Asymmetric synthesis of (*R*)-*S*-(1,2,4-triazol-3-yl)cysteines by nucleophilic addition of triazolethiols to a Ni^{II} complex with a chiral dehydroalanine Schiff base

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An efficient method was developed for the asymmetric synthesis of (*R*)-*S*-(1,2,4-triazol-3-yl)cysteines by the addition of 3,4-disubstituted 1,2,4-triazole-5-thiols at the electrophilic C=C bond in a Ni^{II} complex of a Schiff base of dehydroalanine with (*S*)-*N*-(*N*-benzylprolyl)aminobenzophenone. The stereoselectivity of the formation of diastereomeric complexes with the (*S*,*R*) configuration under conditions of thermodynamic control of the nucleophilic addition exceeds 94%. Acid treatment of the reaction mixtures afforded enantiomerically pure (*R*)-*S*-hetarylcysteines (*ee* >98%).

Key words: dehydroalanine, triazolethiols, asymmetric synthesis, diastereoselectivity, enantiomeric purity, enantiomeric analysis.

Optically active β-substituted α-amino acids serve as important components of many physiologically active peptides, antibiotics, and other pharmaceuticals.[1,2] These compounds include *S*-substituted cysteines,[3,4] which are successfully used in microbiology for selection of highly active producer strains of proteinogenic amino acids.[5—7] (*R*)-Cysteine derivatives containing various heterocyclic substituents can also be of interest in this respect.

Earlier,[8—10] a method has been developed for the asymmetric synthesis of a series of (*R*)-*S*-alkyl- and (*R*)-*S*-arylcysteines by the addition of the corresponding aliphatic and aromatic thiols to a Ni^{II} complex with a Schiff base of dehydroalanine and the chiral carbonyl reagent, *viz.*, (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone ((*S*)-BPB). Subsequent acid treatment of the resulting complexes yielded the target *S*-substituted (*R*)-cysteines.

In the present study, we report the asymmetric synthesis of *S*-substituted (*R*)-cysteines containing 3,4-disubstituted 1,2,4-triazole fragments in the side chain.

The chiral square-planar Ni^{II} complex with the Schiff base formed by dehydroalanine and (*S*)-BPB, *viz.*, [(*S*)-BPB-Δ-Ala]Ni^{II} (**1**), was prepared according to a known procedure.[10]

Thiols **2a—i**, which were synthesized as described earlier,[11,12] were added to complex **1** in MeCN or DMF in the presence of K_2CO_3 or NaOH at 25—50 °C. The reactions afforded pairs of diastereomeric complexes with (*R*) and (*S*) configurations of a new chiral center, *viz.*, (*S*,*R*)- and (*S*,*S*)-**3a—i** (Scheme 1).

The absolute configurations of the diastereomeric complexes of the addition products were determined by comparing the optical rotatory dispersion (ORD) curves of individual diastereomers, which were isolated by chromatography on SiO_2, with the ORD curves of the structurally similar (*R*)-*S*-benzylcysteine and (*S*)-*S*-benzylcysteine complexes prepared earlier.[8] The ORD curves of diastereomeric complexes (*S*,*R*)- and (*S*,*S*)-**3a,b** and the corresponding complexes with (*R*)- and (*S*)-*S*-benzylcysteines are shown in Fig. 1. The diastereomeric complexes with lower R_f (TLC) have an (*R*) configuration ((*S*,*R*)-**3**), whereas the more mobile diastereomeric complexes have an (*S*) configuration of the amino acid residue ((*S*,*S*)-**3**).

The diastereomeric ratio of the addition products depends on the reaction time. At the beginning of the reaction (within ~10 min after the addition of thiol), the excess of the (*S*,*R*) diastereomer, which has a slower TLC mobility, was 85—90%, which is a consequence of relatively low kinetic enantioselectivity. Then the amount of this diastereomer gradually increases due to the establishment of thermodynamic equilibrium. The thermodynamic

