Diastereodivergent, Asymmetric Nucleophilic Fluorination Methodologies

Fluorine, perhaps more so than any other element, has generated an enormous amount of interest across practically every discipline in organic chemistry. The dramatic effect that fluorine can impart on the physical, chemical and biological properties of molecules is well-documented, and fluoroorganics now play a dominant role in pharmaceutical chemistry, agrochemistry and materials science. Recent estimates suggest that 30–40% of agrochemicals contain at least one fluorine atom, while in the pharmaceutical industry 20% of active products are fluorinated, including 5 of the top 10 drugs sold in 2005.[1] In light of this plethora of applications, practical and safe methods for the regio- and stereocontrolled installation of fluorine atoms into organic substrates are currently in high demand:[2] to meet this need, several elegant electrophilic fluorination[3] protocols have been developed, including catalytic asymmetric procedures,[4] although complementary nucleophilic fluorination reagents are not employed as frequently.

Proposed programme of work

This proposal seeks to develop generally applicable asymmetric nucleophilic fluorination methodology to facilitate the preparation of a range of fluoroorganics, utilizing reagents based upon the inexpensive and easily handled tetrafluoroboric acid (HBF_4) and borontrifluoride (BF_3).

Background

Many of the extant fluorination methodologies present drawbacks from an economical standpoint due to the high cost and low atom economy of some reagents, or the requirement for high reaction temperatures over extended periods, deterring their use in large scale applications. Practical issues relating to the handling difficulties of some reagents or the production of reagent-derived by-products can also complicate reaction execution and product isolation, respectively, and these problems are again amplified on scale-up. Thus, the search for efficient, cost effective and easy to use fluorinating reagents represents a great challenge in chemistry. Considering the significant practical and economic benefits (i.e., low cost, high fluorine content and ease of handling in standard glassware) we have investigated the utility of $BF_3{\cdot}OEt_2$ and HBF_4 as a nucleophilic fluoride sources. The results from these investigations enabled us to develop highly selective ring-opening hydrofluorination processes for a range of epoxides. For instance, treatment of a range of substituted aryl epoxides **1** (bearing modestly electron-donating or electron-withdrawing substituents) with $BF_3{\cdot}OEt_2$ (0.33 equiv) gave ring-opening via a stereoselective S_N1-type process (intramolecular transfer of fluoride from the boron atom within intermediate **2**) to give the corresponding β-fluoro alcohols **3** with retention of configuration, consistent with the transfer of all three fluorine atoms from $BF_3{\cdot}OEt_2$. Subsequent transformations allowed elaboration of these substrates to a range of β-fluoroamphetamines **4** (Fig. 1).[5]

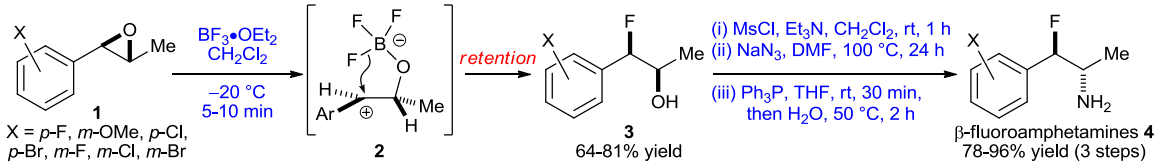

Figure 1. β-Fluoroamphetamines via the stereoselective synthesis of benzylic fluorides.

In a similar manner, treatment of epoxide **6** (derived from chemo- and diastereoselective olefinic oxidation of allylic amine **5**)[6,7] with HBF_4 led to epoxide ring-opening via an S_N2-type process to give fluoro hydroxy amine **8**, consistent with a mechanism involving initial formation of ammonium-ion **7** followed by regioselective ring-opening at the carbon atom distal to the electron withdrawing ammonium moiety (Fig. 2).

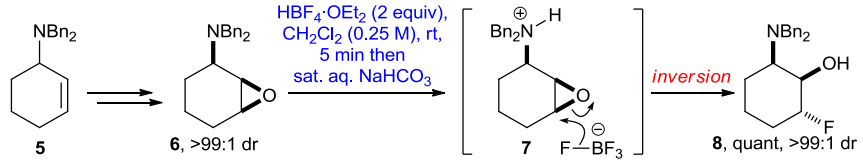

Figure 2. Ring-opening hydrofluorination of epoxy amines with $HBF_4{\cdot}OEt_2$.

