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N-Trityl-aziridinyl alcohols as highly efficient chiral catalysts in asymmetric additions of organozinc species to aldehydes

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ABSTRACT

A synthetic route leading to a series of new chiral catalysts containing the *N*-trityl-aziridine moiety and a primary and a secondary hydroxyl group as nucleophilic centers is described. All the new compounds have been tested as chiral catalysts in the enantioselective addition of diethylzinc and phenylethynylzinc to aryl and alkyl aldehydes, yielding the corresponding chiral alcohols in high chemical yields (up to 96%) and with excellent ee's of ca. 90%. The influence of the stereogenic centers located at the carbon atom bonded with the hydroxyl moiety and on the carbon of the aziridine ring on the stereochemistry of the addition reactions is also discussed.

1. Introduction

The enantioselective production of various chiral compounds constitutes as one of the central topics in modern organic chemistry.[1–4] In recent years, tremendous efforts have been made to elaborate upon stereoselective routes for the synthesis of enantiomerically pure compounds.[5] A crucial factor influencing the chemical yield and stereoselectivity of asymmetric reactions is the use of an appropriate chiral catalyst. Recently, there has been a growing interest in the synthesis and modification of various chiral amine-functionalized compounds, especially amino alcohols, to test their catalytic activity in various asymmetric reactions. Among chiral amine alcohols, aziridine alcohols constitute as a very interesting class of compounds when applied as chiral ligands especially in the asymmetric additions of organozinc species to carbonyl compounds.[6–10] In continuation of our current interests in the field of asymmetric synthesis,[11,12] especially in the application of aziridine-based chiral catalysts[13–21] and taking into account the fact that aziridines strongly coordinate to organozinc species,[22–24] we focused our attention on the synthesis of various *N*-trityl-aziridinyl alcohols and checked their catalytic activity toward the addition of diethylzinc and phenylethynylzinc to aldehydes. According to previous literature reports, such types of chiral catalysts have been tested in model asymmetric additions of diethylzinc to aldehydes to give the corresponding chiral alcohols in high chemical yield (around 90%) and with high enantiomeric excess values (up to 98%).[25,26] It should be noted that either aziridinyl alcohols containing only one stereogenic center located at the aziridine subunit[16,25,26] or aziridinyl alcohols bearing two stereogenic centers (located at C-aziridine atom and C–OH carbon atom[8]) were very efficient in the aforementioned reactions. However, studies on the influence of the C–OH stereogenic center on catalyst effectiveness have not been performed. Savoia suggested that in the series of aziridine ligands containing two stereogenic centers, only the stereogenic center in the aziridine ring is crucial for the efficacy of the ligands.[27] On the other hand, we[21] recently showed that in a series of aziridinyl alcohols constructed on the chiral monoterpene scaffold, the absolute configuration of the products of the asymmetric transformation depends on the configuration of the terpene moiety but not on the aziridine. Hence, further studies on the influence of the C–OH stereogenic center on the stereochemical outcome of organozinc species addition to aldehydes have been conducted. So far, a series of aziridinyl alcohols containing two asymmetric carbon atoms has been synthesized and their catalytic activity has been tested in the aforementioned addition reactions.

2. Results and discussion

2.1. Synthesis of the ligands

The synthetic route leading to *N*-trityl-aziridinyl alcohols **7**–**11** is shown in Scheme 1. The first step of the synthesis was the preparation of methyl (*S*)-*N*-triphenylmethylaziridinate **1**. This ester was obtained via cyclization of an L-serine derivative following the literature.[28] Compound **1** was then converted into the corresponding Weinreb's amide, (*S*)-triphenylmethyl-2-aziridine-

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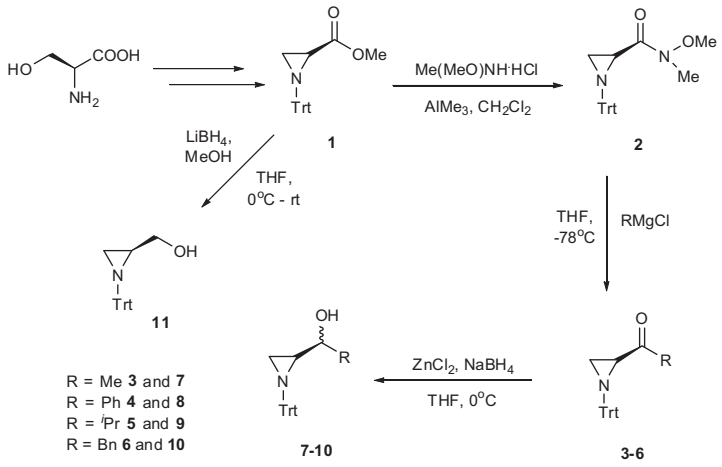


Scheme 1. Synthetic pathway leading to chiral ligands **7**–**11**.