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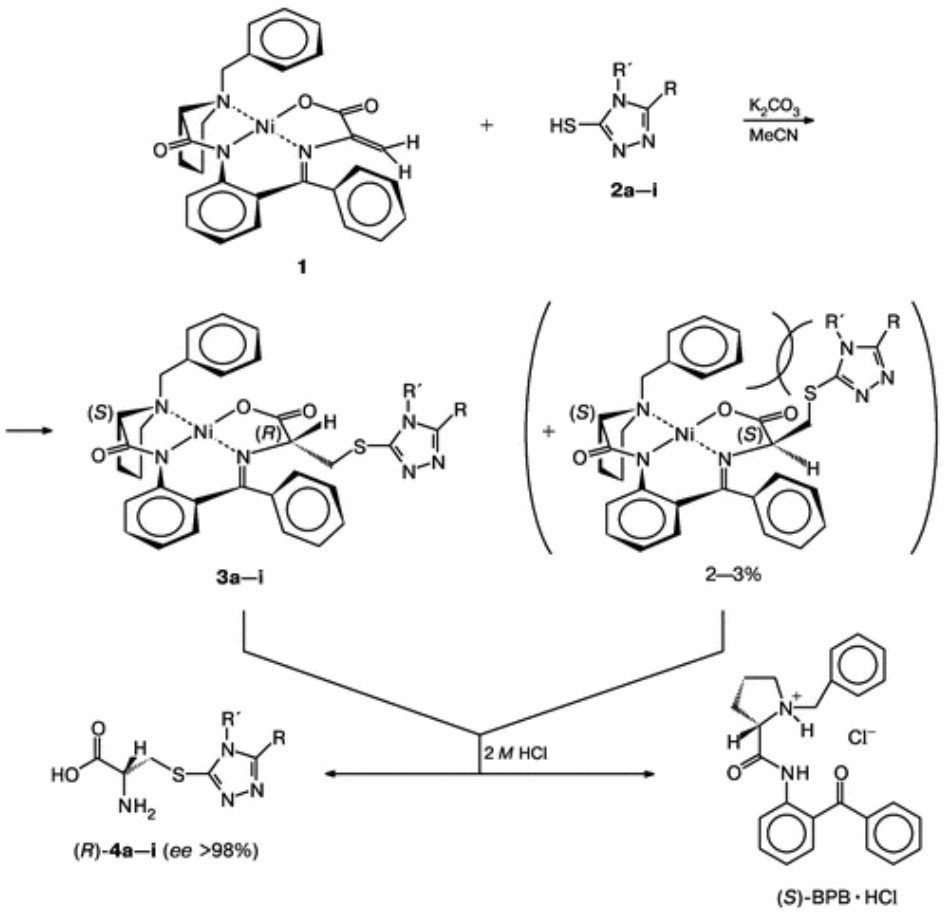
Scheme 1



	R	R′
a	$CH_2CH_2CH_2OH$	Ph
b	$CH_2CH_2CH_2OH$	CH_2—CH=CH_2
c	Pr	Ph
d	Pr	CH_2—CH=CH_2
e	$CH_2CH_2CH(OH)CH_2OCH_2CH_2CHMe_2$	Ph
f	$CH_2CH_2CH(OH)CH_2OCH_2CH_2CHMe_2$	CH_2—CH=CH_2
g	*o*-$MeOC_6H_4$	CH_2—CH=CH_2
h	*o*-ClC_6H_4	CH_2—CH=CH_2
i	$CH_2CH_2CH(OH)C_5H_{11}$	CH_2—CH=CH_2

diastereomeric ratio was determined from the ^{1}H NMR spectra of the reaction mixture by comparing the intensities of the signals for the protons of the benzyl group of the complex (AB system) at δ 4.2—4.4 for the (*S*) isomer and at δ 4.5—4.6 for the (*R*) isomer and spectrophotometrically based on the absorbance of solutions after chromatographic separation of the diastereomers. The equilibrium ratios of the diastereomers and their chemical yields are given in Table 1.

The addition of nucleophiles and establishment of thermodynamic equilibrium between diastereomers occurred rather rapidly (~1 h) in DMF in the presence of NaOH at 45—50 °C. However, this process was accompanied by the formation of up to 10% of by-products. In MeCN, the addition of heterocyclic thiols to complex **1** (K_2CO_3, 45—50 °C) did not afford by-products; however, the establishment of thermodynamic equilibrium between the diastereomeric complexes was more slow (>3 h).

Treatment of a mixture of the diastereomers with HCl after the establishment of thermodynamic equilibrium gave rise to (*R*)-*S*-triazolylcysteines **4a—i** in chemical yields of