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A New Approach towards the Asymmetric Fluorination of Alkenes Using Anionic Phase-Transfer Catalysts[**]

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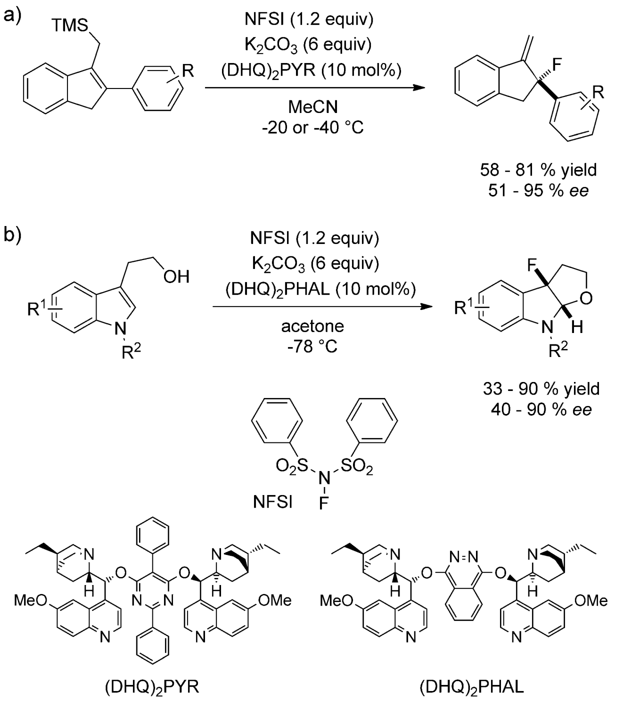
asymmetric catalysis · electrophilic addition · fluorine · halogenation · phase-transfer catalysis

The addition of halogen electrophiles to the carbon–carbon double bond is one of the most common methods for the functionalization of alkenes. Chlorine, bromine, and iodine electrophiles react even with simple, nonactivated alkenes forming cyclic halonium intermediates which are subsequently opened by a suitable nucleophile. Electrophilic fluorination reagents are less reactive towards simple alkenes presumably because cyclic fluoronium ions are not formed. For this reason electrophilic fluorinations are usually conducted on more activated carbon–carbon double bonds like enol ethers or allyl silanes.

A significant challenge is the control of the absolute stereochemistry at the newly formed stereocenters. Reagent-controlled asymmetric halogenation of alkenes has been difficult to achieve and only recently has a range of suitable catalytic methods been developed for the heavier halogens.[1] Again, fluorine proved to be special and asymmetric fluorination of alkenes has been largely limited to stoichiometric approaches using fluorinating agents complexed to cinchona alkaloid derivatives.[2,3]

Recently, the Shibata and Gouverneur groups could show that catalytic versions of these reactions are possible (Scheme 1).[4] Shibata and co-workers discovered that allyl silanes can be catalytically fluorinated with high enantioselectivities using *N*-fluorobenzenesulfonimide (NFSI) and the dimeric cinchona alkaloid catalyst $(DHQ)_2PYR$ (Scheme 1 a). Key to the high enantioselectivities is the tempered reactivity of the fluorinating agent NFSI, which is not reactive enough to add to the allyl silanes without a catalyst, but does so in the presence of $(DHQ)_2PYR$. A similar observation was made by the Gouverneur group, who developed the first enantioselective fluorocyclization reaction on indole derivatives (Scheme 1 b).[4b] Again, the tempered reactivity of NFSI allowed the catalytic use of a dimeric cinchona alkaloid promoter, in this case $(DHQ)_2PHAL$. Up to now the use of these nucleophilic catalysts has been limited to the examples presented and some general problems remain. The best nucleophilic catalysts based on dimeric cinchona alkaloids are not particularly active catalysts for asymmetric halogenation reactions and must be used in relatively large quantities to outcompete the unselective background reaction. The reactivity of the catalyst-activated fluorinating agent towards the alkene substrate is also limited and so far only highly electron-rich double bonds have been fluorinated with this reagent combination.



Scheme 1. Asymmetric fluorination of alkene derivatives using nucleophilic catalysis. a) Fluorination of allyl silanes, b) fluorocyclization reactions of indole derivatives.

