# Improving Enantioselective Fluorination Reactions: Chiral *N*-Fluoroammonium Salts and Transition Metal Catalysts**

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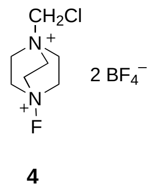
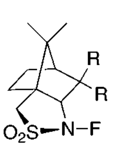
Within the still-growing field of enantiomerically pure compounds, research into chiral fluorinated molecules is gathering momentum due to the unique properties of the carbon–fluorine bond, and the importance of the fluorine moiety in molecules of pharmaceutical and biological interest is undisputed.[1] Among all the asymmetric processes towards organofluoro compounds, the direct synthesis of fluorinated stereogenic centers remains especially challenging. Basically, two different routes are conceivable for their asymmetric construction: 1) nucleophilic substitution reactions with a fluoride anion and 2) electrophilic addition of fluoronium cations to activated or masked carbanions. First attempts on enantioselective nucleophilic fluorination date back to the pioneering work of Hann and Sampson.[2] In an ambitious dehydroxylation/fluorination sequence the authors treated a racemic $\alpha$-trimethylsiloxy ester with half an equivalent of an enantiomerically pure proline-derived aminotrifluorosulfurane in hope of achieving a kinetic resolution. Unfortunately, the fluorinated product was obtained without significant enantiomeric excess.

Ever since then, routes towards fluorinated stereogenic centers have relied on electrophilic fluorine sources for substitution reactions.[3] This caused the development of a variety of suitable achiral N-F-fluorinating reagents[4] and their exploitation in diastereoselective fluorinations that are characterized by efficient substrate control and reasonably high diastereoselectivities.[5a] Important contributions were made by Davies and co-workers,[5b–d] Enders et al.,[5e] Taylor et al.,[3] and Liotta and co-workers.[5f] At about the same time, chiral nonracemic N-fluoro compounds were developed for direct enantioselective fluorination of C–H acidic substrates.

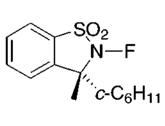


**4**

Initial work on reagent control by Differding and Lang, who introduced chiral *N*-fluorosultam **1a**,[6] was followed by the introduction of modified structures **1b**,**c**[7] and the development of related compounds such as **2**[8] and **3**.[9] All these



**1 a**: R = H
**b**: R = Cl
**c**: R = $OCH_3$



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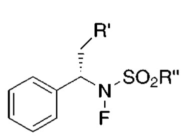
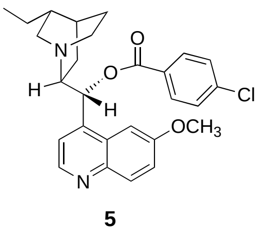


**3** (R' = H, OAc; R'' = $CH_3$, *p*-Tol)

chiral reagents require a sulfonamido group for activation of the N–F bond. Metalated enolates generated in situ serve as substrates and the enantiomeric excesses generally reach satisfying values of up to 80%. However, the disadvantage of these reagents is their tiresome multistep synthesis with use of hazardous fluorine sources, such as $FClO_3$ or $F_2$ itself.

Recently, two reports have described the preparation and application of enantiopure *N*-fluoroammonium salts from cinchona alkaloids. In an elegant contribution, Takeuchi and co-workers used an in situ protocol to generate the active fluorinating species from each of the neutral compounds **5** and **6**, with Selectfluor **4**.[10] (Selectfluor is 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).[11] It is also know as F-TEDA.) Independently, Cahard et al. described the synthesis of preformed cinchona alkaloid ammonium salts such as **7**.[12, 13]



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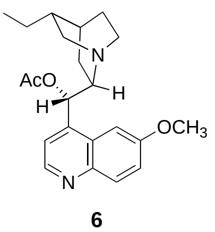

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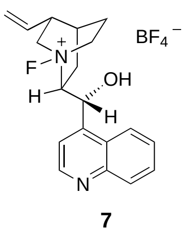

**7**

With the conventional in situ generation of metallated enolates, **7** could be employed for enantioselective fluorination of $\alpha$-methyl tetralone (**8**, Scheme 1 a). Two equivalents of base were necessary to deprotonate the acidic hydroxyl functionality of **7** in order to prevent competitive enolate