N-methoxy-*N*-methylcarboxamide **2** using *N*,*O*-dimethylhydroxylamine hydrochloride and trimethylaluminum.[29] The reaction was performed under an argon atmosphere in anhydrous methylene chloride for 5 h and the corresponding product **2** was isolated by extraction in 94% yield. This substance was used for the next step without additional purification. Amide **2** was treated with four various Grignard reagents: methylmagnesium, phenylmagnesium, isopropylmagnesium and benzylmagnesium chlorides in anhydrous tetrahydrofurane at −78 °C under argon.[30] Aziridinylketones **3**–**6** isolated via extraction were subjected to column chromatography on silica gel using a mixture of hexane and ethyl acetate (1:9) as the eluent to afford pure products **3**–**6**. The chemical yields of the reactions of amide **2** with the Grignard reagents are shown in Table 1.

Table 1
Reactions of amide **2** with Grignard reagents

Entry	Grignard reagent	Product	Yield (%)
1	CH_3MgCl	**3**	88
2	PhMgCl	**4**	93
3	$(CH_3)_2CHMgCl$	**5**	91
4	BnMgCl	**6**	95

Ketones **3**–**6** were subjected to reduction using freshly dried zinc chloride and sodium borohydride.[23] Previously, we reported that such a reduction of aziridinyl ketones without any substituent on the nitrogen atom proceeded in a fully stereoselective manner to give the *erythro* diastereoisomer. Moreover, Lee and Ha described that this reaction remains fully stereoselective for enantiomerically pure aziridinyl ketones bearing an (*R*)-(+)-α-methylbenzyl substituent on the nitrogen atom and, additionally, the use of L-Selectride led to the second *threo* diastereoisomer. We found a significant decrease in the stereoselectivity for aziridinyl ketones bearing the *N*-trityl substituent. The reduction reactions were performed under argon at 0 °C leading to the formation of an inseparable mixture of diastereoisomers (with the same predominant isomer, although its absolute configuration was not determined) in a ratio of 59:41 for $NaBH_4/ZnCl_2$ and of 87:13 for L-Selectride. Chiral ligands **7**–**10** were obtained as a mixture of diastereoisomers [i.e., possessing an (*R*)- or (*S*)-configuration at C*–OH] and were isolated by extraction with diethyl ether and purified via column chromatography on silica gel (ethyl acetate and hexane 1:4 as eluent). The chemical yields and specific rotation values are shown in Table 2.

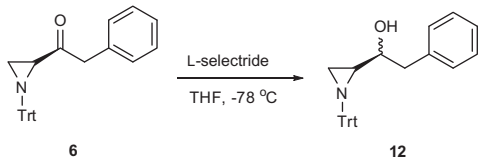
Table 2
Stereoselective reduction of ketones **3**–**6** to form chiral ligands **7**–**10**

Entry	Product	Yield (%)	$[\alpha]_D$[a]
1	**7**	92	−2.7
2	**8**	94	−2.9
3	**9**	89	−2.5
4	**10**	94	−3.0

[a] In chloroform (*c* 1 at 20 °C).

Aziridine alcohol **11** bearing a primary hydroxyl group was synthesized from ester **1** via reduction using lithium borohydride and methanol in anhydrous THF at 0 °C. After extraction with ethyl acetate, compound **11** was isolated in almost quantitative yield (99%).

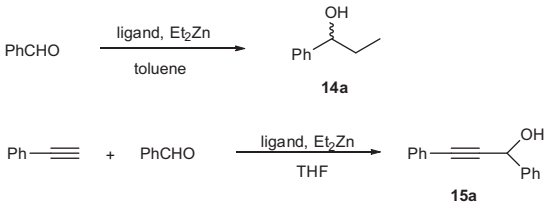
In order to obtain ligand **12** with an opposite absolute configuration at the carbon bonded with the OH group, ketone **6** was subjected to reduction using L-Selectride in anhydrous tetrahydrofuran at −78 °C (Scheme 2). After extraction with dichloromethane and purification via column chromatography, chiral ligand **12** was obtained in 90% yield.



