ENANTIOSELECTIVE FLUORINATION VIA PHASE-TRANSFER CATALYSIS

Reported by Craig Seymour October 7th, 2013

INTRODUCTION

The synthesis of fluorine containing molecules is an important area of organic chemistry due to the unique and often desirable stereoelectronic properties exhibited by fluorinated molecules. The importance of organofluorine compounds is highlighted by the fact that approximately 18% of all pharmaceuticals and 28% of all agrochemicals contain a fluorine substituent.[1] However, a vast majority of these fluorine substituents do not reside on a stereogenic carbon. There is a need across the fields of applied chemistry for enantioenriched organofluorines. However, early enantioselective methods were often cumbersome, necessitating the need for mild conditions that improved chemo-, regio- and stereoselectivities.[2] The first catalytic enantioselective fluorination, using chiral metal Lewis acids, was reported by Togni and co-workers in 2000.[3] Over the past decade, the development of asymmetric methods to incorporate fluorine using metal complexes and, more recently, organocatalysts, has grown.[4] The most promising of these asymmetric methodologies are those that utilize phase-transfer catalysis (PTC). PTC is appealing because it avoids the use of transition metals and the need to rigorously exclude air and moisture.[5] More importantly, phase-transfer methodologies feature robust catalyst turnover and show excellent functional group tolerance, allowing for the synthesis of complex scaffolds.

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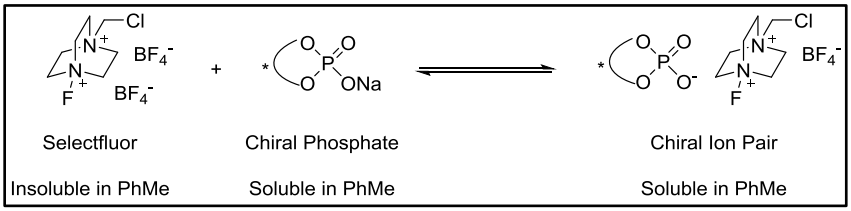
In phase-transfer catalysis, a lipophilic chiral ionic salt mediates the reaction between substrate and reagent, which are in two different phases, while imbuing its chiral information to the substrate. Due to the poor solubility of common electrophilic fluorinating reagents in non-polar solvents, the background reaction between F^+ and nucleophile is negligible, providing highly enantioselective transformations.

This first report of enantioselective fluorination by PTC was by Kim and Park, who used cinchona alkaloid-derived quaternary ammonium salts.[6] They were able to obtain α-fluoro β-keto esters from the treatment of β-keto esters with *N*-fluorobenzenesulfonimide as the fluorine source in excellent yields with enantiomeric ratios up to 84.5:15.5. This work was improved upon in 2010 by Maruoka and co-workers using quaternary ammonium bromides derived from BINOL.[7] They achieved near-quantitative yields with enantiomeric ratios up to 99.5:0.5.

Scheme 1. Formation of a chiral fluorinating reagent via anionic PTC



The latest advance in asymmetric fluorination using PTC has been out of the Toste lab. The chiral ion pair used by Toste and co-workers was a chiral phosphate anion and cationic Selectfluor (Scheme 1). The slow introduction of the fluorination agent into solution gave high enantiomeric ratios (up to 98.5:1.5) with high yields. This analogous anionic methodology does not require a specific olefin geometry, in contrast to cationic PTC. As such, a wider substrate scope can be achieved. Toste and coworkers have reported fluorination of alkenes,[5] enamides,[8] phenols,[9] oxyfluorination of enamides,[10] and fluoroamination of 1,4-dienes.[11] Recently, Alexakis and co-workers reported a fluorination-induced Wagner-Meerwein rearrangement of allylic alcohols using a chiral phosphate PTC.[12]

The authors employ the model of BINOL-derived phosphoric acid-catalyzed reactions proposed by Simón and Goodman to rationalize the observed enantioselectivities (Figure 1). The phosphate anion is able to form an ion pair with Selectfluor on one oxygen while activating the substrate (in the example depicted, an enamide) through hydrogen bonding on another oxygen atom. The substrate resides such that its bulk occupies an open quadrant.

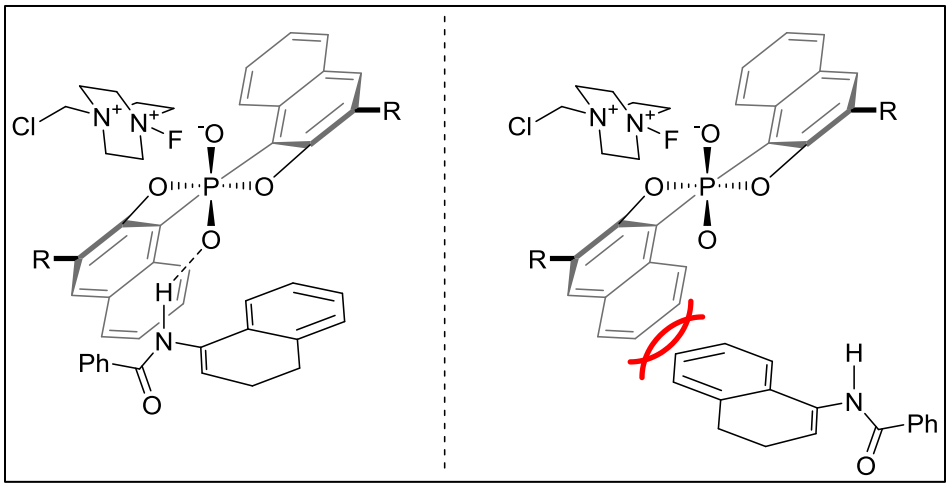


Figure 1. Mechanistic proposal for observed stereochemistry. R= Bulky aromatic.

SUMMARY

Asymmetric PTC is an effective method to obtain stereogenic centers containing fluorine, a desired transformation for use in therapeutics, agrochemicals, and materials. Despite transformations of high yield and enantiopurity, anionic phase-transfer catalysts have proven more versatile than their cationic counterparts.

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