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Asymmetric Synthesis of *N*-Fmoc-(*S*)-7-aza-tryptophan via Alkylation of Chiral Nucleophilic Glycine Equivalent

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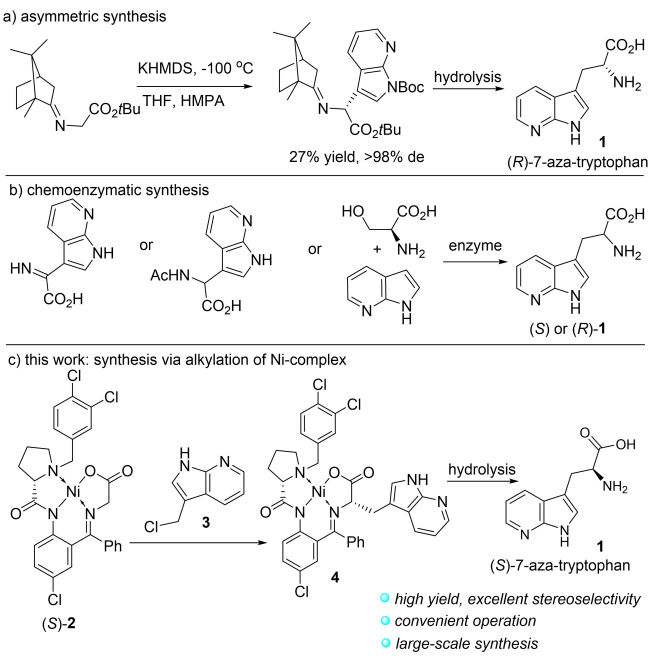
In Memory of Professor Ferenc Fülöp.

Ni(II)-complexes, derived from glycine Schiff bases with chiral tridentate ligands, have been used as powerful tools for the synthesis of structurally diverse tailor-made amino acids. In this manuscript, asymmetric alkylation reaction between chiral nucleophilic glycine derived Ni-complex and 3-(chloromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine has been developed under convenient conditions, which affords the corresponding alkylated Ni-complex in 74% yield and excellent diastereoselectivity (only one isomer). This reaction features convenient conditions and completely controlled diastereoselectivity, which provides a highly valuable approach for asymmetric synthesis of 7-aza-tryptophan.

Amino acids (AAs) belong to the most ubiquitous class of naturally occurring compounds,[1] which have been used as an important type of structural units in the design of modern drugs due to several advantageous features, such as high structural diversity, wide scope of functional groups, good solubility in aqueous media, and few safety concerns.[2] Currently, a number of small-molecule, peptidomimetics, and peptide containing residues of tailor-made AAs or their derivatives serve as key structural features in many blockbuster drugs.[3] Among these natural and non-natural AAs, 7-aza-tryptophan occupies an important position, which has been widely used as biological fluorescent probes,[4] antiplasmodial compounds,[5] and inhibitors of checkpoint kinase 1.[6,7] Although there have been several reports on the synthesis of aza-tryptophanes,[8] the synthesis of 7-aza-tryptophan still remained less developed, in particular in the asymmetric mode. One of the first asymmetric methods was based on alkylation reaction between (1*R*,4*R*)-camphor imine and *tert*-butylglycinate, which proceeded with poor chemical yield (Scheme 1a).[9] Chemoenzymatic synthesis represents an alternative strategy for the preparation of optical pure 7-aza-tryptophan using aspergillus genus acylase,[10] L-amino acid oxidase[11] or tryptophan synthase from Salmonella typhimurium[12] as biocatalyst



Scheme 1. Asymmetric synthesis of 7-aza-tryptophan.

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(Scheme 1b). Thus, there is a room for the development of convenient, efficient, and easy scalable methods for preparation of chiral 7-aza-tryptophan.

Consistent with our long-standing interest in preparation of tailor-made AAs, in particular phosphorus-[13] and fluorine-containing derivatives,[14] we were developing general approach for asymmetric synthesis of AAs via Ni(II) complexes of chiral Schiff bases.[15] Typically, chiral ligands (*S*)-**5**–**7** are used for the preparation of nucleophilic glycine-based Ni-complex for the introduction of the desired side-chain(s) (Figure 1).[16]] Several types of reactions of these nucleophilic Ni-complexes have been developed, such as alkyl halide alkylation[17] aldol,[18] Mannich[19] and Michael[20] addition reactions. Based on the literature data and our own experience in application of Ni(II)-complexes of Schiff bases for the synthesis of "Tailor-Made Amino Acids™",[21,22] we eversion that reaction between Ni-complex and suitable alkyl halide would provide a method to chiral 7-aza-tryptophan. Herein, report an asymmetric method for the synthesis of chiral 7-aza-tryptophan via an alkylation of chiral Ni-complex with corresponding alkyl chloride (Scheme 1c).

