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Synthesis of quinazolinone-based aziridine diols as chiral ligands: dual stereoselectivity in the asymmetric ethylation of aryl aldehydes

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Dedicated to Professor Dr. Metin Balci on the occasion of his retirement

ABSTRACT

A new class of quinazoline-based enantiomerically pure aziridine diols **4a**–**d** were prepared from the aziridination of mesityl oxide **3** with in situ generated 3-acetoxyaminoquinazolinone (*S*)-**2b** followed by $NaBH_4$ reduction. Aziridine diols **4a**–**d** were purified by means of column chromatography on silica gel and their stereochemistries were assigned by X-ray crystallography and NMR analysis. These aziridine diols **4** were evaluated as chiral ligands in the asymmetric addition of diethylzinc to aryl aldehydes, and ligand (*S*,*R*,*R*)-**4a** yielded (*R*)-1-phenylpropanol derivatives with up to 92% ee, while the diastereomer (*S*,*S*,*R*)-**4c** gave the opposite enantiomers (*S*)-1-phenylpropanol derivatives with up to 86% ee. The results demonstrate that switching the configuration of the aziridine alcohol moiety in ligand gives a remarkable reversal of enantioselectivity in the asymmetric addition of diethylzinc to aryl aldehydes.

1. Introduction

Catalytic asymmetric synthesis using chiral auxiliaries, ligands or catalysts[1] remains one of the most attractive research areas in both academia and industry. Chiral ligands are highly promising tools for the efficient construction of chiral building blocks in the asymmetric synthesis of natural products and biologically active compounds, and much effort has been devoted to the design of new efficient chiral ligands capable of chirality transfer.[2] Among the asymmetric C–C bond-forming reactions using chiral ligands, the enantioselective addition of organozinc reagents to aldehydes has been extensively studied in the field of asymmetric synthesis and serves as a test reaction for new catalytic systems.[3] Since the pioneering report by Oguni and Omi,[4] several oxygen- and nitrogen-based chiral ligands have been synthesized, such as amino alcohols,[5] BINOLs,[6] TADDOLs,[7] salen ligands[8] and pyridyl alcohols.[9]

Quinazolinones and quinazolines are an important class of heterocyclic compounds that exhibit a broad range of biological activities.[10] Moreover, the simple synthesis of the corresponding homochiral derivatives and their potential use in asymmetric applications make them an important class of compounds for synthetic organic chemistry. Recently, we reported the synthesis of some quinazoline- and quinazolinone-based chiral ligands,[11] that were effective catalysts for asymmetric C–C bond formation reactions. Ulukanli et al.[12] reported the catalytic enantioselective addition of diethylzinc to aldehydes, catalysed by (*S*)-**1b**, to afford (*S*)-1-phenyl-1-propanol in moderate selectivity (50% ee). 3-Aminoquinazolinones are also used as aziridination reagents for electron-rich and electron-deficient alkenes.[13] For example, we recently reported the diastereoselective aziridination of chiral allylic alcohols with aziridinating reagent 3-acetoxyaminoquinazolinone **2a**, generated in situ from 3-amino-2-ethylquinazolin-4(3*H*)-one **1a** in the presence of lead(IV) acetate (LTA) or (diacetoxyiodo)benzene (PIDA) to give *threo*-aziridine alcohols with up to >99:1 stereoselectivity (Scheme 1).[14]

Aziridines are known to efficiently coordinate to organozinc compounds,[15] and aziridine alcohols containing a three-membered cyclic β-amino alcohol moiety are efficient chiral catalysts for asymmetric synthesis.[16] Herein, we report the successful synthesis of quinazolinone-based chiral aziridine diols **4a**–**d** via oxidative aminoaziridination of mesityl oxide **3** with chiral 3-aminoquinazolinone (*S*)-**1b** followed by $NaBH_4$ reduction and chromatographic separation (Fig. 1), and their applications in the asymmetric addition of diethylzinc to aryl aldehyde as a test reaction.

2. Results and discussion

The chiral aziridination agent 3-aminoquinazolinone (*S*)-**1b** was readily synthesized from (*S*)-lactic acid according to literature[17] procedures with over 99% ee. Aziridination of mesityl oxide **3** with 3-acetoxyaminoquinazolinone (*S*)-**2b**, generated in situ from (*S*)-**1b** and phenyliodine diacetate (PIDA) as the oxidant, produced the desired diastereomeric mixture of aziridine **5** in approximately

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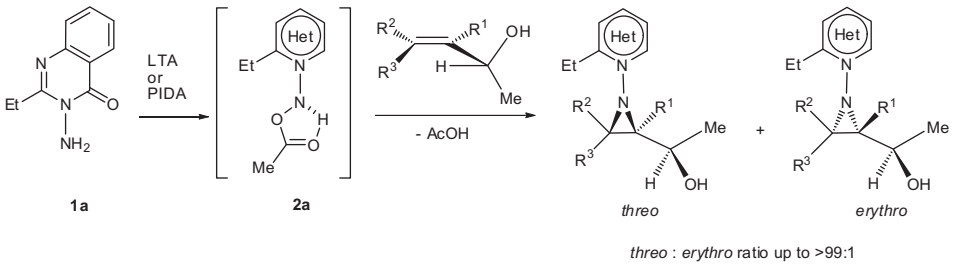


Scheme 1. Diastereoselective aziridination of chiral allylic alcohols.