Scheme 2. Reduction of ketone **6** using L-Selectride to form ligand **12**.

2.2. Screening of the ligands

In order to check the catalytic activity of novel aziridine alcohols **7**–**12** in the additions of organozinc species to aldehydes, the reactions of diethylzinc and phenylethynylzinc with benzaldehyde were chosen as the model transformations (Scheme 3). All of



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

Table 3
Screening of the catalysts **7**-**13**

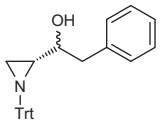
Entry	Ligand	Product **14a**				Product **15a**			
		Yield (%)	$[\alpha]_D$[a]	ee (%)[b]	Abs config.	Yield (%)	$[\alpha]_D$[a]	ee (%)[b]	Abs config.[c]
1	**7**	91	−39.5	88	(*S*)	90	−4.6	91	(*S*)
2	**8**	90	−39.3	87	(*S*)	88	−4.6	90	(*S*)
3	**9**	94	−41.8	93	(*S*)	93	−4.6	91	(*S*)
4	**10**	97	−41.8	93	(*S*)	96	−4.8	94	(*S*)
5	**11**	nd	nd	nd	nd	90	−4.1	81	(*S*)
6	**12**	85	−40.0	89	(*S*)	89	−4.4	88	(*S*)
7	**13**	95	+40.9	91	(*R*)	93	+4.6	92	(*R*)

[a] In chloroform (*c* 1).
[b] Determined using chiral HPLC.
[c] According to literature data.[31]

the additions were carried out under standard reaction conditions (in toluene or THF),[13,14] and the results are shown in Table 3.

The results shown in Table 3 clearly prove that all of the aziridines **7**–**12** are able to catalyze the model addition reactions leading to desired products **14a** and **15a** in high chemical yields (>90%) and with excellent enantiomeric excesses of >90%. Ligand **11** was only tested in the asymmetric addition of phenylethynylzinc to benzaldehyde due to the fact that it was tested earlier in the addition of diethylzinc to benzaldehyde by Zwanenburg et al. leading to alcohol **14a** in 90% yield and with moderate ee (64%).[32] The fact, that ligands **7**–**12** can be used as mixtures of diastereoisomers, that is, 59:41 ($NaBH_4/ZnCl_2$) and 87:13 (L-Selectride) and give an identical enantioselectivity suggests that the C*–OH configuration has no influence on the stereochemical outcome of the addition. The stereogenic center at the aziridine moiety is probably of crucial importance. The absolute configurations at the newly generated stereogenic centers of **14a** and **15a** were assigned according to the literature.[31]

Finally, in order to prove the decisive influence of the stereogenic center located on the aziridine subunit on the stereochemistry of the addition reactions, diastereomeric ligand **13** (Scheme 4) with the opposite absolute configuration of the carbon atom at the aziridine moiety was synthesized according to the procedure depicted in Scheme 1 starting from commercially available D-serine. After reduction of the corresponding ketone, compound **13** was afforded in 91% yield as a 59:41 mixture of diastereoisomers.



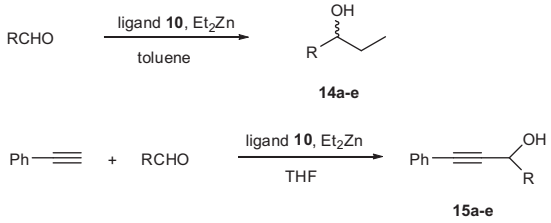
13

Scheme 4. Ligand **13** (as a mixture of diastereoisomers) obtained from D-serine.

With enantiomerically pure catalyst **13** in hand, asymmetric addition reactions of diethylzinc and phenylethynylzinc to benzaldehyde were carried out under standard conditions with ligand **13** as the chiral promoter. As can be seen in Table 3 (entry 7), both reactions proceeded very efficiently in terms of chemical yield and enantiomeric excess. It should be also mentioned that the absolute configurations of products **14a** and **15a** were opposite to those obtained earlier, thus the change of the absolute configuration on the carbon atom located at the aziridine subunit led to addition products with opposite configurations. This phenomenon may prove that the stereogenic center located at the aziridine moiety is crucial for the stereochemical outcome of the addition reactions of organozinc compounds to aldehydes.

