Asymmetric Fluorination

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Catalytic Asymmetric Fluorination Comes of Age

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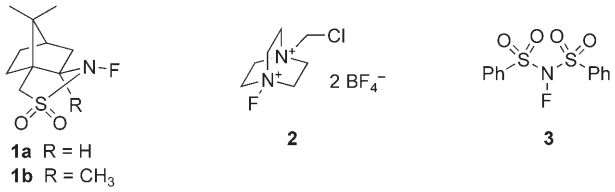
The C–F bond is a fundamental unit of organic chemistry, and its introduction into organic compounds has been widely deployed to optimize the properties of performance materials.[1] Important contemporary applications are in organic materials such as liquid crystals for display technologies,[2] the refinement of catalysts for asymmetric transformations,[3] as well as the important role of strategic fluorination for lead optimization in the pharmaceuticals sector.[4] Although fluorine is very often found on aromatic rings in, for example, pharmaceutical and agrochemical products, the enantioselective introduction of the C–F bond at a stereogenic center has emerged as a clear goal in organic chemistry ever since the first asymmetric fluorination reagents, *N*-fluorocamphorsultams **1a,b**, were reported by Differding and Lang[5] in 1988 (Scheme 1).

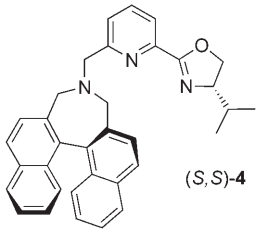


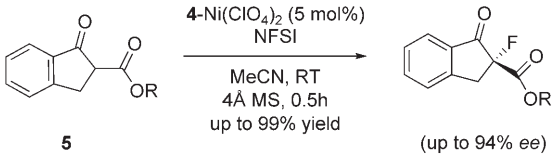
Scheme 1. Electrophilic fluorinating reagents.

There are obvious advantages in medicinal chemistry in replacing hydrogen with fluorine at metabolically vunerable carbon atoms and at enolizable centers in drugs, to lengthen in vivo half-lives. The quest for methods to mediate the introduction of the C–F bond with high enantioselectivity and with catalytic efficiency has been intense, and successes have been emerging rapidly as illustrated by related Highlights in 2006[6,7] and in other recent reviews.[8–10] The major focus in asymmetric C–F bond formation has involved catalytic enolate/α-carbonyl fluorination of amides, β-cyano-, β-nitro-, and β-keto esters, as well as malonates. In 2005 there were a flurry of papers reporting the successful asymmetric fluorination of aldehydes using pyrrolidine or imidazolidinone organocatalysts in combination with electrophilic fluorinating reagents.[11] This progress has recently been reviewed in a Highlight.[6] Developments in asymmetric fluorination were slow for a decade after the discovery of the *N*-fluorosultams **1a,b**,[5] but subsequent progress has been rapid and impressive, particularly in using selectfluor (**2**) and *N*-fluorodibenzenesulfonimide (NFSI, **3**) as electrophilic fluorine-transfer reagents for catalytic processes. The first efficient enantioselective fluorinations used reagents derived from cinchona alkaloid, which were independently discovered in 2000 in the laboratories of Cahard[12] and Shibata.[13] These protocols demonstrated high enantioselectivities (up to 91% *ee*) but with stochiometric reagents. Catalytic fluorinations using selectfluor/NFSI as transfer reagents were demonstrated; however, they were not efficient.

Asymmetric Lewis acid based catalysts also emerged in 2000.[13] Hintermann and Togni were the first to demonstrate such fluorination reactions,[14] using taddol–titanium complexes in combination with selectfluor to mediate the α-fluorination of β-keto esters. Such an approach has evolved to the present, in that chiral ligand–metal complexes have been discovered which can now mediate catalytic and highly enantioselective fluorination protocols. This Highlight summarizes such progress during the early half of 2007.