These studies demonstrate that a compromise in intermediate carbocation stability versus reactivity may be necessary for successful incorporation of fluorine, meaning that the rate of both cation formation and trapping by fluorine must outpace competing side reactions.

Research goals: generally applicable, stereodivergent nucleophilic fluorination methodology

In relation to the examples highlighted above, we propose that a range of $BF_3{\cdot}Et_2O$ derived alkoxy fluoroborates **9–12** may be produced with tailor-made properties to fine-tune reactivity: a range of alkyl or aryl substitutents may be used to increase or decrease the steric and electronic requirements of the system in order that the required balance in cation stability versus reactivity may be attained. The scope of this methodology may also be extended to include a range of potential electrophilic substrates, including aziridines **13** (or aziridinium ions), oxetanes **14**, oxazolidinones **15**, and oxathiazolidine-2-oxides **16**, in addition to studying a structurally diverse range of epoxides (Fig. 3).

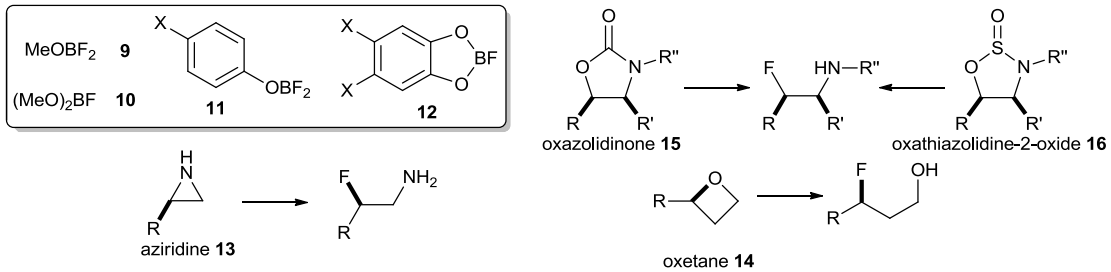

Figure 3. The proposed method for nucleophilic fluorination with alkoxy fluoroborates.

In accordance with this hypothesis, recent exploratory studies concerning the ring-opening hydrofluorination of epoxide **17** with $BF_3{\cdot}Et_2O$ showed that none of the desired fluorohydrin **18** was produced, and almost complete formation of ketone **19** (via a carbocation rearrangement pathway) was observed. Modification of the structure of the fluorinating agent by the use of $(MeO)_2BF$ resulted in effective suppression of the undesired cation rearrangement pathway, and **18** was isolated in 25% yield in addition to **19**, presumably formed via transfer of a methoxy group from the boron species. Tethering the two alkoxy groups in the case of fluorinating agent **21** was found to produce **18** exclusively (Fig. 4).

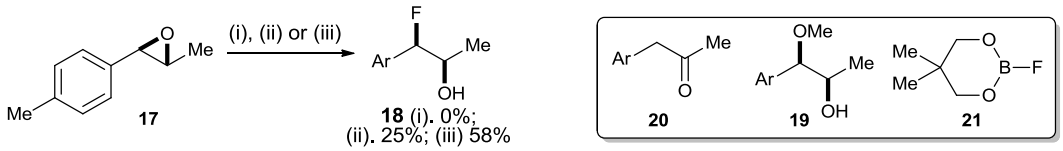

Figure 4. Fine-tuning the reactivity of the fluorination reagent. *Reagents and conditions*: (i) BF3•OEt_2 (1.0 eq), CH_2Cl_2, –20 °C, 5 min; (ii) $(MeO)_2BF{\bullet}OEt_2$ (1.0 eq), CH_2Cl_2, –20 °C, 5 min; (iii) **21** (1.0 eq), CH_2Cl_2, –20 °C, 5 min.