Ligand (*S*)-**6** derived glycine Ni-complex **2** was chosen as the starting material for this alkylation reaction (Scheme 2), which usually shows enhanced control in stereoselectivity due

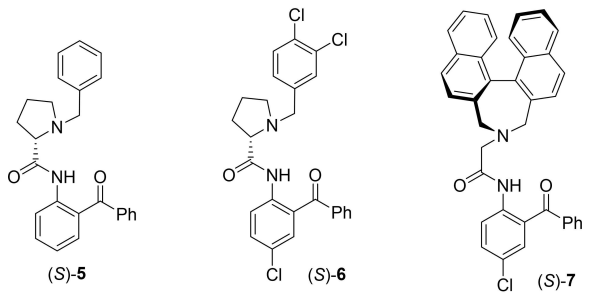
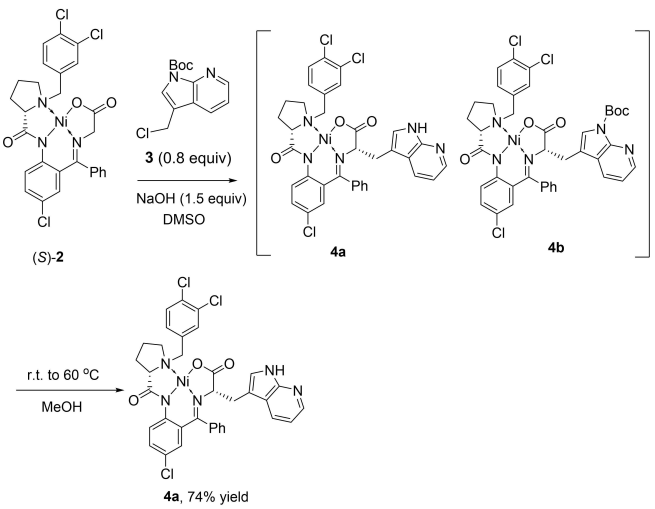


Figure 1. Chiral tridentate ligands **5**–**7**.



Scheme 2. Alkylation of chiral glycine-Ni(II) complex **2** with compound **3**.

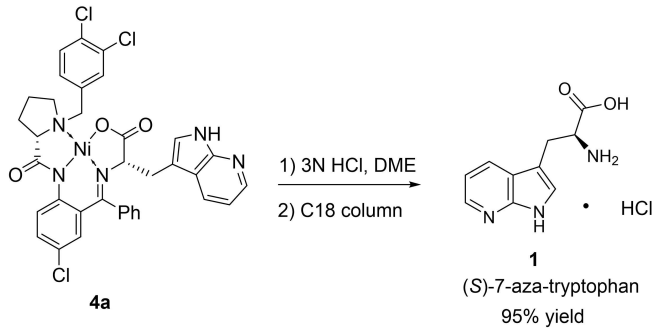
to a parallel displaced type of aromatic interactions between the selectively chlorinated *o*-amino-benzophenone and Pro *N*-benzyl rings.[23] The desired alkyl chloride **3**, Boc-protected 3-(chloromethyl)-1*H*-pyrrolo[2,3-b]pyridine, was prepared with 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde as the starting reagent (for details, see SI file).

Having prepared alkyl chloride **3**, we then studied its alkylation reaction with Ni(II)-complex **2** (Scheme 2). To find an optimal reaction condition to achieve high selectivity and clean conversion to the desired Ni (II) complex **4a**, several screens were carried out. The optimization study led to the very specific condition using DMSO as a reaction solvent, which had rarely been used in the past applications of this methodology.[21] Using DMSO showed a significant difference in purity of the product **4a** during the reaction, exhibiting the high diastereomeric selectivity as well as the lowering impurities formation. After more refining studies were conducted to find an optimal stoichiometry of base and alkyl chloride minimizing the key bis-alkylation byproduct, we found that the reaction with DMSO as a solvent in the presence of NaOH (1.5 equiv.) and alkyl chloride (0.8 equiv.) provided the best yield and diastereoselectivity. To address this question, we added the following sentence: The beneficial effect of DMSO on the reaction outcome is likely multifactorial. However, what could be clearly noticed is a significantly reduced amount of the oxidation products that usually observed under strongly basic reaction conditions.[24]

