Catalytic Asymmetric Nucleophilic Fluorination Using $BF_3{\cdot}Et_2O$ as Fluorine Source and Activating Reagent

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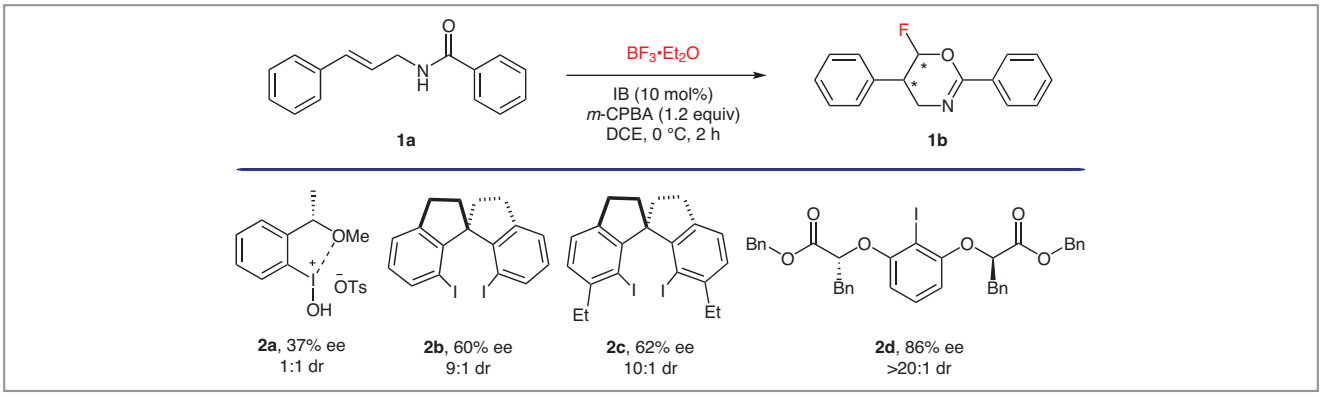
With the growing applications of fluorinated compounds in modern organic chemistry, pharmaceutical sciences, agrochemistry and materials chemistry, the development of innovative strategies for achieving the selective fluorination of organic molecules represents one of the most hectic areas in chemical research.[1,2] In particular, the construction of stereogenic C–F bond-substituted centers is a critically important, albeit still challenging, task in fluorine chemistry.[3] Professor Xianxing Jiang from Sun Yat-sen University (P. R. of China), who is strongly interested in organofluorine chemistry, reckons that asymmetric fluorinations using nucleophilic fluorine sources are much less developed as compared to electrophilic strategies, due to the unique features of fluorine atoms (such as high oxidation potential, high hydration energy).[1] "In current research, the main nucleophilic fluorine sources applied in asymmetric fluorinations are PhCOF, pyridine·HF, $Et_3N{\cdot}HF$ and metal fluorides," he noted, adding: "Despite elegant works reported in the literature, several practical disadvantages discouraged further large-scale utilization of these compounds for nucleophilic fluorinations: for example, the high toxicity and biohazardous nature of HF-bases, and the poor solubility of metal fluorides in organic solvents, coupled with limited strategies to control their reactivity, are among the main reasons."[4]

According to Professor Jiang, compared to metal catalysts, chiral hypervalent iodine catalysts have recently attracted much attention in organic synthesis due to their excellent properties, such as mild reaction conditions, ease of preparation, the ability to dispense with complex ligands, and being metal-free.[5,6] "Importantly, Jacobsen and co-workers reported the viability of catalytic asymmetric nucleophilic fluorinations using a chiral iodine catalyst and pyridine·HF in the presence of *m*-CPBA," he noted.[7]

Professor Jiang and his research group have been interested in hypervalent iodine catalyzed/promoted reactions (such as asymmetric halogenations, oxidative cyclization and oxyaminations) and Lewis acid catalyzed/mediated chemical synthesis. Professor Jiang explained: "The initial phase of our research was focused on catalytic asymmetric nucleophilic fluorinations using the 'chiral iodine catalyst + pyridine·HF' catalytic system, inspired by Jacobsen's work. We found that $BF_3{\cdot}Et_2O$, which is a versatile and cheap Lewis acid, could also be applied as fluorine source in some fluorinations. We thought that if we could combine the hypervalent chiral iodine catalyst and $BF_3{\cdot}Et_2O$ together, we could then apply the 'combination' to reactions with appropriate substrates to form chiral fluorinated products. If so, it would be a welcome and significant step in fluorine chemistry."