Most recently Iwasa and co-workers[15] have explored enantiopure N,N,N-tridentate ligands such as (*S*,*S*)-**4** at 5 mol% with a variety of Lewis acids for the asymmetric





Scheme 2. N,N,N-tridentate $Ni(ClO_4)_2$ mediated asymmetric fluorinations.[15]

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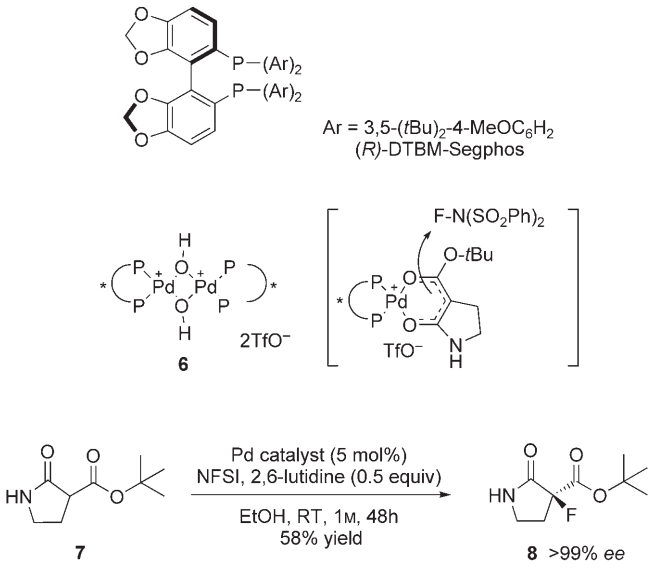
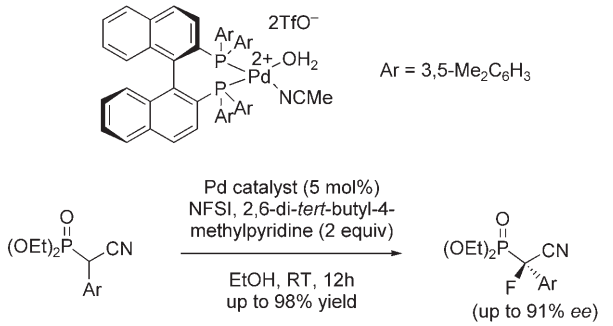


Scheme 3. Pd^{II}-mediated fluorinations of lactams.[16]



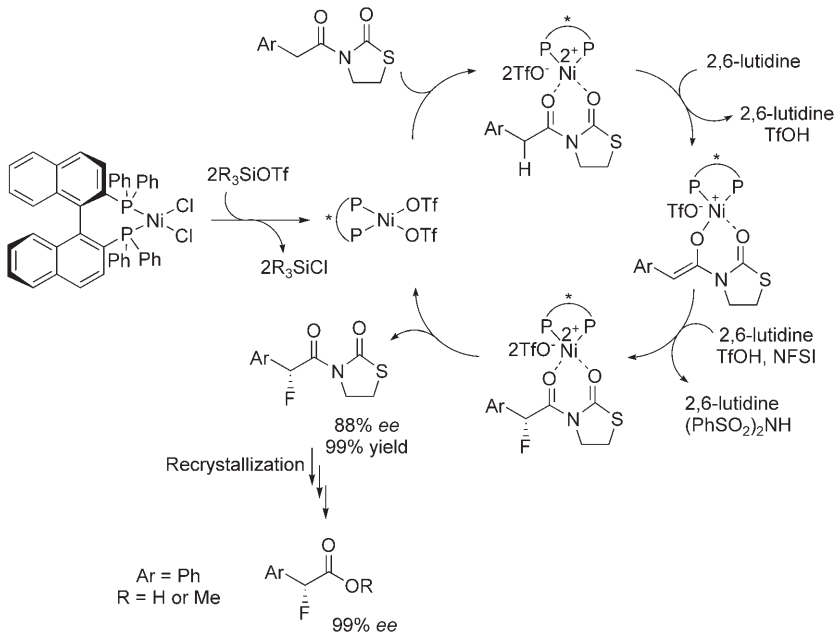
Scheme 4. Pd^{II}-mediated fluorinations of phosphonates.[18]

fluorination of β-keto esters such as **5** with NFSI as the electrophilic fluorine source (Scheme 2). The most impressive yields and enantioselectivities were found when $Ni(ClO_4)_2$ or $Mg(ClO_4)_2$ was used as the Lewis acid.