2.3. Asymmetric additions of diethyl- and phenylethynylzinc to various aldehydes promoted by ligand 10

With efficient ligands in hand, we next determined the scope of the catalytic activity of selected ligand **10**. Hence, it was used as the chiral catalyst for the title reactions carried out with a series of aldehydes (Scheme 5). The results are summarized in Table 4.



Scheme 5. Additions of diethyl- and phenylethynylzinc to aldehydes promoted by ligand **10**.

The results collected in Tables 3 and 4 indicate that the selected ligand **10** should be considered as a highly effective catalyst for the title reactions leading to the target alcohols in excellent yields and ee's.

3. Conclusion

The chiral aziridine ligands synthesized from both enantiomers of commercially available serine containing two stereogenic centers were found to be highly effective catalysts for the enantioselective addition of diethylzinc and phenylethynylzinc to various aldehydes. The stereogenic center located at the carbon atom bonded with the hydroxyl group is not crucial for the stereochemical outcome of the addition because the use of mixtures with various contaminations of both diastereoisomers led to the same stereochemical results. On the other hand, the change of the absolute configuration at the center located at the aziridine subunit led to the addition products with opposite absolute configurations. This may prove that for the stereochemical outcome of the addition of organo zinc reagents to aldehydes, the stereogenic center at the aziridine moiety is crucial. The above conclusions are relevant only for ligands containing non-expanded OH-functionalized aziridinyl derivatives, but are not applicable for aziridinyl alcohols built on more complex chiral scaffolds such as monoterpenes.

4. Experimental

4.1. General

Unless otherwise specified, all reagents were purchased from commercial suppliers and used without further purification. Toluene and tetrahydrofuran were distilled from the sodium benzophenone ketyl radical. ^{1}H 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).

Table 4
Additions of diethyl- and phenylethynylzinc to aldehydes promoted by ligand **10**

Entry	R	Products **14a–e**				Products **15a–e**			
		Yield (%)	$[\alpha]_D$[a]	ee (%)[b]	Abs config.[c]	Yield (%)	$[\alpha]_D$[a]	ee (%)[b]	Abs config.[c]
1	Ph	97	−41.8	93	(*S*)	96	−4.8	94	(*S*)
2	2-MeOC$_6$H$_4$	94	−47.0	90	(*S*)	92	−7.7	92	(*R*)
3	*n*-Pr	92	+6.4	91	(*S*)	90	−3.0	86	(*S*)
4	4-BrC$_6$H$_4$	89	−7.6	87	(*S*)	88	+3.7	91	(*R*)
5	2-MeC$_6$H$_4$	93	−41.1	92	(*S*)	89	−11.2	90	(*R*)

[a] In chloroform (*c* 1, 20 °C).
[b] Determined using chiral HPLC.
[c] According to the literature data.[13,14,33,34]

4.2. Starting materials

Methyl (*S*)-*N*-triphenylmethyl aziridinate **1** was prepared according to the literature.[28]

4.3. Synthesis of (*S*)-*N*-triphenyl-2-aziridine *N*-methoxy-*N*-methyl carboxamide 2

To a suspension of *N*,*O*-dimethylhydroxylamine HCl (880 mg, 9,11 mmol) in anhydrous CH_2Cl_2 (5 mL) at −20 °C trimethylaluminum (2 M, 4.55 mL, 9.11 mmol) was added dropwise under a nitrogen atmosphere. The reaction mixture was warmed to 25 °C and stirred for 1 h. After this time, the reaction mixture was again cooled to −20 °C and methyl (*S*)-*N*-triphenylmethyl aziridinate **1** (0.343 g, 1 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise. After stirring at rt for 4 h, the reaction was cooled to 0 °C, and then carefully quenched with H_2O (2 mL). The resulting mixture was extracted with Et_2O (3 × 10 mL), the combined organic layers were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to yield **2** as a colorless oil (0.350 g, 94%). The product was used in the next step without further purification; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.43 (dd, *J* = 6.0, 1.6 Hz, 1H), 2.37–2.39 (m, 2H), 3.24 (s, 3H), 3.42 (s, 3H), 7.18–7.32 (m, 9H), 7.56–7.58 (m, 6H). Other spectroscopic data were in agreement with the literature.[35]