Professor Jiang continued: "Firstly, we applied the combination of hypervalent iodine compound and $BF_3{\cdot}Et_2O$ to reactions with the amide **1a** in DCM at 0 °C (Scheme 1). To our delight, the fluorinated products **1b** could be generated through the catalytic process. On the basis of this experimental result, we then used chiral iodine reagents instead of iodobenzene



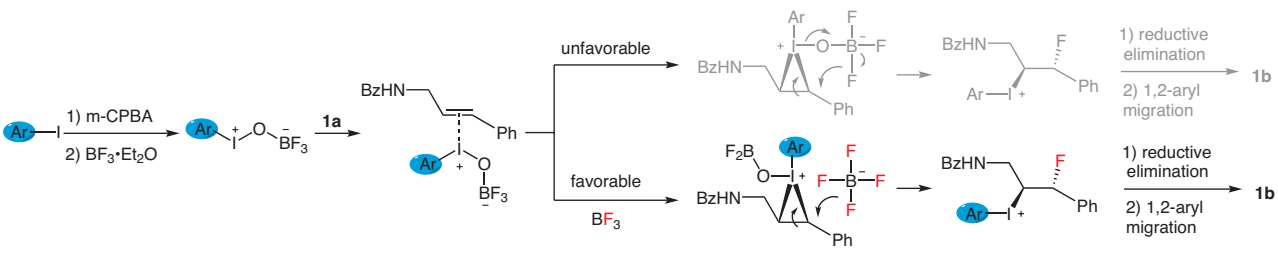
Scheme 1 Catalyst screening

(IB) to carry out the reaction. At first, the chiral iodine(III) reagent **2a** was applied to catalyze the fluorinations, affording the desired product with 37% ee (major diastereomer). Next, we examined spirobiindane chiral iodine catalysts **2b** and **2c** which gave the desired products with higher ee and dr values. Axisymmetric chiral iodine catalysts were then examined to improve the stereoselectivity of the fluorinated product. Catalyst screening indicated that **2d** was the best choice (Scheme 1). After several initial trials aimed at studying the effect of different experimental factors such as solvents, reaction temperature, concentration, we set out to optimize the model catalytic asymmetric aminofluorination of **1a** in the presence of 15 mol% of ligand loading, using $BF_3 \cdot Et_2O$ as the fluorine reagent in DCE at –25 °C. This part of the research project was carried out by Dr. Weiwei Zhu and Xiang Zhen."

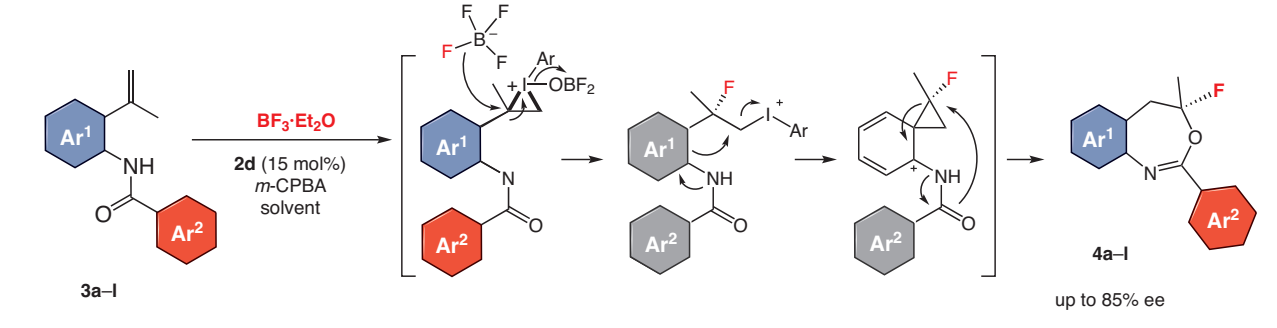
To gain a better understanding of this catalytic fluorination system, the authors conducted control experiments and DFT calculations. Professor Jiang said: "It is worth noting that when $PhIF_2$, Py·HF or $Et_3N \cdot HF$ were used as fluorine source, **1b** could NOT be obtained. In the beginning we thought fluoride was produced from Ph-I-OBF_3 directly during the catalytic cycle. However, DFT calculations didn't support this initial hypothesis, as it was found to be energetically disfavored. Then we modified the possible mechanism: the 'fluorine source' was hypothesized to be the BF_4^- anion (generated in situ) and this turned out to be energetically possible (Scheme 2). The process would thus follow a fluorination/1,2-aryl migration/cyclization cascade.[8] In this scenario, $BF_3 \cdot Et_2O$ plays the role of a fluorinating reagent, as well as the activating reagent for activation of iodosylbenzene."