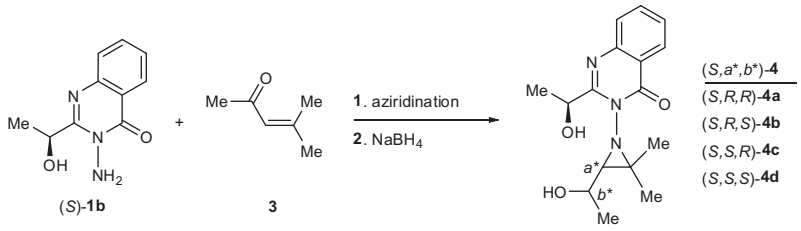
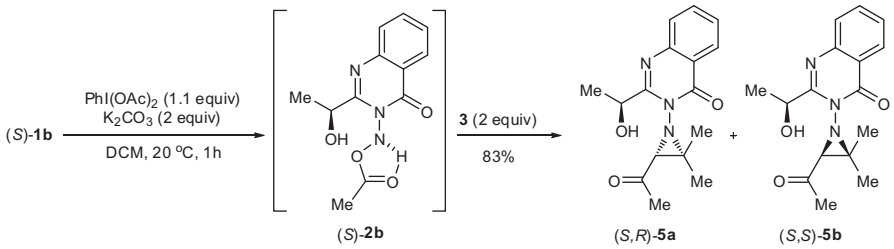


Figure 1. Novel quinazolinone-based chiral aziridine diols synthesized in this work.

a 1:1 ratio (Scheme 2). Fortunately, the two diastereomers were easily separated through a silica gel column with *n*-hexane/EtOAc to give (*S*,*R*)-**5a** and (*S*,*S*)-**5b** as the pure diastereomer in a total yield of 83%.

This result clearly assigned the absolute stereochemistry as (*S*,*R*) for **5a** and (*S*,*S*) for **5b**. The pure diastereoisomers (*S*,*R*)-**5a** and (*S*,*S*)-**5b** were each reacted with $NaBH_4$ in methanol at room temperature to give diastereomeric mixtures (Scheme 4). The

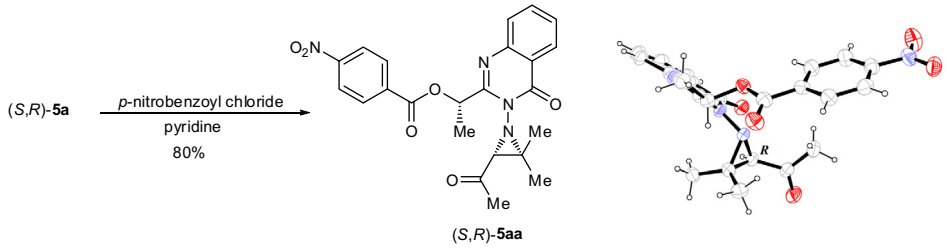


Scheme 2. Aziridination of mesityl oxide **3** with 3-aminoquinazolinone (*S*)-**1b** and PIDA.

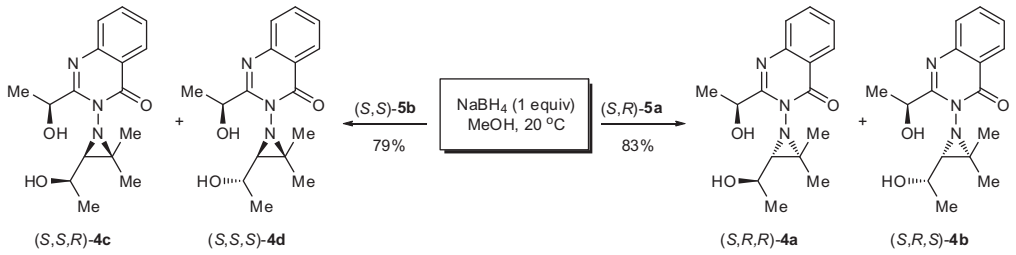
The enantiomeric purities of (*S*,*R*)-**5a** and (*S*,*S*)-**5b** were confirmed by chiral HPLC to be more than 99% ee after the purification step. The absolute stereochemistry of the diastereomers was determined by X-ray analysis of the corresponding *p*-nitrobenzoate derivative (*S*,*R*)-**5aa** of aziridine (*S*,*R*)-**5a** as a single crystal from hexane/EtOAc. The absolute configuration of the newly formed asymmetric centre of the aziridine moiety in **5aa** was unambiguously determined to be (*R*) by the reference to the (*S*)-absolute configuration of the 2-position of quinazolinone ring part (Scheme 3).

mixtures were successfully separated by column chromatography and aziridine alcohols **4a**,**b** and **4c**,**d** were isolated as single stereoisomers with a total yield of 83% and 79%, respectively. The structures of **4a**–**d** were confirmed by IR, NMR, elemental analysis and HRMS. The stereochemical purity of the all aziridine alcohols was determined to be >99% by chiral HPLC analysis.