4.4. Reactions of aziridine amide with Grignard reagents: general procedure

To a solution of aziridine amide **2** (0.372 g, 1 mmol) in anhydrous THF (5 mL) at −78 °C, the Grignard reagent (2 M, solution in THF, 1 mL, 2 mmol) was added dropwise. The solution was stirred for 1 h at −78 °C, after which the solution was slowly warmed to room temperature. The progress of the reaction was monitored by TLC (AcOEt/hexane 1:1). The reaction was cooled to 0 °C, and then carefully quenched with H_2O (5 mL). The reaction mixture was extracted with Et_2O (3 × 10 mL), the combined organic layers were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The products were purified by flash chromatography on silica gel with AcOEt/hexane (1:9). The chemical yields of ketones **3–6** are collected in Table 1.

*Ketone **3** (colorless oil):* ^{1}H NMR ($CDCl_3$): δ = 1.47 (dd, *J* = 6.4 Hz, 1.0 Hz, 1H), 2.01 (dd, *J* = 6.4 Hz, 3.0 Hz, 1H), 2.23 (dd, *J* = 2.7 Hz, 1.0 Hz, 1H), 2.31 (s, 3H), 7.24–7.32 (m, 9H), 7.47–7.49 (m, 6H); ^{13}C NMR ($CDCl_3$): δ = 25.1 (*C*H$_3$), 28.9 (*C*H$_2$), 39.4 (*C*H), 74.5 (*C*$_q$), 127.9 (*C*$_{ar}$), 127.0 (*C*$_{ar}$), 127.7 (*C*$_{ar}$), 129.3 (*C*$_{ar}$), 143.5 (*C*$_{q\ ar}$), 207.5 (*C*═O).

*Ketone **4** (colorless oil):* ^{1}H NMR ($CDCl_3$): δ = 1.07 (d, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.46 (dd, *J* = 6.0 Hz, 1.5 Hz, 1H), 2.05 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 2.25 (dd, *J* = 3.0 Hz, 1.5 Hz, 1H), 2.88–2.93 (m, 1H), 7.23–7.31 (m, 9H), 7.50–7.52 (m, 6H); ^{13}C NMR ($CDCl_3$): δ = 18.1 (*C*H$_3$), 18.9 (*C*H$_3$), 29.8 (*C*H$_2$), 36.5 (*C*H), 38.1 (*C*H), 74.5 (*C*$_q$), 126.9 (*C*$_{ar}$), 127.6 (*C*$_{ar}$), 129.3 (*C*$_{ar}$), 129.3 (*C*$_{ar}$), 143.7 (*C*$_{q\ ar}$), 212.2 (*C*═O).

*Ketone **5** (colorless oil):* ^{1}H NMR ($CDCl_3$): δ = 1.62 (dd, *J* = 6.0 Hz, 1.5 Hz, 1H), 2.45 (dd, *J* = 2.7 Hz, 1.5 Hz, 1H), 2.76 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 7.24–7.34 (m, 9H), 7.41–7.45 (m, 2H), 7.54–7.59 (m, 7H), 7.86–7.88 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 30.7 (*C*H$_2$), 34.9 (*C*H), 74.8 (*C*$_q$), 126.9 (*C*$_{ar}$), 127.6 (*C*$_{ar}$), 128.2 (*C*$_{ar}$), 128.5 (*C*$_{ar}$), 129.4 (*C*$_{ar}$), 133.0 (*C*$_a$), 137.3 (*C*$_{q\ ar}$), 143.8 (*C*$_{q\ ar}$), 196.9 (*C*═O).

