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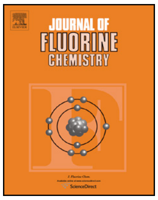

Synthesis of fluorine-containing α-amino acids in enantiomerically pure form via homologation of Ni(II) complexes of glycine and alanine Schiff bases

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Dedicated to Professor Iwao Ojima on the occasion of his winning ACS Award for creative and seminal contributions to organofluorine chemistry.

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ABSTRACT

Development of synthetic methodology for preparation of enantiomerically pure fluorine containing amino acids (FAAs) is one of the most actively pursued areas of fluoroorganic chemistry. This review provides a comprehensive treatment of literature data dealing with asymmetric synthesis of FAAs via homologation of chiral and achiral Ni(II) complexes of glycine and alanine Schiff bases using fluorinated electrophilic reagents. The homologation approaches include: (1) alkyl halide alkylations; (2) aldol; (3) Michael and (4) Mannich addition reactions. Furthermore, Ni(II) complexes of Schiff bases of FAAs can be used for deracemization of racemic FAAs and (*S*) to (*R*) interconversion, providing additional synthetic opportunities for preparation of enantiomerically pure FAAs. Particular attention is given to the mechanistic considerations where fluorine can significantly influence the stereochemical outcome of the asymmetric transformation, as compared with the reactions of fluorine-free substrates. Aspects of practicality, cost-structure and large-scale synthesis of FAAs using this methodology are critically discussed.

1. Introduction

In recent decades, fluorine has become a very special element in the design of pharmaceuticals, agrochemicals and a variety of healthcare products. There are many effects that fluorine can impart on the biological activity of natural products, including its electronegativity, size, omniphobicity and electrostatic properties that can be used in the design of biologically active compounds [1]. However, the major factor that makes fluorine really unique is that the carbon–fluorine bond is metabolically inert [2]. Obviously, such property is of great value for rational design of molecules with a presupposed biological activity. Thus, considering the important role of natural amino acids in the biochemistry of life, it is difficult not to foresee some great potential of fluorinated amino acids (FAAs) in various areas of life-sciences. Consequently, since about 1960 the synthesis of alpha- and beta-FAAs has been quite a favorite target of many research groups [3–12]. First comprehensive review of synthesis and properties of FAAs was made in form of a monograph (422 pages) published in 1995 [13]. Since then quite regularly, review articles have been appearing in the literature covering various aspects of synthesis [14], properties and applications [15] of various structural types of FAAs. However, one particular type of chemistry, widely used for the asymmetric synthesis of FAAs, has never been reviewed since 1992 [16] which is the homologation of Ni(II) complexes **1–3** of glycine and higher amino acids (Fig. 1).

The original complex **1**, introduced in 1985 [17], can be prepared in (*S*) or (*R*) configuration on large scale [18] starting from

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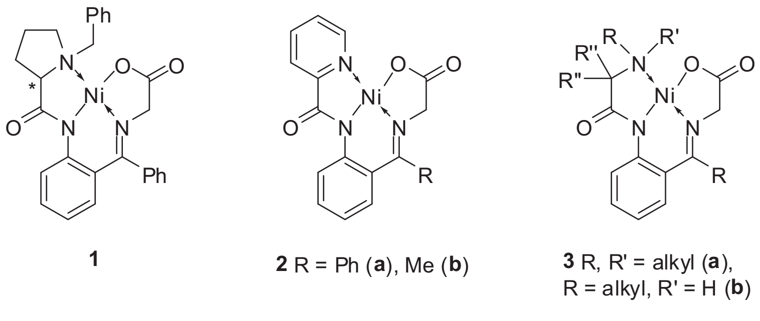


