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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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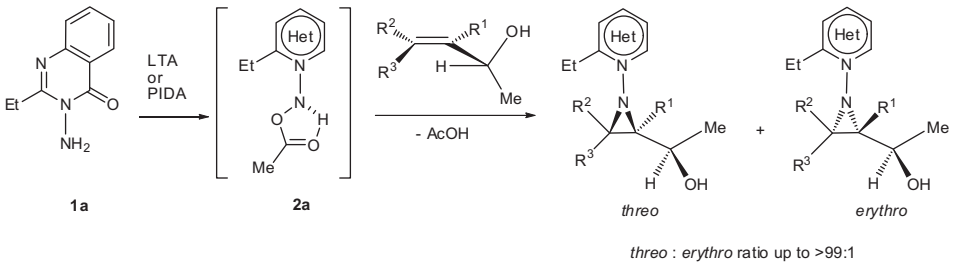


Scheme 1. Diastereoselective aziridination of chiral allylic alcohols.

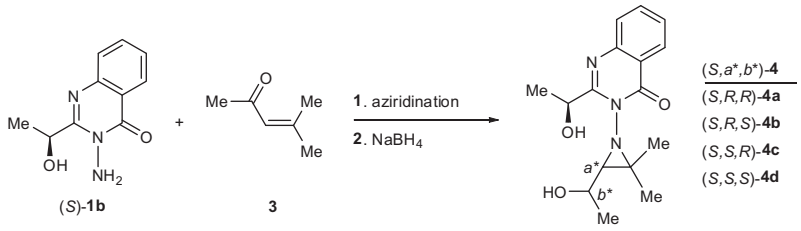
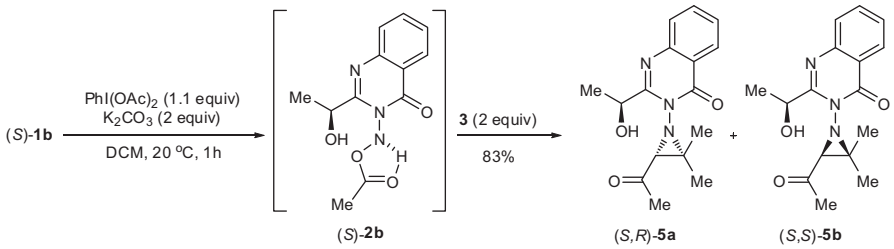


Figure 1. Novel quinazolinone-based chiral aziridine diols synthesized in this work.

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

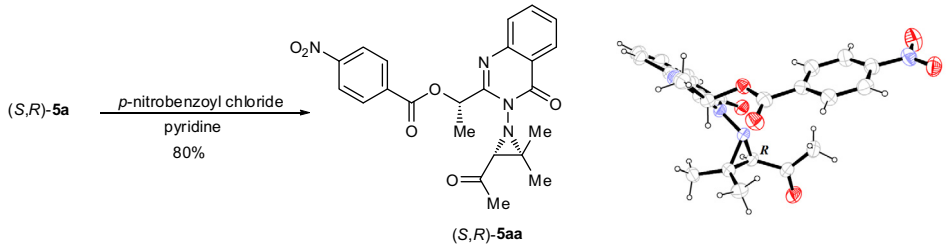


Scheme 2. Aziridination of mesityl oxide **3** with 3-aminoquinazolinone (*S*)-**1b** and PIDA.

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).