*Ketone **6** (colorless oil):* ^{1}H NMR ($CDCl_3$): δ = 1.44 (dd, *J* = 6.4 Hz, 1.0 Hz, 1H), 2.07 (d, *J* = 6.4 Hz, 2.7 Hz, 1H), 2.28 (dd, *J* = 3.0 Hz, 1.0 Hz, 1H), 3.83 (d, *J* = 15.6 Hz, 1H), 3.96 (d, *J* = 15.6 Hz, 1H), 7.19–7.33 (m, 14H), 7.42–7.44 (m, 6H); ^{13}C NMR ($CDCl_3$): δ = 29.6 (*C*H$_2$), 38.1 (*C*H), 45.9 (*C*H$_2$), 74.5 (*C*$_q$), 126.9 (*C*$_{ar}$), 127.6 (*C*$_{ar}$), 129.3 (*C*$_{ar}$), 129.6 (*C*$_{ar}$), 133.9 (*C*$_{q\ ar}$), 143.4 (*C*$_{q\ ar}$), 206.1 (*C*═O).

4.5. Stereoselective reduction of aziridinyl ketones 3–6: general procedure

The corresponding aziridinyl ketone (1 mmol) was dissolved in 5 mL of anhydrous THF at 0 °C. Next a catalytic amount of freshly dried $ZnCl_2$ (1.5 mmol) was added. The solution was stirred for 1 h, after which the reaction mixture was again cooled to 0 °C, $NaBH_4$ (2 mmol) was added in portions and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC (AcOEt/hexane 1:1). After completion, the reaction was quenched with an aqueous solution of NaOH (5 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude products were purified by flash chromatography on silica gel with AcOEt/hexane (1:4). The chemical yields and specific rotation values of alcohols **7–10** are summarized in Table 2.

*Alcohol **7** (colorless solid):* mp 38–40 °C (as a mixture of diastereoisomers); ^{1}H NMR ($CDCl_3$): major diastereoisomer δ = 1.07 (d, *J* = 6.0 Hz, 1H), 1.13 (d, *J* = 6.0 Hz, 3H), 1.51–1.53 (m, 1H), 1.89 (d, *J* = 3.0 Hz, 1H), 3.08 (s, OH), 4.15–4.19 (m, 1H), 7.29–7.32 (m, 9H), 7.45–7.47 (m, 6H); minor diastereoisomer δ = 1.16 (d, *J* = 6.4 Hz, 1H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.41–1.44 (m, 1H), 1.84 (d, *J* = 3.0 Hz, 1H), 2.31 (d, *J* = 4.6 Hz, OH), 3.76–3.79 (m, 1H), 7.23–7.27 (m, 9H), 7.52–7.54 (m, 6H); ^{13}C NMR ($CDCl_3$): major diastereoisomer δ = 21.0 (*C*H$_3$), 24.5 (*C*H), 38.8 (*C*H$_2$), 68.4 (*C*H), 73.7 (*C*$_q$), 126.8 (*C*$_{ar}$), 127.5 (*C*$_{ar}$), 129.4 (*C*$_{ar}$), 144.3 (*C*$_{q\ ar}$) (as superposition for both diastereoisomers); minor diastereoisomer δ = 19.7 (*C*H$_3$), 21.8 (*C*H), 37.2 (*C*H$_2$), 63.3 (*C*H), 73.8 (*C*$_q$), 126.8 (*C*$_{ar}$), 127.6 (*C*$_{ar}$), 129.3 (*C*$_{ar}$), 142.4 (*C*$_{q\ ar}$); MS (CI): *m*/*z* 330 (M+H); HRMS (EI): calcd for $C_{23}H_{23}NO$: 329.1767, found: 329.1779.

*Alcohol **8** (colorless solid):* mp 47–49 °C (as a mixture of diastereoisomers); ^{1}H NMR ($CDCl_3$): major diastereoisomer δ = 1.25 (d, *J* = 6.2 Hz, 1H), 1.72–1.74 (m, 1H), 1.99 (d, *J* = 3.2 Hz, 1H), 2.76 (d, *J* = 4.2 Hz, OH), 4.65–4.67 (m, 1H), 7.21–7.27 (m, 9H), 7.50–7.52 (m, 6H); minor diastereoisomer δ = 1.11 (d, *J* = 6.2 Hz, 1H), 1.76–1.78 (m, 1H), 2.10 (d, *J* = 3.2 Hz, 1H), 3.68 (s, OH), 5.08–5.10