1

2 R = Ph (**a**), Me (**b**)

3 R, R' = alkyl (**a**),
R = alkyl, R' = H (**b**)

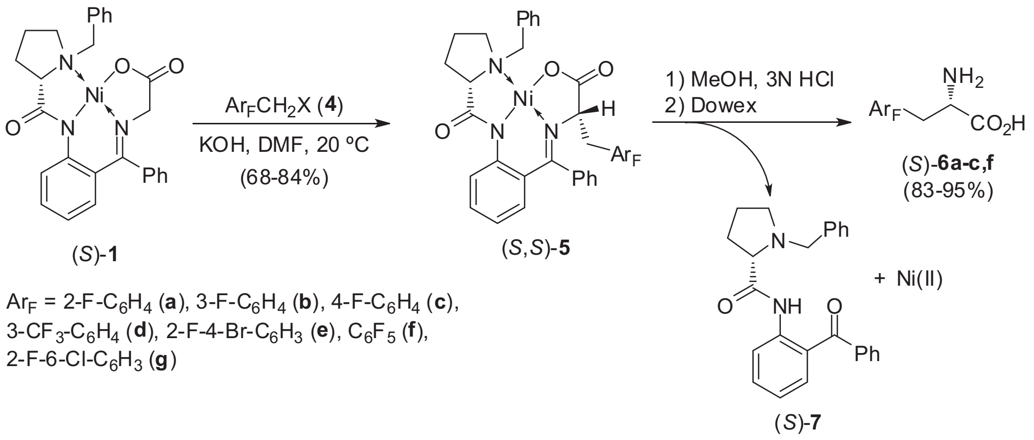
R" = H or Me

Fig. 1. Structures of Ni(II) complexes **1**–**3**.

the corresponding enantiomers of proline. The corresponding Cu(II) complexes are less practical due to their lower stability and reactivity [19]. In addition, the paramagnetic character of the Cu(II) complexes impedes their analysis using NMR techniques. The proline nitrogen coordinated to Ni(II) ion is chiral and configurationally stable. However, its absolute configuration is completely controlled by the proline carbon stereochemistry and do not lead to any problems with the formation of diastereomers. Usually, and this is adopted here, the nitrogen absolute configuration is not depicted. Another types of glycine Schiff base Ni(II) complexes discussed in this review are achiral derivatives of picolinic acid **2a**,**b**, introduced in 1997 [20] and 2000 [21], correspondingly. These compounds are easier to prepare [22] but they have some limited applications as compared to **1** because they do not have stereochemistry information. However compound **2a** can be effectively used for the synthesis of very biologically important achiral α,α-bis-amino acids [23]. Complexes **2a**,**b** can be also used for asymmetric synthesis of amino acids using chiral reagents [23,24]. Finally, interesting type of compounds **3a**,**b** contain two glycine moieties (when R″ = H): the corresponding Schiff base and the *N*,*N*-disubstituted derivative. However, it was demonstrated that even under drastic basic condition only the activated Schiff base part undergoes derivatization while the second glycine moiety remains intact [25]. This type of Ni(II) complexes was reported relatively recently (2005) and still undergoes some new developments [26]. For example, incorporation of chirality information via *N*-mono-substituted moiety, in so-called "NH" type **3b**. Homologation of complexes **1**–**3** can be conducted using a variety of reaction types separated in this review in different sections. These include: alkyl halide alkylation, Michael, aldol and Mannich additions. Two final sections describe application of chiral "NH" type of complexes **3b** for deracemization and (*R*) to (*S*) interconversion of several higher ω-CF_3 containing amino acids. The disassembly of the homologation products is operationally convenient, requiring heating in a mixture of methanol and HCl (1–6 N); followed by isolation of the target amino acids using ion-exchange chromatography on Dowex-type resins. It is very important to emphasize that the disassembly step proceeds with no loss of enantiomeric purity of the target amino acids and the chiral ligands can be quantitatively recovered.

2. Alkyl halide alkylations

In general, alkyl halide alkylation of Ni(II) complex (*S*)-**1** is the most versatile and general homologation reaction. Virtually any type of alkyl halide can be used, including highly sterically constrained ones [27], and the reactions can be conducted on relatively large scale [28]. The diastereoselective α-alkylation of chiral Ni(II) complex (*S*)-**1** with alkyl halides is based on the high acidity of the α-protons, and the corresponding enolate generated in the only one geometrically possible (*E*) configuration [29] can undergo alkylation reactions with predictable stereochemical outcome, high reaction yields and diastereoselectivity using operationally convenient reaction conditions [30]. For preparing fluorine-containing phenylalanine derivatives, alkylation of Ni(II) complex (*S*)-**1** with fluorinated benzyl halides **4** are usually conducted in DMF solution in the presence of NaOH to give cleanly the alkylation products (*S*,*S*)-**5** in high chemical yield and diastereomeric purity (>90% de) [31] (Scheme 1). The (*S*) absolute configuration of the *N*-(benzyl)proline residue in (*S*)-**1** effectively induced the (*S*) stereochemistry of the newly formed stereogenic center of amino acids under thermodynamically controlled



Ar_F = 2-F-C_6H_4 (**a**), 3-F-C_6H_4 (**b**), 4-F-C_6H_4 (**c**), 3-CF_3-C_6H_4 (**d**), 2-F-4-Br-C_6H_3 (**e**), C_6F_5 (**f**), 2-F-6-Cl-C_6H_3 (**g**)

Scheme 1. Alkylations of complex (*S*)-**1** with fluorinated benzyl bromides **4** under homogeneous conditions.

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