It is anticipated that the knowledge gleaned from these reactions will allow a diastereodivergent method for nucleophilic fluorination of a wide range of substrates to be developed. For instance, treatment of epoxide **22** with X_2BF is expected to lead to S_N1-type ring-opening to give **24** whilst treatment of the same epoxide with X_2BF in the presence of an additional fluoride source is expected to give rise to S_N2-type ring-opening to give **23**. The student will initially focus on the fluorination of a structurally diverse range of epoxides using derivatives of $BF_3{\cdot}Et_2O$ incorporating an increasing number of alkoxy ligands at the boron atom; a systematic study of the structural requirements of the substrate and the reaction conditions will allow an optimized, stereodivergent protocol for nucleophilic fluorination to be developed, prior to application to a wider range of electrophiles (Fig. 5).

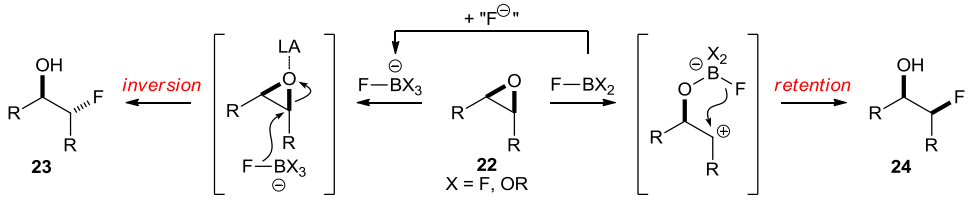

Figure 5. The proposed stereodivergent nucleophilic fluorination protocol.

Further applications: asymmetric fluorination protocols

Use of 'chiral BF_3 equivalents' such as dialkyl tartrate derived **27** or binol derived **28** will allow for an asymmetric variant of this methodology to be developed, for instance for application in the desymmetrisation of meso epoxides **25** or the kinetic resolution of racemic epoxides **26**. If these reactions are carried out with an external fluoride source (to generate the analogous 'chiral HBF_4 equivalent' reagents) complementary diastereoselectivities should also be observed (Fig. 6).

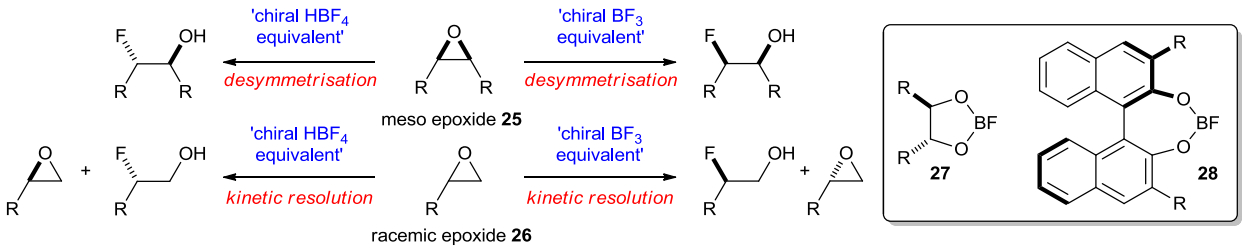

Figure 6. Proposed asymmetric nucleophilic fluorination with chiral $BF_3{\cdot}Et_2O$ derived alkoxy fluoroborates.

Further applications: 'hot' organofluorine compounds

The notable speed (~5 min reaction time) of the fluorination processes of the proposed methodology should show utility in the preparation of ^{18}F radioisotope (half-life of 110 min) labelled compounds if applied to the late-stage introduction of fluorine in a synthetic sequence. The resultant 'hot' organofluorine compounds may be useful for conducting positron emission tomography (PET) studies. The Siemens Oxford Molecular Imaging Laboratory (SOMIL) is part of Oxford Chemistry's portfolio, and houses hot cells for the preparation of ^{18}F labelled compounds.

Summary

A generally applicable protocol for nucleophilic fluorination, with *in situ* formed alkoxy fluoroborates derived from $BF_3{\cdot}Et_2O$, would complement existing approaches in organofluorine chemistry. The proposed methodology will expand the range of accessible fluorinated substrates by trapping electron deficient intermediates with activated, non-basic fluoride equivalents. This methodology is superior to current methods available for nucleophilic fluorination as $BF_3{\cdot}Et_2O$ is inexpensive, readily available and easily handled in laboratory/industrial equipment. The methodology will be extended to the generation of cascade processes, creating multiple stereogenic centres, with functionalized architectures leading to a wider range of available fluorinated building blocks, including chiral organofluorine compounds.

References

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