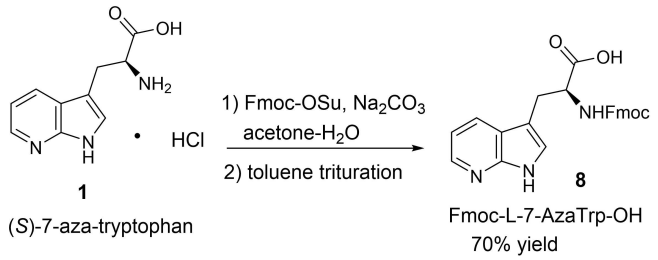
During the workup procedure, surprisingly, the Boc group was partially removed during the reaction even under basic conditions providing a mixture of compounds (**4a** and **4b**). Thus, we developed a one-pot procedure for the synthesis of pure alkylated Ni-complex **4a**. The Boc remaining protected product **4b** was completely converted to compound **4a** by the treatment of the crude reaction mixture with MeOH.

Thus, the reaction was conducted in 2.0 g scale of (*S*)-**2**, 0.8 equiv. of alkyl chloride **3**, 1.5 equiv. of NaOH, in DMSO (40 mL) under nitrogen atmosphere at room temperature for 1.5 h. The resulted reaction mixture was treated with MeOH (40 mL) and stirred at 20 °C for 2 h, and then heated to 60 °C for 1 h, which afforded the corresponding product **4a** in 74% yield and completely controlled stereochemical outcome.

The alkylated Ni (II) complex (*S*,2*S*)-**4a** was then disassembled in the presence of 3 N HCl (aqueous) with 1,2-dimethoxyethane (DME) as a solvent, which afforded the corresponding free amino acid, (*S*)-7-aza-tryptophan (**1**) hydrochloric acid salt in 95% yield (Scheme 3). DME was chosen as a solvent, instead of methanol, although methanol has been generally employed for this step.[22] This is because the use of methanol as solvent for this disassembly procedure was found to cause undesired esterification. The reaction proceeded smoothly, and the isolation of the amino acid was successfully carried out by filtering off most of the chiral ligand precipitated after the reaction and partitioning between water and dichloromethane to sequester the residual ligand into organics. C18 flash column chromatography was utilized to remove the residual Ni^{2+} prior to the following Fmoc protection. It should be pointed out the C18 flash column method was used during this trace experiment. This is proved to be the most straightfor-



Scheme 3. Disassembly of Ni-complex **4a**.



Scheme 4. Fmoc protection of (*S*)-**1**.

ward for small scale, which worked well to provide the desired amino acid **1** in good yield and high purity. It should be emphasized that chiral ligand (*S*)-**6**, as well as Ni(II), can be recycled and reused for continuous production of this and other types of AAs, as illustrated in the recent publications.[22,25]

The Fmoc protection was carried out employing general conditions using Fmoc-OSu in the presence of sodium carbonate (Scheme 4). The reaction proceeded smoothly and furnished the desired Fmoc-L-7-AzaTrp-OH (**8**) in 70% yield. It should be mentioned that the residual Ni^{2+} seems to complicate the Fmoc reaction and care must be taken to remove Ni^{2+} completely before this step. The crystalline product **8** was easy to isolate from the reaction. For the purification, the hydrolyzed impurity derived from unreacted Fmoc-OSu was effectively sequestered by the trituration with toluene. The synthesized compound **1** could be easily obtained with a high chemical purity as measured by ^{1}H-NMR and HPLC.

In summary, the first total synthesis of Fmoc-L-7-AzaTrp-OH via tridentate chiral auxiliary derived Ni(II)-complexes methodology was successfully accomplished, which could be operated under convenient conditions resulting in an overall 49% yield (three-step). In particular, excellent diastereoselectivity was obtained for the alkylation step (only one isomer).

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Aza-tryptophanes · Asymmetric synthesis · Chiral tridentate ligands · Ni catalysis · Tailor-Made Amino Acids™ · Schiff bases

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