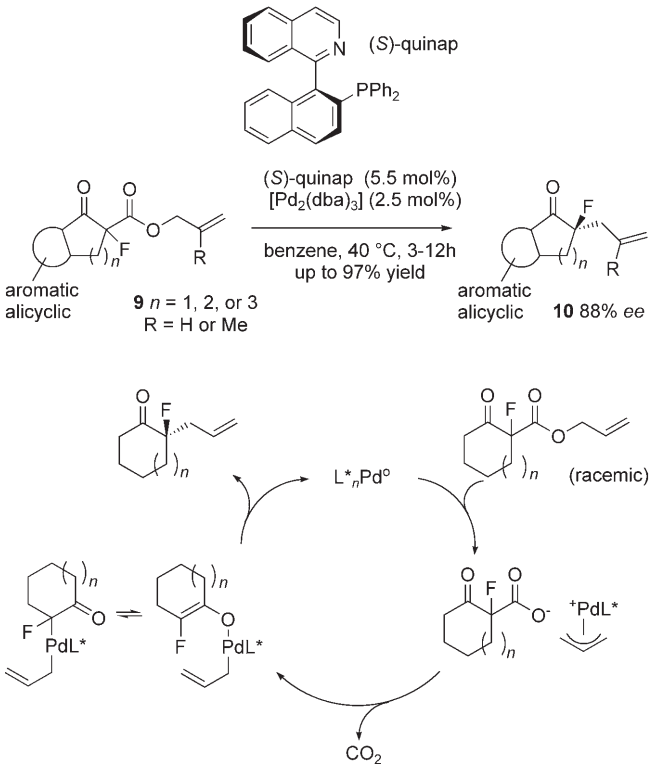
Sodeoka and co-workers[16] have also reported impressive asymmetric α-fluorination reactions of *tert*-butoxycarbonyl lactones and lactams with chiral bis-phosphine–Pd^{II} complexes as **6** (5 mol%; Scheme 3). A combination of the Pd^{II} complexes and 2,6-lutidine was highly effective in mediating fluorination of the less enolizable lactams. For example, **7** was converted into **8** (58% yield, >99% *ee*). This general methodology has been extended by the groups of Sodeoka[17] and Kim,[18] who have independently demonstrated the asymmetric fluorination of α-cyanophosphonates (Scheme 4). In this case an organic base (for example, two equivalents 2,6-lutidine or 2,6-di-*tert*-butyl-4-methylpyridine) was essential for the efficient fluorination of these substrates, and the method gave product α-fluorophosphonates with high enantioselectivities.

Sodeoka et al.[19] have also developed an efficient methodology based on the combination of Ni^{II}, (*R*)-binap, trimethylsilyl triflate, and 2,6-lutidine for the preparation of enantioenriched α-fluorothiazolidinones and demonstrated their conversion into α-fluoroarylacetic acid derivatives (Scheme 5).

In an indirect approach to the preparation of enantiomerically enriched α-fluoroketones, Tunge and co-workers[20] have recently extended the work of Nakamura and co-workers[21] and investigated Pd^{II}-mediated decarboxylative allylation reactions on already fluorinated (racemic) β-keto allyl esters such as **9** with ligands such as quinap. A catalytic cycle is shown in Scheme 6, and this process generated, for example, ketone **10** in 88% *ee* with a fluorinated quarternary stereogenic center.

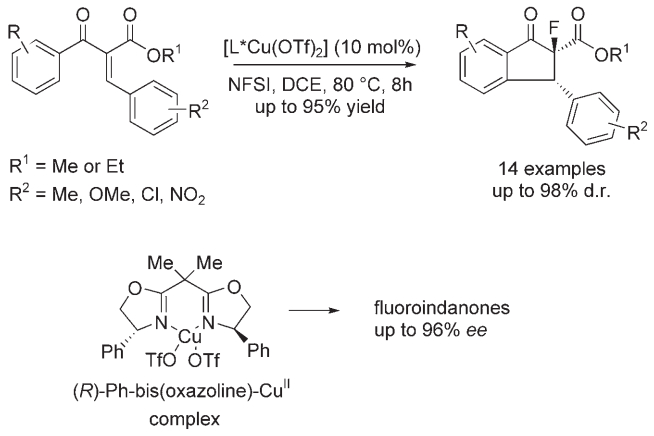


Scheme 5. Asymmetric fluorination of α-fluorothiazolidinones.[19]