The assignment of the relative configurations of each of the resulting *threo* **4a** and **4d** and *erythro* **4b** and **4c** diastereomeric pairs was based using characteristic signals in the ^1H NMR spectra.



Scheme 3. Synthesis and X-ray structures of *p*-nitrobenzoate derivative (*S*,*R*)-**5aa**. Thermal ellipsoids are shown at 30% probability level. Selected bond lengths (Å) and angles (°): C7–C9 1.535(8), N2–N3 1.441(5), N1–C7 1.269(6), O5–C9 1.463(7), N2–C8 1.384(8), O1–N4 1.214(7), N3–C18 1.539(7), C11–O5–C9 115.1(5), N2–N3–C21 116.1(4), N2–N3–C18 113.8(4), C8–N2–C7–N1 16.0(8), N3–N2–C7–N1 −170.1(5).



Scheme 4. Synthesis of enantiomerically pure aziridine alcohols **4a**–**d**.

For example, in the ^{1}H NMR spectra, there is a distinct difference in the chemical shift for the methine protons (H_a) on the hydroxy-bearing carbon atom of the *erythro*- and *threo*-isomers (Fig. 2).

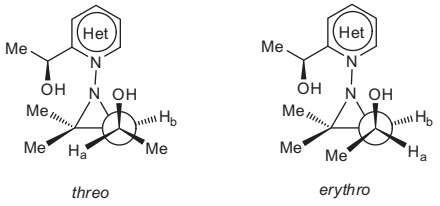


Figure 2. Model for the assignment of absolute configuration of **4**.

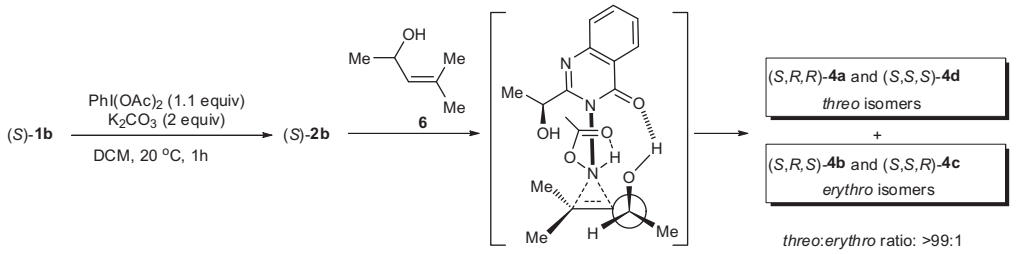
It is known that the H_a proton gives a signal further up-field in the *threo*-isomer as compared to the *erythro*-isomer, as observed for epoxides and aziridines of the chiral allylic alcohols.[14,18] For aziridine diols obtained from (*S*,*R*)-**5a**, the H_a proton of the *threo*-isomer **4a** appears at 3.80 ppm, while in the *erythro*-isomer **4b**, this resonance is shifted downfield to 4.17 ppm. In the other diastereomeric pair of the aziridine diols, the H_a proton of the *erythro*-isomer **4c** similarly resonates downfield (4.21 ppm) from the corresponding *threo*-isomer **4d** (3.77 ppm). Furthermore, the coupling constant between the two neighbouring methine protons (H_a and H_b) of the *threo*-isomers is always larger (J = 9.0 Hz for **4a** and **4d**) than that between the corresponding protons in the *erythro*-isomers (J = 5.7 Hz for **4b** and 5.8 Hz for **4c**).[18b] Thus, the relative and absolute configurations of all aziridine diols **4a**–**d** were determined.

We have recently found that the oxidative aminoaziridination of chiral allylic alcohols with reactive intermediate **2a** shows high *threo*-diastereoselectivity (up to >99:1) due to the hydrogen bonding between the hydroxy functionality of the allylic alcohol and the remote carbonyl group of the quinazolinone (Scheme 1).[14] To confirm the stereochemistry of the aziridine alcohols **4**, we carried out the diastereoselective aziridination of mesityl alcohol **6** with 3-acetoxyaminoquinazolinone (*S*)-**2b**, which was generated in situ from (*S*)-**1b** (Scheme 5).

In this reaction, *threo*-aziridine alcohols (*S*,*R*,*R*)-**4a** and (*S*,*S*,*S*)-**4d** were obtained with high diastereoselectivity (>99:1). The stereochemistries of aziridine alcohols **4** were also confirmed by comparison of the NMR spectra to authentic *threo*-aziridine alcohols **4a** and **4d** produced independently.

