, J = 15.7 Hz, 1H), 4.75 (d, J = 15.7 Hz, 1H), 6.94–7.02 (m, 3H), 7.30–7.34 (m, 2H).

Amide **3c** (colorless oil, 215 mg, 98%), ^{1}H NMR ($CDCl_3$): δ = 0.96 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 1.65–1.70 (m, 1H), 2.12 (d, J = 3.7 Hz, 1H), 2.39–2.42 (m, 1H), 2.45 (d, J = 6.1 Hz, 1H), 4.71

Table 3
Screening of ligands **4a–c**

Entry	Ligand	Product **5a**				Product **6a**			
		Yield (%)	$[\alpha]_D$[a]	ee[b] (%)	Abs. config.[c]	Yield (%)	$[\alpha]_D^{20}$ [a]	ee[b] (%)	Abs. config.[c]
1	**4a**	90	−41.8	93	(*S*)	92	−4.6	91	(*S*)
2	**4b**	96	−43.6	97	(*S*)	94	−4.7	93	(*S*)
3	**4c**	94	+40.9	91	(*R*)	91	+4.4	88	(*R*)

[a] In chloroform (*c* 1).
[b] Determined using chiral HPLC.
[c] According to literature data.[10,20]



Scheme 4. Additions of diethyl- and phenylethynylzinc to aldehydes in the presence of ligand **4b**.

(d, *J* = 15.7 Hz, 1H), 4.75 (d, *J* = 15.7 Hz, 1H), 6.94–7.02 (m, 3H), 7.30–7.34 (m, 2H).

4.4. Synthesis of ligands 4a–c

In a round-bottomed flask zinc acetate (1 mmol), triethoxysilane (5.0 mmol), and freshly distilled dry THF (3 mL) were placed. The mixture was stirred for 30 min under argon followed by the addition of the corresponding amide **3** (1.0 mmol) in THF (2 mL). The mixture was heated at reflux on an oil bath and after 6 h was cooled to room temperature and treated with 1 M NaOH (10 mL). After 3 h of stirring, the mixture was extracted with diethyl ether, and the combined organic phases were dried over anhydrous Na_2SO_4, and concentrated in vacuo using an ice bath to afford the crude products, which after column chromatography (CH_2Cl_2) gave the final ligand structures **4a–c**. The chemical yields and specific rotation values of ligands **4a–c** are summarized in Table 2.

Ligand **4a** (colorless oil, 157 mg, 89%), ^{1}H NMR ($CDCl_3$): δ = 1.22 (d, *J* = 5.5 Hz, 3H), 1.38 (d, *J* = 6.3 Hz, 1H), 1.51–1.54 (m, 1H), 1.57 (d, *J* = 3.7 Hz, 1H), 2.63–2.72 (m, 2H), 4.14–4.19 (m, 2H), 6.94–6.98 (m, 3H), 7.29–7.32 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 18.2 (*C*H$_3$), 34.2 (*C*H$_2$), 35.0 (*C*H), 60.3, 69.2 (2 *C*H$_2$), 112.8, 119.4, 128.2 (5 C$_{ar}$), 138.2 (C$_{q\ ar}$); HRMS (ES+): calcd for $C_{11}H_{15}NO$: 177.1232, found: 177.1231.

Ligand **4b** (colorless oil, 189 mg, 92%), ^{1}H NMR ($CDCl_3$): δ = 0.86 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 1.13–1.18 (m, 1H), 2.26 (d, *J* = 6.0 Hz, 1H), 1.53–1.56 (m, 2H), 2.34–2.38 (m, 1H), 2.77–2.81 (m, 1H), 4.04–4.07 (m, 2H), 6.83–6.88 (m, 3H), 7.19–7.22 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 19.6, 20.4 (2 *C*H$_3$), 31.7 (*C*H$_2$), 32.9 (*C*H), 46.3 (*C*H), 61.9, 71.4 (2 *C*H$_2$), 112.4, 119.8, 128.4 (5 C$_{ar}$), 138.5 (C$_{q\ ar}$); HRMS (ES+): calcd for $C_{13}H_{19}NO$: 205.1545, found: 205.1545.