Scheme 6. Decarboxylative allylation to α-fluoroketones.[20]

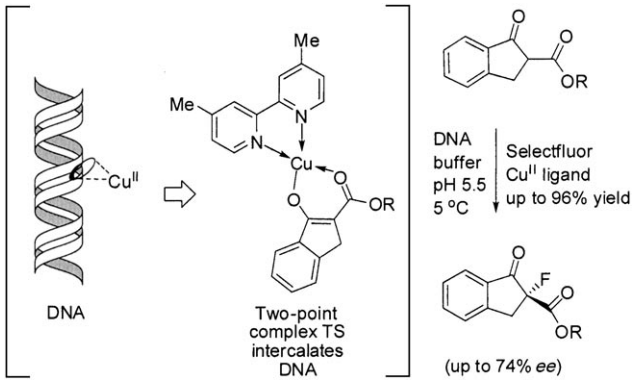
Cu^{II} complexes are proving to be effective catalysts in the arena of enolate fluorination. A series of $Cu(OTf)_2$-mediated (10 mol%) tandem Nazarov cyclizations, followed by electrophilic fluorination (with NFSI), has been demonstrated to generate α-fluoroindanones with very high diastereoselectivity (Scheme 7).[22] A preliminary investigation, progressing



Scheme 7. Nazarov cyclization/fluorination.[22]

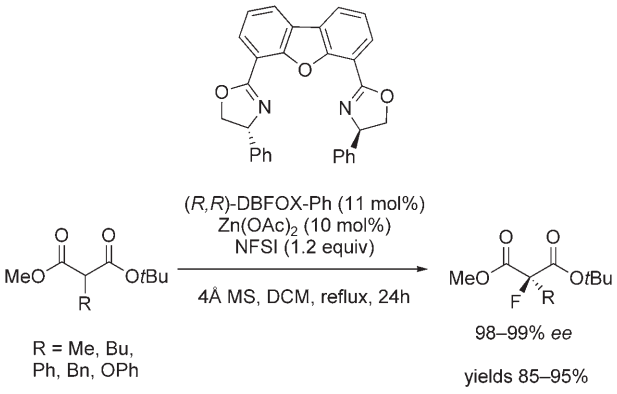
towards a catalytic asymmetric process, explored (*R*)-Ph-bis(oxazoline) as chiral ligand (10 mol%). Fluorinated products were isolated in up to 96% *ee* (Scheme 7).

In an intriguing approach Shibata and co-workers[23] have used a catalytic ensemble involving a Cu–bipyridyl complex, intercalated with DNA, for Cu^{II}-catalyzed asymmetric fluorinations. These remarkable reactions, which were inspired by a related methodology exploring asymmetric Diels–Alder reactions,[24] utilize selectfluor as the fluorine-transfer reagent to the catalyst in an aqueous buffer. The DNA-intercalated Cu-bound catalyst mediates fluorination of indanone β-keto esters with modest to good enantioselectivity (up to 74% *ee*) induced by the inherent chirality of the DNA molecule (Scheme 8).



Scheme 8. Asymmetric fluorination with DNA.[23]

In a recent issue of *Angewandte Chemie*, Shibata, Toru, and co-workers[25] have also demonstrated the power and utility of their asymmetric fluorination methodology. They have explored a variety of Lewis acids complexed to the (*R*,*R*)-DBFOX-Ph ligand to explore catalytic (10 mol%) asymmetric fluorinations of nonsymmetrical malonate esters, which are among the most challenging substrates to date for enantioselective fluorination and which extend from their recent investigations on the fluorination of β-keto ester substrates.[26] After optimization, $Zn(OAc)_2$ and $Ni(ClO_4)_2$ emerged as the best catalysts, and products were recovered in very high yields and with almost complete enantioselectivity (99% *ee*; Scheme 9).



Scheme 9. Malonate catalytic asymmetric fluorination.[25]

Several substrates have been progressed to relevant peptide and pharmaceutical analogues in each case with fluorine at a quarternary stereogenic center.[25] The power of

this methodology and its ability to deliver highly enantiopure starting materials in sufficient quantities for medicinal chemical synthesis programs are a clear indication of the progress that has been made in catalytic asymmetric fluorination since the pioneering studies of Differding and Lang[5] 20 years ago.

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