Following the successful synthesis of ligands **4a**–**d**, we tested their efficiencies as catalysts in the enantioselective addition of diethylzinc to arylaldehydes. Initial experiments were performed with benzaldehyde as a model substrate using 2 equiv of diethylzinc in the presence of 10 mol % **4a**–**d** at 0 °C. Enantioselectivities were assessed by GC on a β-DEX 120 column after 20 h and some representative results are shown in Table 1. Ligand (*S*,*R*,*R*)-**4a** afforded (*R*)-1-phenyl-propan-1-ol with 86% ee (Table 1, entry 1), whereas ligands **4b**–**d** provided the corresponding (*S*)-alcohol with 50%, 70% and 58% ee, respectively, (Table 1, entries 2, 3 and 4). The reaction conditions were then optimized with ligands (*S*,*R*,*R*)-**4a** and (*S*,*S*,*R*)-**4c**, because they gave the best enantioselectivities in the formation of (*R*)- and (*S*)-1-phenyl-propan-1-ol. Detailed screening was carried out in order to optimize the reaction conditions including the choice of solvent and reaction temperature, which might play an important role in the enantioselectivities of the reaction. For (*S*,*R*,*R*)-**4a**: Et_2O/hexane (2:1, v/v) was found to be the most effective solvent mixture at −15 °C in terms of selectivity (92% ee) (Table 1, entry 9). On the other hand, (*S*,*S*,*R*)-**4c** gave the best result with a solvent mixture of toluene/hexane (2:1, v/v) at −30 °C (86% ee) (Table 1, entry 16). For entries 9 and 16 in Table 1, the recovered ligand was also reused in subsequent cycles as the catalyst without any detectable loss in its activity.

Various other reaction parameters, such as ligand loadings, addition methods and the amount of diethylzinc were examined (data not shown). Using the optimized conditions for benzaldehyde, ligands (*S*,*R*,*R*)-**4a** and (*S*,*S*,*R*)-**4c** were also utilized in the asymmetric ethylation of other aromatic aldehydes with different steric and electronic properties. The results are summarized in Table 2. Aldehydes with electron donating groups exhibited lower reactivity compared to the aldehydes substituted with electron withdrawing groups. In all cases, catalyst (*S*,*R*,*R*)-**4a** induced the formation of the corresponding (*R*)-alcohols while (*S*,*S*,*R*)-**4c** induced the formation of the (*S*)-alcohols. We found that both (*S*,*R*,*R*)-**4a** and (*S*,*S*,*R*)-**4c** gave the best enantioselectivity with benzaldehyde (Table 2, entries 1 and 2). With (*S*,*R*,*R*)-**4a**, *para*-substituted benzaldehydes generally exhibited higher enantiomeric excesses (*p*-Cl, 74%; *p*-OMe, 84%) (Table 2, entries 19 and 25), while the *ortho*- and *meta*-substituted benzaldehydes showed lower enantiomeric excesses,



Scheme 5. Diastereoselective aziridination of mesityl alcohol **6** with 3-acetoxyaminoquinazolinone (*S*)-**2b**.

Table 1
Asymmetric addition of diethylzinc to benzaldehyde using **4a–d** as catalysts[a]

Entry	Ligand	Solvent (2:1, v/v)	T (°C)	ee[b] (%)
1	**4a**	Toluene/hexane	0	86 (*R*)
2	**4b**	Toluene/hexane	0	50 (*S*)
3	**4c**	Toluene/hexane	0	70 (*S*)
4	**4d**	Toluene/hexane	0	58 (*S*)
5	**4a**	Decane/hexane	0	70 (*R*)
6	**4a**	Hexane	0	76 (*R*)
7	**4a**	TBME/hexane	0	82 (*R*)
8	**4a**	Et_2O/hexane	0	90 (*R*)
9	**4a**[c]	Et_2O/hexane	−15	92 (*R*)
10	**4a**	Et_2O/hexane	−30	86 (*R*)
11	**4c**	Decane/hexane	0	24 (*S*)
12	**4c**	Hexane	0	44 (*S*)
13	**4c**	Et_2O/hexane	0	54 (*S*)
14	**4c**	DCM/hexane	0	56 (*S*)
15	**4c**	Toluene/hexane	−15	70 (*S*)
16	**4c**[c]	Toluene/hexane	−30	86 (*S*)

[a] Reaction conditions: benzaldehyde (1 mmol), Et_2Zn (2 mmol), catalyst **4** (10 mol %), argon atmosphere.
[b] Enantiomeric ratios were assessed by GC on a β-DEX 120 column after 20 h.
[c] The recovered ligand (*S*,*R*,*R*)-**4a** and (*S*,*S*,*R*)-**4c** could be reused in subsequent cycles without any loss in activity.

with the exception of *o*-methylbenzaldehyde (80% ee) (Table 2, entries 7), *m*-bromobenzaldehyde (70% ee) (Table 2, entries 13) and *m*-methoxybenzaldehyde (78% ee) (Table 2, entries 17). Ethylation of α-naphthaldehyde and β-naphthaldehyde showed good enantioselectivities (82% and 76% ee, respectively) (Table 2, entries 27 and 29). When (*S*,*S*,*R*)-**4c** was used as the catalyst, halogens at the *meta*- or *para*-position, and electron donating substituents (inductive or mesomeric) at the *ortho*-position exhibited higher enantiomeric excesses (*o*-Me, 84%; *o*-OMe, 72%; *m*-Cl, 80%; *p*-Br, 66%) (Table 2, entries 8, 10, 12 and 22). α- and β-naphthaldehyde yielded low enantioselectivities when (*S*,*S*,*R*)-**4c** was used as the chiral catalyst.

