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Review

New approaches to enantioselective fluorination: Cinchona alkaloids combinations and chiral ligands/metal complexes

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Abstract

The selective construction of carbon–fluorine bonds is of great interest to medicinal chemists because the replacement of a hydrogen or an oxygen atom with a fluorine atom in biologically active molecules can confer the molecules with improved physicochemical properties and biological activities. Since the first discovery of enantioselective fluorination using *N*-fluorocamphorsultam, our synthetic interest had been focused on the development of chiral *N*-fluorosulfonamide derivatives capable of enantioselective fluorination. However, these initial efforts revealed several limitations in both chemical yields and enantioselectivities of the fluorinated products. We present here the background of our personal story of the enantioselective fluorination reaction and some successful applications of the methods to the design and synthesis of biologically active products. Two novel approaches using cinchona alkaloid/Selectfluor® combinations and chiral ligands/metal complexes have been pursued, respectively. In addition, the recent advances in this area by other groups are also described briefly.

Keywords: Fluorination; Enantioselective; Asymmetric reaction; Cinchona alkaloids; Metal; Organocatalysts; Medicinal chemistry

Contents

1. Introduction

The synthesis of chiral fluoro-organic compounds is an important topic in modern pharmaceutical chemistry [1]. The replacement of a hydrogen or a hydroxyl group with a fluorine atom is an extensively used strategy for enhancement of

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biological activity in the design of analogues of biologically important molecules [2]. The analogues are often regarded as isosteres of the parent molecules because of the following considerations [3]. First, fluorine most closely resembles hydrogen in size among atoms; therefore, the fluorine replacement is often regarded as an isosteric substitution. Second, both from the structural and electronegativity points of view, fluorine and oxygen, not fluorine and hydrogen, are very nearly isosteric. Recent evidence indicated that the advantages of the fluorine substitution include an increase in stability, changes in lipophilicity, introduction of a highly electronegative center, and altered patterns of reactivity of the C–F versus the C–H or C–OH bond. A variety of methodologies of enantioselective synthesis of fluoro-organic compounds have been described [4]. Undoubtedly, an electrophilic introduction of a fluorine atom into a molecule via enantioselective fluorination is a highly versatile synthetic transformation [5]. In this process, fluorine is directly and asymmetrically transferred to an achiral anion. Chiral sulfonamide-type fluorinating reagents were developed for this purpose [6]. Differding and Lang, who first introduced this idea, reported electrophilic enantioselective fluorination of enolates using *N*-fluorocamphorsultam **1a** in 1988 [6a]. Several other reagents of this type including the Davis' reagents [6b,c] **1b,c** and saccharin-type reagents **1d,e** contributed by one of us followed (Fig. 1) [6e–g]. However, these are far from ideal because of low chemical yields and low optical enrichment of the fluorinated products. Furthermore, the reagents themselves are still relatively unavailable because their preparation requires tedious and multi-step procedures, including fluorination with toxic molecular fluorine or explosive gaseous perchloryl fluoride. Due to these drawbacks, there are no reports of the use of these reagents for asymmetric fluorination except for the original papers.

Progress toward truly efficient methodologies for practical use had to await breakthroughs in enantioselective fluorination for a decade. In late 2000, three communications were disclosed along these lines simultaneously. Cinchona alkaloid-mediated enantioselective fluorination by us [7] and Cahard's group [8], and TADDOLato/Ti(II)-catalyzed enantioselective fluorination by Togni's group [9] are two major discoveries. They are so different from the previously reported approach in that they enable access to chiral fluoro-organic compounds with practical levels of enantiomer excess for the first time. Our procedure is based on *in situ-generated N*-fluoroammonium salts of cinchona alkaloids named *cinchona alkaloid/Selectfluor® combinations*. Cahard et al. reported the substantially same approach except for the use of *isolated N*-fluoroammonium salts of cinchona alkaloids (*N*F-CA) instead. Both methodologies have displayed broader substrate generality than so far examined. Silyl enol ethers, metal enolates, α-cyano esters, β-keto esters, oxindoles, lactones, dipeptides, allylsilanes and even more are able to be fluorinated with high enantioselectivities. Togni's approach using TADDOLato/Ti(II) is the first example of a catalytic enantioselective fluorination of β-keto esters and their concept has become an important milestone in this field. As elegantly reviewed articles [10] have now become available concerning recent progress of asymmetric fluorination reaction, this account focuses on the contributions from our laboratory to this dynamic field [7f]. The recent advances in this area by other groups are also summarized briefly.

2. Cinchona alkaloid/Selectfluor® combinations

Our interest in the reagent-controlled enantioselective fluorination prompted us to seek a simple and powerful method, which can be carried out with ease using commercially available reagents without any special requirements. First, we had to shake ourselves free from the conventional idea using *N*-fluorosulfonamides. In recent years, Selectfluor® has been widely used for electrophilic fluorination [11]. It is a quaternary *N*-fluoroammonium salt of 1,4-diazabicyclo[2,2,2]octane (DABCO) with an interesting implication for designing asymmetric reagents based on the use of chiral, non-racemic *N*-fluoroammonium salts. On examining the structural features of Selectfluor®, we noticed that it is analogous to cinchona alkaloids that have a praiseworthy history in asymmetric synthesis [12] (Fig. 2). A chiral version of Selectfluor® surprisingly was unknown in the literature at that time, to the best of our knowledge. It would be produced via a transfer-fluorination from Selectfluor® to a cinchona alkaloid, which is likely to be associated with the special features of their structures. Relief from the dication state of Selectflour® to generate two monocations of ammonium salts provides the thermodynamic driving force for the transfer (Scheme 1). Indeed, Banks et al. demonstrated in their early report, albeit with simple compounds, transfer fluorination reactions [13].

We tested this idea using a quinine/Selectfluor® combination prepared in situ from both commercially available quinine and Selectfluor® to enable the enantioselective fluorination of

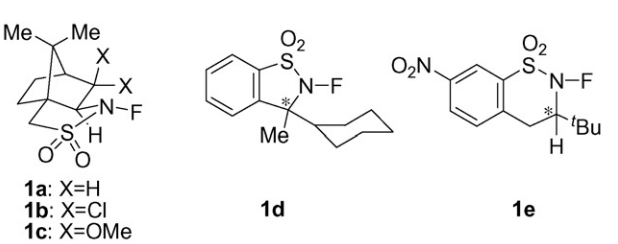

Fig. 1. 1st Generation for enantioselective fluorination: *N*-fluorocamphorsultam and related reagents.

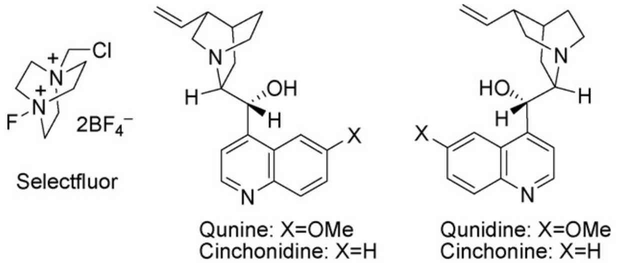

Fig. 2. Selectfluor® and cinchona alkaloids, quinine, quinidine, cinchonidine and cinchonine.