(m, 1H), 7.30–7.37 (m, 9H), 7.47–7.49 (m, 6H); ^{13}C NMR ($CDCl_3$): major diastereoisomer δ = 25.4 (*C*H), 37.5 (*C*H$_2$), 73.8 (*C*H), 74.9 (C_q), 125.8 (C_{ar}), 126.8 (C_{ar}), 127.6 (C_{ar}), 127.7 (C_{ar}), 128.3 (C_{ar}), 129.4 (C_{ar}), 142.1 ($C_{q\ ar}$), 144.2 ($C_{q\ ar}$) (as superposition for both diastereoisomers); minor diastereoisomer δ = 22.4 (*C*H), 39.8 (*C*H$_2$), 69.3 (*C*H), 74.9 (C_q), 126.3 (C_{ar}), 126.9 (C_{ar}), 127.4 (C_{ar}), 127.6 (C_{ar}), 128.3 (C_{ar}), 129.3 (C_{ar}), 141.5 ($C_{q\ ar}$), 144.1 ($C_{q\ ar}$); MS (CI): *m*/*z* 392 (M+H); HRMS (EI): calcd for $C_{28}H_{25}NO$: 391.1920, found: 391.1936.

Alcohol ***9*** *(colorless solid):* mp 43–45 °C (as a mixture of diastereoisomers); ^{1}H NMR ($CDCl_3$): major diastereoisomer δ = 0.80 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.23 (d, *J* = 6.4 Hz, 1H), 1.48–1.50 (m, 1H), 1.58–1.67 (m, 1H), 1.89 (d, *J* = 3.2 Hz, 1H), 2.34 (d, *J* = 4.2 Hz, OH), 3,16–3,19 (m, 1H), 7,23–7,33 (m, 9H), 7,44–7,46 (m, 6H); minor diastereoisomer δ = 0.86 (d, *J* = 6.8 Hz, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.4 Hz, 1H), 1.58–1.67 (m, 2H), 1.93 (d, *J* = 3.2 Hz, 1H), 3.27 (s, OH), 3.73–3.76 (m, 1H), 7.23–7.33 (m, 9H), 7.44–7.46 (m, 6H); ^{13}C NMR ($CDCl_3$): major diastereoisomer δ = 18.3 (*C*H$_3$), 18.7 (*C*H$_3$), 25.6 (*C*H), 33.0 (*C*H), 35.5 (*C*H$_2$), 73.7 (C_q), 77.8 (*C*H), 126.8 (C_{ar}), 127.6 (C_{ar}), 129.4 (C_{ar}), 144.3 ($C_{q\ ar}$) (as superposition for both diastereoisomers); minor diastereoisomer δ = 18.2 (*C*H$_3$), 18.7 (*C*H$_3$), 22.2 (*C*H), 32.5 (*C*H), 34.4 (*C*H$_2$), 71.3 (*C*H), 73.9 (C_q), 126.8 (C_{ar}), 127.9 (C_{ar}), 129.3 (C_{ar}), 144.2 ($C_{q\ ar}$); MS (CI): *m*/*z* 358 (M+H); HRMS (EI): calcd for $C_{25}H_{27}NO$: 357.2103, found: 357.2093;

Alcohol ***10*** *(colorless solid):* mp 51–52 °C (as a mixture of diastereoisomers); ^{1}H NMR ($CDCl_3$): major diastereoisomer δ = 1.10 (d, *J* = 6.4 Hz, 1H), 1.49–1.51 (m, 1H), 1.83 (d, *J* = 3.2 Hz, 1H), 2.61–2.73 (m, AB part of ABX system, 2H), 2.87–2.92 (m, X part of ABX system, 1H), 3.84–3.87 (m, 1H), 7.18–7.31 (m, 9H), 7.48–7.50 (m, 6H); minor diastereoisomer δ = 1.09 (d, *J* = 6.4 Hz, 1H), 1.58–1.60 (m, 1H), 1.92 (d, *J* = 3.2 Hz, 1H), 2.61–2.73 (m, AB part of ABX system, 2H), 2.87–2.92 (m, X part of ABX system, 1H), 4.19–5.10 (m, 1H), 7.30–7.37 (m, 9H), 7.47–7.49 (m, 6H); ^{13}C NMR ($CDCl_3$): major diastereoisomer δ = 24.6 (*C*H), 36.3 (*C*H$_2$), 41.2 (*C*H$_2$), 68.4 (*C*H), 73.7 (C_q), 126.2 (C_{ar}), 126.8 (Car), 127.5 (Car), 128.3 (Car), 129.3 (Car), 129.5 (Car), 138.2 (Cq ar), 144.1 ($C_{q\ ar}$) (as superposition for both diastereoisomers); minor diastereoisomer δ = 22.3 (*C*H), 35.9 (*C*H$_2$), 42.4 (*C*H$_2$), 72.3 (*C*H), 73.8 (C_q), 126.2 (C_{ar}), 126.9 (C_{ar}), 127.6 (C_{ar}), 128.2 (C_{ar}), 129.2 (C_{ar}), 129.4 (C_{ar}), 138.3 ($C_{q\ ar}$), 144.2 ($C_{q\ ar}$); MS (CI): *m*/*z* 406 (M+H); HRMS (EI): calcd for $C_{29}H_{27}NO$: 405.2077, found: 405.2092.