3. Conclusion

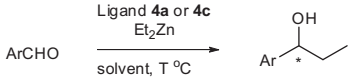
We have prepared a new class of chiral aziridine diol ligands **4a–d** from aminoquinazolinone (*S*)-**1b** and mesityl oxide, and the absolute stereochemistry of each isomer was successfully identified by NMR and X-ray analysis. Their catalytic efficiencies were evaluated by the reaction of Et_2Zn with aldehydes. Ligands (*S*,*R*,*R*)-**4a** and (*S*,*S*,*R*)-**4c** provide access to both enantiomers with good enantiomeric excess in the enantioselective addition of diethylzinc to various substituted benzaldehydes. Ligand (*S*,*R*,*R*)-**4a** directed the catalytic process towards the formation of the (*R*)-1-phenylpropanol derivatives. Switching the configuration of the aziridine alcohol moiety in ligand (*S*,*R*,*R*)-**4a** switches the facial preference and (*S*,*S*,*R*)-**4c** induces the formation of the (*S*)-1-phenylpropanol derivatives. In conclusion, we have developed a new class of aziridine diol ligands, which can easily be derivatized with different substituents for asymmetric synthesis.

4. Experimental

4.1. General

All reagents and solvents were purchased from commercial sources with the highest purity available and were used without further purification unless otherwise stated. All reactions were carried out in anhydrous solvents. Melting points were obtained on a Gallenkamp apparatus and are not corrected. Infrared spectra were recorded on a Perkin–Elmer spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury (400 MHz) and a Bruker Avance (400 MHz) spectrometer as solutions in $CDCl_3$. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CHCl_3$ as an internal standard. All coupling constants are absolute values and J values are expressed in Hertz (Hz). Enantiomeric excesses were determined by HPLC analysis using a chiral column or chiral GC analysis using a Supelco β-DEX 120 column. Optical rotations were measured with a Bellingham + Stanley, ADP220, 589 nm spectropolarimeter in a 1 dm tube; concentrations are given in g/100 mL. Air- and moisture-sensitive reactions were performed using oven-dried glassware under a dry argon atmosphere.

Table 2
Asymmetric addition of Et_2Zn to aryl aldehydes catalysed by ligand (*S*,*R*,*R*)-**4a**[a] and (*S*,*S*,*R*)-**4c**[b]



Entry	Aldehyde	Ligand	Convn[c] (%)	MB[c,d] (%)	ee[e] (%)
1	C_6H_5CHO	(*S*,*R*,*R*)-**4a**	80	95	92 (*R*)
2		(*S*,*S*,*R*)-**4c**	54	81	86 (*S*)
3	*o*-ClC_6H_4CHO	(*S*,*R*,*R*)-**4a**	89	90	64 (*R*)
4		(*S*,*S*,*R*)-**4c**	84	92	62 (*S*)
5	*o*-BrC_6H_4CHO	(*S*,*R*,*R*)-**4a**	80	99	52 (*R*)
6		(*S*,*S*,*R*)-**4c**	82	83	52 (*S*)
7	*o*-MeC_6H_4CHO	(*S*,*R*,*R*)-**4a**	81	74	80 (*R*)
8		(*S*,*S*,*R*)-**4c**	37	95	84 (*S*)
9	*o*-$OMeC_6H_4CHO$	(*S*,*R*,*R*)-**4a**	49	87	36 (*R*)
10		(*S*,*S*,*R*)-**4c**	70	90	72 (*S*)
11	*m*-ClC_6H_4CHO	(*S*,*R*,*R*)-**4a**	58	96	64 (*R*)
12		(*S*,*S*,*R*)-**4c**	63	91	80 (*S*)
13	*m*-BrC_6H_4CHO	(*S*,*R*,*R*)-**4a**	59	99	70 (*R*)
14		(*S*,*S*,*R*)-**4c**	60	95	62 (*S*)
15	*m*-MeC_6H_4CHO	(*S*,*R*,*R*)-**4a**	56	87	60 (*R*)
16		(*S*,*S*,*R*)-**4c**	50	82	60 (*S*)
17	*m*-$OMeC_6H_4CHO$	(*S*,*R*,*R*)-**4a**	71	73	78 (*R*)
18		(*S*,*S*,*R*)-**4c**	30	96	48 (*S*)
19	*p*-ClC_6H_4CHO	(*S*,*R*,*R*)-**4a**	87	70	74 (*R*)
20		(*S*,*S*,*R*)-**4c**	69	75	76 (*S*)
21	*p*-BrC_6H_4CHO	(*S*,*R*,*R*)-**4a**	78	58	60 (*R*)
22		(*S*,*S*,*R*)-**4c**	61	88	66 (*S*)
23	*p*-MeC_6H_4CHO	(*S*,*R*,*R*)-**4a**	60	99	76 (*R*)
24		(*S*,*S*,*R*)-**4c**	33	97	70 (*S*)
25	*p*-$OMeC_6H_4CHO$	(*S*,*R*,*R*)-**4a**	55	85	84 (*R*)
26		(*S*,*S*,*R*)-**4c**	20	97	44 (*S*)
27	α-Naphthaldehyde	(*S*,*R*,*R*)-**4a**	46	93	82 (*R*)
28		(*S*,*S*,*R*)-**4c**	38	92	32 (*S*)
29	β-Naphthaldehyde	(*S*,*R*,*R*)-**4a**	82	70	76 (*R*)
30		(*S*,*S*,*R*)-**4c**	54	81	46 (*S*)