In order to expand the applications of this catalytic fluorination system, Professor Jiang and co-workers designed and synthesized substrates **3a–l** to undergo the fluorination reaction (Scheme 3). "As expected, the fluorinated products **4a–l** could be obtained as we hoped, based on the possible catalytic cycle. Screening of different reaction parameters gave the optimal reaction conditions for the formation of fluorinated products with good to excellent ee values," remarked Professor Jiang.

Professor Jiang recalls at the onset of this novel research program, three main challenges were identified. "The first was the choice of the fluorinating reagent. As mentioned above,



Scheme 2 Mechanistic studies



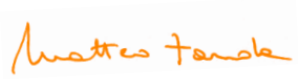
Ar^1 = phenyl, 5-methylphenyl, benzo[*d*][1,3]dioxol
Ar^2 = 4-methylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, 4-isopropylphenyl, 4-*tert*-butylphenyl, 3,5-di-*tert*-butylphenyl, 3,5-ditrifluoromethylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 3,5-dimethoxyphenyl

Scheme 3 Substrate scope expansion

currently the most applied fluorine sources in nucleophilic fluorinations are Py·HF, Et_3N·HF or metal fluorides, which have been used in elegant works, but the practical disadvantages described earlier are detrimental in terms of large-scale utilization. Considering that $BF_3 \cdot Et_2O$ could be applied in achiral fluorinations as nucleophilic fluorine source and inspired by the asymmetric fluorinations achieved with chiral iodine catalysts, we came up with the idea that the combination of 'chiral iodine catalyst and $BF_3 \cdot Et_2O$' may be an alternative for asymmetric fluorinations. The second was the design of the substrates. Based on the previous related work on fluorination reactions and the possible mechanism of hypervalent iodine catalyzed fluorination reactions, we designed and synthesized the original substrate **1a**. By the way, **1a** was tested for halogenations in previous work.[9–11] What inspired us to study the catalytic system further for catalytic asymmetric fluorinations was that the substrate **1a** could react with the 'IB + $BF_3 \cdot Et_2O$' system in the presence of *m*-CPBA to generate fluorinated products. The third challenge was the possible competition between Lewis acid promoted cyclization reaction and catalytic fluorinations. In our previous work, we reported a Lewis acid promoted cyclization of unsaturated alkenes."[12]

The current catalytic system had an important influence on the group's research. In view of the advantages of using $BF_3 \cdot Et_2O$ as fluorine source in asymmetric nucleophilic fluorinations, Professor Jiang revealed that his group will continue to focus on catalytic, asymmetric nucleophilic fluorinations using $BF_3 \cdot Et_2O$ as fluorine source and activating reagents in their future research. Professor Jiang explained: "We aim to expand the substrate scope and synthesize more chiral fluorinated molecules using our "chiral hypervalent iodine + $BF_3 \cdot Et_2O$" catalytic system. In addition, asymmetric fluorinations using other nucleophilic fluorine sources are still one of our main research topics."

Professor Jiang concluded: "Fluorinated oxazine derivatives could be obtained with high stereoselectivities (up to > 20% ee and > 20:1 dr), whereas benzocycloheptane derivatives could be synthesized with high enantioselectivities (up to 85% ee) and in one step, through this metal-free and complex-ligand-free catalytic system. Oxazine derivatives are widely present in bioactive and pharmaceutical molecules, and fluorinated 1,2-amino alcohols, which are important intermediates in organic synthesis and pharmaceutical chemistry, could be obtained through hydrolysis of the products. Besides, ring-opening polymerization of the N,O-heterocycles can be applied to prepare functional materials. We believe that this process provides not only a direct access to fluoro–oxazine/benzoxazepine skeletons, but also a foundation for further development of new types of asymmetric nucleophilic fluorinations in future applications. Studies on the applicability of this asymmetric fluorination methodology using other substrates are presently ongoing in our group."



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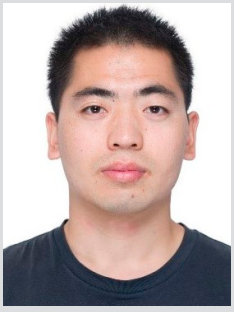

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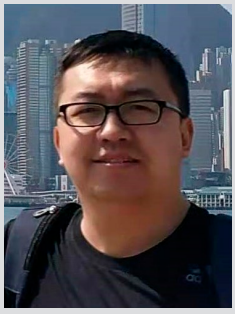

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