4.6. Synthesis of (*S*)-*N*-triphenylmethyl-aziridinylmethanol 11

To a solution of methyl (*S*)-*N*-triphenylmethyl aziridinate **1** (0.858 g, 2.5 mmol) in THF (25 mL) was added $LiBH_4$ (0.202 g, 9.2 mmol) at 0 °C. Methanol (6 mL) was added then dropwise over a period of 6 h and the mixture was stirred for 16 h at room temperature. After completion of the reaction, water was added, and it was extracted with AcOEt. The combined organic fractions were dried over $MgSO_4$, and the solvent was evaporated under vacuum to afford **11** in 99% yield (0.781 g) as colorless crystals, mp 118–120 °C; $[\alpha]_D$ = +7.1 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.05 (d, *J* = 6.0 Hz, 1H), 1.49–1.51 (m, 1H), 1.79 (d, *J* = 3 Hz, 1H), 2.10 (dd, *J* = 4.2 Hz, 7.8 Hz, OH), 3.61–3.64 (m, 1H), 3.79–3.82 (m, 1H), 7.14–7.40 (m, 15H); ^{13}C NMR ($CDCl_3$): δ = 23.8 (*C*H$_2$), 33.2 (*C*H), 61.6 (*C*H$_2$), 73.8 (C_q), 126.9 (C_{ar}), 127.6 (C_{ar}), 129.4 (C_{ar}), 144.3 ($C_{q\ ar}$). Other spectroscopic data are in agreement with the literature.[36]

4.7. Stereoselective reduction of aziridinyl ketone 6 to form alcohol 12[29]

To a solution of ketone **6** (0.403 g, 1 mmol) in anhydrous THF (5 mL) under a nitrogen atmosphere at −78 °C, L-Selectride (1.0 M, 2 mL, 2 mmol) was added. The mixture was stirred for 30 min at −70 °C and then warmed to room temperature. The reaction mixture was then treated with 10% aqueous NaOH solution, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification via column chromatography on silica gel (EtOAc/hexane 3:7) provided alcohol **12** as a white powder, mp 49–51 °C (0.365 g, 90%); $[\alpha]_D$ = −2.1 (*c* 1, $CHCl_3$).The spectroscopic data were analogous with those for compound **10**.

4.8. Synthesis of diastereomeric ligand 13

Alcohol **13** was synthesized following all the aforementioned procedures starting from D-serine. After reduction of the corresponding ketone, compound **13** was obtained in 89% yield as a white powder, mp 52–54 °C; $[\alpha]_D$ = +5.0 (*c* 1, $CHCl_3$) (measured for the 59:41 mixture of diastereoisomers) .The spectroscopic data were analogous with those for compounds **10** and **12**.

4.9. Asymmetric addition of diethylzinc to aldehydes: general procedure

The chiral catalyst (0.1 mmol) in dry toluene (5 mL) was 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, an 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, the 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 crude alcohols **14**, 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 **14** are shown in Table 4. The spectroscopic data were in full agreement with those reported in the literature.[13]

4.10. Asymmetric addition of phenylethynylzinc to aldehydes: general procedure

To a solution of ligand (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, 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). The resulting mixture was stirred for 2 h at 0 °C and then overnight at room temperature. After completion of the reaction (TLC monitoring), 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 **15**. The yields, specific rotations, enantiomeric excess values, and the absolute configurations of the products **15** are shown in Table 4. The spectroscopic data were in full agreement with those reported in the literature.[14]

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