[a] Reaction conditions: 10 mol % (*S*,*R*,*R*)-**4a**, 2.0 equiv Et_2Zn, Et_2O/hexane (2:1, v/v), 48 h, −15 °C, argon atmosphere.
[b] Reaction conditions: 10 mol % (*S*,*S*,*R*)-**4c**, 3.0 equiv Et_2Zn, toluene/hexane (2:1, v/v), 48 h, −30 °C, argon atmosphere.
[c] The conversions and mass balances (MB) were assessed by ^1H NMR analysis with diphenylmethane as an internal standard.
[d] MB refers to the sum of the yields of the characterized product 1-phenylpropan-1-ol, benzyl alcohol and the recovered aldehyde.
[e] Determined by GC on a β-DEX 120 column.[11b]

4.2. Representative procedure for the aziridination of mesityl oxide 3

(*S*)-3-Amino-2-(1-hydroxyethyl)quinazolin-4(3*H*)-one **1b** (1.026 g, 5.0 mmol), mesityl oxide **3** (0.981 g, 10 mmol) and anhydrous K_2CO_3 (1.382 g, 10 mmol) were placed into a 25 mL round bottom flask equipped with a magnetic stirrer bar and dissolved in 20 mL of DCM at room temperature. Next, PIDA (1.772 g, 5.5 mmol) was added in

small portions (within 15 min) to the reaction mixture and stirring was continued for 30 min, while the reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was washed with water (15 mL) and the aqueous phase was extracted with DCM (2 × 25 mL). The combined organic phases were washed with saturated $NaHCO_3$ (10 mL) and dried over Na_2SO_4. After removal of the solvents under reduced pressure, the diastereoisomers were separated on a silica gel column by elution with hexane–EtOAc in a yield of 83%.

4.3. 3-[(3*R*)-3-Acetyl-2,2-dimethylaziridin-1-yl]-2-[(1*S*)-1-hydroxyethyl]quinazolin-4(3*H*)-one 5a

Colourless oil. Yield: 46%; R_f 0.30 (hexane–EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.18 (dd, J = 8.0, 1.1 Hz, 1H), 7.78–7.73 (m, 1H), 7.71–7.69 (m, 1H), 7.46 (ddd, J = 8.0, 7.0, 1.2 Hz, 1H), 5.05–4.99 (m, 1H), 4.65 (d, J = 4.2 Hz, 1H), 4.26 (s, 1H), 2.46 (s, 3H), 1.64 (d, J = 5.6 Hz, 3H), 1,46 (s, 3H), 1,38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ = 202.3, 161.1, 157.2, 145.2, 134.2, 127.4, 127.1, 126.3, 121.6, 65.9, 57.0, 53.2, 29.4, 20.1, 19.9, 19.5; HRMS (TOF MS ES$^+$) m/z calcd for $C_{16}H_{20}N_3O_3$ $[M+H]^+$ 302.1505, found 302.1506; $[\alpha]_D^{20}$ = −16 (c 1, DCM); 99% ee; retention time: 11.3 min, Chiralcel OD-H, n-hexane/iPrOH, 90:10, flow rate of 1 mL/min, 254 nm.

4.4. 3-[(3*S*)-3-Acetyl-2,2-dimethylaziridin-1-yl]-2-[(1*S*)-1-hydroxyethyl]quinazolin-4(3*H*)-one 5b

Colourless oil. Yield: 37%; R_f 0.37 (hexane–EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.18 (dd, J = 8.0, 1.4 Hz, 1H), 7.76 (ddd, J = 8.2, 7.0, 1.4 Hz, 1H), 7.69–7.67 (m, 1H), 7.49 (ddd, J = 8.0, 7.0, 1.2 Hz, 1H), 4.88 (qd, J = 8.2, 6.4 Hz, 1H), 4.49 (d, J = 8.2 Hz, 1H), 3.65 (s, 1H), 2.47 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H), 1.45 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ = 203.6, 160.0, 158.8, 144.8, 134.3, 127.0, 126.8, 126.5, 121.4, 65.7, 58.4, 54.0, 29.3, 22.0, 19.9, 19.4; HRMS (TOF MS ES$^+$) m/z calcd for $C_{16}H_{20}N_3O_3$ $[M+H]^+$ 302.1505, found 302.1492; $[\alpha]_D^{20}$ = +73 (c 1, DCM); 99% ee; retention time: 8.5 min, Chiralcel OD-H, n-hexane/iPrOH, 90:10, flow rate of 1 mL/min, 254 nm.

4.5. Representative procedure for the reduction of aziridinyl ketones 5

To a stirring solution of aziridinyl ketone **5** (301 mg, 1 mmol) in ethanol (10 mL), $NaBH_4$ (38 mg, 1 mmol) was added in small portions over 10 min, after which the reaction mixture was allowed to stir until the starting aziridinyl ketone was consumed as monitored by TLC (10 min). Approximately 5 mL of water was added to the reaction mixture, and the majority of the ethanol was removed in vacuo. The residual solution was extracted with DCM (3 × 15 mL), and the combined organic phases were dried over Na_2SO_4. After removal of the solvent, the crude diastereomeric mixture was subjected to column chromatography on silica gel using a 3:1 hexane/ethyl acetate mixture to obtain enantiomerically pure aziridine diols **4a**–**d**.