Ligand **4c** (colorless oil, 185 mg, 90%), ^{1}H NMR ($CDCl_3$): δ = 0.86 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 1.13–1.18 (m, 1H), 2.26 (d, *J* = 6.0 Hz, 1H), 1.53–1.56 (m, 2H), 2.34–2.38 (m, 1H), 2.77–2.81 (m, 1H), 4.04–4.07 (m, 2H), 6.83–6.88 (m, 3H), 7.19–7.22 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 19.6, 20.4 (2 *C*H$_3$), 31.7 (*C*H$_2$), 32.9 (*C*H), 46.3 (*C*H), 61.9, 71.4 (2 *C*H$_2$), 112.4, 119.8, 128.4 (5 C$_{ar}$), 138.5 (C$_{q\ ar}$); HRMS (ES+): calcd for $C_{13}H_{19}NO$: 205.1545, found: 205.1546.

4.5. Asymmetric addition of diethylzinc to aldehydes: general procedure[10]

Chiral catalysts of type **4** (0.1 mmol) in dry toluene (5 mL) were placed in a round-bottom flask. The mixture was cooled to 0 °C and a solution of diethylzinc (1.0 M in hexane, 3.0 mmol) was added under argon. After stirring for 30 min, the corresponding aldehyde (1.0 mmol) was added at 0 °C, and the mixture was stirred at room temperature overnight. Next, 5% HCl aqueous solution was added, layers were separated and the aqueous phase was extracted with diethyl ether (4 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous $MgSO_4$. The solvents were evaporated to afford the crude alcohols **5a–e**, which were purified via column chromatography on silica gel (hexane with ethyl acetate in gradient). The yields, specific rotations, enantiomeric excess values and the absolute configurations of products **5a–e** are collected in Table 4. The spectroscopic data are in full agreement with those reported in the literature.[10,12,20,21]

4.6. Asymmetric addition of phenylethynylzinc to aldehydes—general procedure[12]

To a solution of a ligand of type **4** (0.2 mmol) in THF (5 mL), was added a solution of diethylzinc (1.4 mL, 1.4 mmol, 1.0 M in hexane) at room temperature under argon. After the mixture was stirred at ambient temperature for 30 min, phenylacetylene (154 μL,

Table 4
Additions of diethyl- and phenylethynylzinc to aldehydes in the presence of ligand **4b**

Entry	R	Products **5a–e**				Products **6a–e**			
		Yield (%)	$[\alpha]_D$[a]	ee[b] (%)	Abs. config.[c]	Yield (%)	$[\alpha]_D^{20}$ [a]	ee[b] (%)	Abs. config.[c]
1	Ph	96	−43.6	97	(*S*)	94	−4.7	93	(*S*)
2	2-MeOC$_6$H$_4$	92	−46.5	89	(*S*)	88	−7.1	85	(*R*)
3	*n*-Pr	88	+6.0	85	(*S*)	89	−3.1	88	(*S*)
4	4-BrC$_6$H$_4$	91	−8.1	93	(*S*)	91	+3.6	89	(*R*)
5	2-MeC$_6$H$_4$	89	−40.0	85	(*S*)	86	−10.4	84	(*R*)

[a] In chloroform (*c* 1).
[b] Determined using chiral HPLC.
[c] According to literature data.[10,12,21,22]

1.4 mmol) was added, and stirring was continued for another 30 min. The solution was cooled to 0 °C (ice bath) and treated with the corresponding aldehyde (1.0 mmol), after which the resulting mixture was stirred for 2 h at 0 °C and then overnight at room temperature. After completion of the reaction (TLC control), it was quenched with 5% aqueous HCl. The resulting mixture was extracted with diethyl ether (4 × 10 mL) and the combined organic layers were washed with brine. After the organics were dried over anhydrous $MgSO_4$, the solvents were removed in vacuo. The residue was purified by column chromatography (silica gel, hexane with ethyl acetate in gradient) to afford the corresponding products **6a–e**. The yields, specific rotations, enantiomeric excess values, and the absolute configurations of the products **6a–e** are collected in Table 4. The spectroscopic data are in full agreement with those reported in the literature.[10,12,20,21]

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