Recently, Toste and co-workers described a very different approach for the catalytic enantioselective fluorination of alkenes. They decided to apply lipophilic chiral anion salts as phase-transfer catalysts for insoluble fluorinating agents.[5] Asymmetric phase-transfer catalysis using cationic catalysts is a well-established strategy in enantioselective catalysis and has been applied to a range of different reactions.[6] However, the opposite, charge-inverted strategy has been used only in a few isolated examples.[7] Toste et al. selected a cationic

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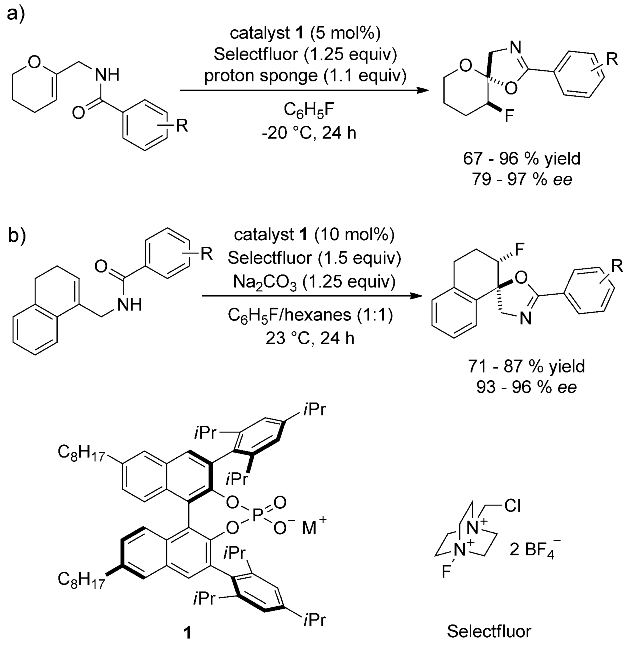
fluorination reagent, the commonly used Selectfluor, in combination with the lipophilic chiral BINOL phosphate **1** as the phase-transfer catalyst and applied this system to asymmetric fluorocyclization reactions (Scheme 2). The dicationic Selectfluor, which itself is not soluble in the reaction solvent fluorobenzene, is solubilized after anion metathesis with the lipophilic BINOL phosphate anion. The BINOL phosphate Selectfluor salt is now responsible for the fluorination of the enol ether substrate followed by the diastereoselective intramolecular cyclization leading to the product (Scheme 2a).



Scheme 2. Asymmetric fluorocyclization reactions under phase-transfer conditions.

The efficient stereoinduction observed—enantioselectivities of up to 97% *ee*—is remarkable for the electrophilic fluorination of alkenes. Although currently the information about the actual fluorinating species is limited, it can be assumed that a tight ion pair between Selectfluor and the chiral BINOL phosphate anion **1** is responsible for the high stereoinduction. A small nonlinear effect indicates that both counterions of Selectfluor are exchanged for BINOL phosphate anions. BINOL phosphates similar to **1** are known as very powerful chiral counteranions and have been used in chiral-counteranion-directed catalysis.[8] The application of these anions in asymmetric halocyclization reactions using electrophilic brominating or iodinating agents was demonstrated last year in haloetherification reactions where moderate to good enantioselectivities could be obtained.[9] But these haloetherification reactions differ from the present catalytic system in one key feature: when an insoluble fluorinating agent is used under phase-transfer conditions, the unselective background reaction can be completely suppressed and very high enantioselectivities can be obtained even with rather low catalyst loadings.

The complete suppression of the background reaction due to the insolubility of the fluorinating agent has several more advantages in these types of reactions. It allows the application of more-reactive fluorine sources and higher reaction temperatures (up to 60 °C), making the fluorination of less-activated alkenes possible (Scheme 2b). Dihydronaphthalene derivatives underwent efficient fluorocyclization reactions with high enantioselectivities under optimized phase-transfer catalysis conditions. Asymmetric fluorination of such less-activated alkenes had not been achieved before. Another advantage was observed in related cyclizations of benzothiophene derivatives. When these starting materials were treated with Selectfluor under homogenous conditions, only small amounts of the desired product were observed due to competing side reactions. The application of phase-transfer conditions, however, led to the efficient formation of the desired product with high enantioselectivities. This shows that the limited amount of reagent that is available under phase-transfer conditions can be beneficial not only for the stereo- but also for the chemoselectivity of this reaction class.

The chiral-anion-mediated phase-transfer strategy reported by Toste and co-workers is certainly of general interest in asymmetric catalysis. In the area of asymmetric electrophilic addition reactions to carbon–carbon double bonds many of the currently applied nucleophilic catalysts do not lead to high rate accelerations and have to be used in significant quantities to outcompete the background reaction that leads to racemic product. As many electrophilic reagents are available in cationic form, these reactions should profit greatly from asymmetric anionic phase-transfer catalysis. This is especially true for the chiral BINOL phosphates used in the present study as they have already proven their value as excellent catalyst in many asymmetric reactions under homogenous conditions.[8,10]

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