4.6. 2-[(1*S*)-1-Hydroxyethyl]-3-{(3*R*)-3-[(1*R*)-1-hydroxyethyl]-2,2-dimethylaziridin-1-yl}quinazolin-4(3*H*)-one 4a

Colourless oil. Yield: 42%; R_f 0.23 (hexane–EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.17–8.15 (m, 1H), 7.75–7.68 (m, 2H), 7.49–7.44 (m, 1H), 5.08 (br s, 1H), 5.03–4.98 (m, 1H), 4.50 (d, J = 2.0 Hz, 1H), 3.83–3.76 (m, 1H), 2.95 (d, J = 9.0 Hz, 1H), 1.69 (d, J = 6.3 Hz, 3H), 1.51 (s, 3H), 1.32 (d, J = 6.4 Hz, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ = 161.5, 156.1, 145.5, 134.3, 127.9, 127.4, 126.4, 121.7, 67.2, 66.87 59.9, 52.3, 20.9, 20.6, 19.0, 18.6; HRMS (TOF MS ES$^+$) m/z calcd for $C_{16}H_{22}N_3O_3$ $[M+H]^+$ 304.1661, found 304.1667; $[\alpha]_D^{20}$ = −103 (c 1, DCM); 99% ee; retention time: 24.1 min, Chiralcel OD-H, n-hexane/iPrOH, 90:10, flow rate of 1 mL/min, 254 nm.

4.7. 2-[(1*S*)-1-Hydroxyethyl]-3-{(3*R*)-3-[(1*S*)-1-hydroxyethyl]-2,2-dimethylaziridin-1-yl}quinazolin-4(3*H*)-one 4b

Colourless oil. Yield: 41%; R_f 0.19 (hexane–EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.19 (ddd, J = 8.0, 1.4, 0.5 Hz, 1H), 7.76–7.68 (m, 2H), 7.48 (ddd, J = 8.0, 6.8, 1.5 Hz, 1H), 5.05 (dq, J = 6.4, 3.8 Hz, 1H), 4.72 (d, J = 3.8 Hz, 1H), 4.21–4.13 (m, 1H), 3.50 (d, J = 5.7 Hz, 1H), 2.14 (d, J = 3.9 Hz, 1H), 1.70 (d, J = 5.9 Hz, 3H), 1.62 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ = 160.8, 156.9, 145.2, 133.9, 127.5, 127.0, 126.2, 121.8, 66.3, 66.2, 57.0, 51.4, 21.0, 20.9, 19.2, 18.9; HRMS (TOF MS ES$^+$) m/z calcd for $C_{16}H_{22}N_3O_3$ $[M+H]^+$ 304.1661, found 304.1668; $[\alpha]_D^{20}$ = −192 (c 1, DCM); 99% ee; retention time: 9.2 min, Chiralcel OD-H, n-hexane/iPrOH, 90:10, flow rate of 1 mL/min, 254 nm.

4.8. 2-[(1*S*)-1-Hydroxyethyl]-3-{(3*S*)-3-[(1*R*)-1-hydroxyethyl]-2,2-dimethylaziridin-1-yl}quinazolin-4(3*H*)-one 4c

Colourless oil. Yield: 32%; R_f 0.21 (hexane–EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.15 (dd, J = 8.0, 1.2 Hz, 1H), 7.69 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 7.64–7.62 (m, 1H), 7.43 (ddd, J = 8.0, 7.0, 1.3 Hz, 1H), 4.91–4.85 (m, 1H), 4.56 (d, J = 7.9 Hz, 1H), 4.24–4.18 (m, 1H), 3.12 (d, J = 5.8 Hz, 1H), 2.46 (br s, 1H), 1.57 (s, 3H), 1.55 (d, J = 6.3 Hz, 3H), 1.51 (d, J = 6.4 Hz, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ = 160.4, 159.7, 144.9, 134.2, 127.0, 126.9, 126.6, 121.7, 66.1, 65.8, 57.6, 52.0, 22.1, 21.2, 20.8, 19.1; HRMS (TOF MS ES$^+$) m/z calcd for $C_{16}H_{22}N_3O_3$ $[M+H]^+$ 304.1661, found 304.1667; $[\alpha]_D^{20}$ = +240 (c 1, DCM); 99% ee; retention time: 7.1 min, Chiralcel OD-H, n-hexane/iPrOH, 90:10, flow rate of 1 mL/min, 254 nm.

4.9. 2-[(1*S*)-1-Hydroxyethyl]-3-{(3*S*)-3-[(1*S*)-1-hydroxyethyl]-2,2-dimethylaziridin-1-yl}quinazolin-4(3*H*)-one 4d

Colourless oil. Yield: 47%; R_f 0.35 (hexane–EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.19 (dd, J = 8.1, 1.4 Hz, 1H), 7.75 (ddd, J = 8.4, 7.1, 1.4 Hz, 1H), 7.68–7.66 (m, 1H), 7.49–7.45 (m, 1H), 5.26 (d, J = 1.2 Hz, 1H), 4.91–4.84 (m, 1H), 4.48 (d, J = 8.4 Hz, 1H), 3.80–3.72 (m, 1H), 2.71 (d, J = 9.0 Hz, 1H), 1.55 (d, J = 6.4 Hz, 3H), 1.46 (s, 3H), 1.29 (d, J = 6.4 Hz, 3H),1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ = 161.1, 159.2, 144.9, 134.5, 127.2, 126.9, 126.7, 121.3, 67.2, 66.0, 60.0, 52.0, 22.2, 20.8, 20.6, 19.0; HRMS (TOF MS ES$^+$) m/z calcd for $C_{16}H_{22}N_3O_3$ $[M+H]^+$ 304.1661, found 304.1669; $[\alpha]_D^{20}$ = +126 (c 1, DCM); 99% ee; retention time: 8.9 min, Chiralcel OD-H, n-hexane/iPrOH, 90:10, flow rate of 1 mL/min, 254 nm.

4.10. (1*S*)-1-{3-[(3*R*)-3-Acetyl-2,2-dimethylaziridin-1-yl]-4-oxo-3,4-dihydroquinazolin-2-yl}ethyl 4-nitrobenzoate 5aa

To a stirring solution of (*S*,*R*)-**5a** (30 mg, 0.10 mmol) in DCM (2 mL), pyridine (16 mg, 0.20 mmol) and *p*-nitrobenzoyl chloride (56 mg, 0.30 mmol) were added at 0 °C. The reaction was stirred at room temperature for 6 h and then quenched by the addition of saturated aqueous sodium bicarbonate. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was subjected to column chromatography with silica gel and a 3:1 hexane/ethyl acetate ratio to afford (*S*,*R*)-**5aa** (36 mg,

0,08 mmol, 80% yield) as a colourless needles crystal. mp 161–163 °C (EtOH); R_f 0.60 (hexane–EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.26 (m, 5H), 7.76 (m, 2H), 7.53 (m, 1H), 6.36 (q, J = 6.4 Hz, 1H), 3.84 (s, 1H), 2.31 (s, 3H), 1.90 (d, J = 6.4 Hz, 3H), 1.51 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ = 203.2, 164.3, 160.5, 152.7, 150.7, 145.3, 135.0, 134.1, 131.0, 127.7, 127.5, 126.3, 123.5, 121.9, 69.0, 58.7, 54.4, 29.0, 20.4, 20.0, 17.6; HRMS (TOF MS ES$^+$) m/z calcd for $C_{23}H_{23}N_4O_6$ $[M+H]^+$ 451.1618, found 451.1613; $[\alpha]_D^{20}$ = +220 (c 1, DCM); 99% ee; retention time: 18.1 min, Chiralcel OD-H, n-hexane/iPrOH, 90:10, flow rate of 1 mL/min, 254 nm.

4.11. Typical procedure for the addition of diethylzinc to aldehyde

To a solution of **4** (0.05 mmol) in freshly distilled diethyl ether (1 mL) diethylzinc (1 mL of 1 M hexane solution, 1 mmol) was added at ambient temperature under argon. The mixture was stirred for 1 h and then cooled to −15 °C. A solution of aldehyde (0.5 mmol) in diethyl ether (1 mL) was added via syringe and the mixture was stirred for 48 h. The reaction was then quenched by the addition of saturated NH_4Cl solution (4 mL), and diphenylmethane (0.25 mmol) was added as an internal standard. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Conversion and yield were determined from the crude mixture by ^{1}H NMR analysis. The crude product was purified by preparative thin layer chromatography on silica gel (hexane/EtOAc, 90:10) and the enantiomeric excess of the addition product was determined by GC on a Chiral β-DEX 120 capillary column.[11b]

4.12. X-Ray structure analysis

For the crystal structure determination, a single-crystal of compound (*S*,*R*)-**5aa** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). Graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) and oscillation scans technique with Δw = 5° for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement were performed using CrystalClear (Rigaku/MSC Inc., 2005) software.[19] The structures were solved by direct methods using SHELXS-97[20] and refined by a full-matrix least-squares procedure using the program SHELXL-97.[20] H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. *Crystal data for* (*S*,*R*)-**5aa**: $C_{23}H_{22}N_4O_6$, crystal system, space group: monoclinic, C2; (no: 5); unit cell dimensions: a = 22.9393(17), b = 6.7784(10), c = 14.3646(11) Å, α = 90, β = 97.507(5), γ = 90 Å; volume: 2214.4 (4) Å^3; Z = 4; calculated density: 1.351 g/cm^3; absorption coefficient: 0.100 mm^{-1} ; F(000): 944; θ-range for data collection 2.1–26.6°; refinement method: full matrix least-square on F^2; data/parameters: 2911/299; goodness-of-fit on F^2: 0.995; final R-indices [$I > 2\sigma(I)$]: R_1 = 0.071, wR_2 = 0.184; largest diff. peak and hole: 0.211 and −0.178 e Å^{-3}.

CCDC-986551 contains the supplementary crystallographic data for (*S*,*R*)-**5aa**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

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