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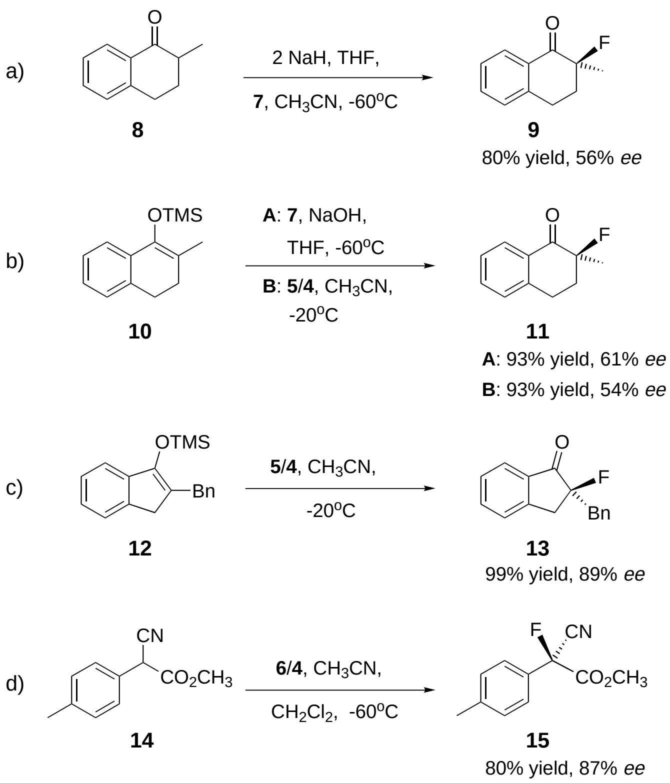
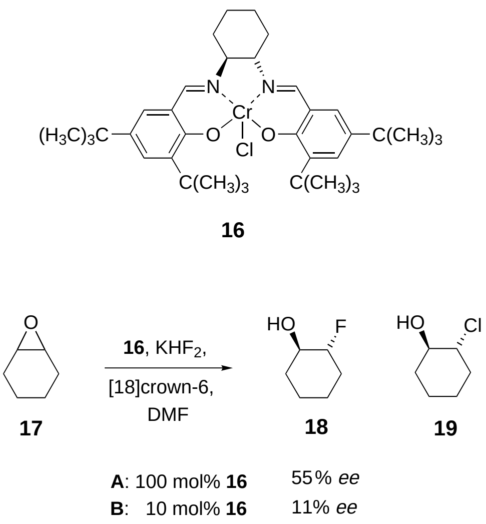


Scheme 1. Representative examples of enantioselective fluorinations with chiral quaternary *N*-fluoroammonium salts. TMS = trimethylsilyl, Bn = benzyl.

protonation. Unlike the cases for the unreactive neutral compounds **1**–**3**, preformed silyl enol ether **10** was now cleanly fluorinated by both the synthesized reagent **7** and the combination of **4** and **5** (Scheme 1b). This shows that the cationic nature of the new reagents results in higher fluorination power. However, since in the present systems both rate and enantioselectivity appear to be highly dependent on the reaction temperature, a precise comparison of the results is difficult. Under otherwise unchanged conditions, Takeuchi and co-workers observed an increase in *ee* value for five-membered substrates such as **12** relative to the *ee* value observed for **11** (Scheme 1c). Further successful examples include $\beta$-keto esters (up to 80% *ee*) and acyclic $\beta$-cyano esters such as **14** (Scheme 1d). For the latter case, preformation of the ammonium reagent from **6** and **4** was required to achieve high enantioselectivity.

Obviously, the switch from neutral N–F compounds to N–F ammonium salts did not only have a strong beneficial effect on reactivity; the commercial availability of both Selectfluor and cinchona alkaloids also ensures easy accessability of the chiral reagents. Still, from an economical point of view a catalytic version of the process would certainly be desirable. Preliminary $^{19}$F NMR studies reveal that the $F^+$ transfer from Selectfluor onto the cinchona alkaloid is seemingly fast and irreversible,[10, 13] which brings a catalytic version within reach.[14]

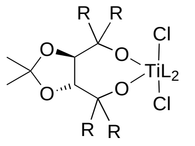
Within the context of asymmetric synthesis, it is intriguing that no use of chiral nonracemic metal complexes for fluorination reactions was reported for a long time. Given the extreme success of asymmetric metal-mediated and -catalyzed processes,[15] such an approach must appear highly attractive. Bruns and Haufe have now described the first examples of a transition metal complex mediated asymmetric ring-opening (ARO) of both *meso*- and racemic epoxides by formal hydrofluorination.[16] Initial attempts with chiral Eu$^{III}$ complexes led to very low asymmetric induction. Opening of cyclohexene oxide **17** with potassium hydrogen difluoride in the presence of [18]crown-6 and a stoichiometric amount of Jacobsen's chiral chromium salen complex **16**[17a] finally yielded two products **18** and **19** in an 89:11 ratio and 92% combined yield, with the desired product **18** being formed with 55% *ee*. Limiting **16** to a catalytic amount of 10 mol% led to an increase in the ratio of **18**; however, the enantiomeric excess dropped to 11% (Scheme 2).



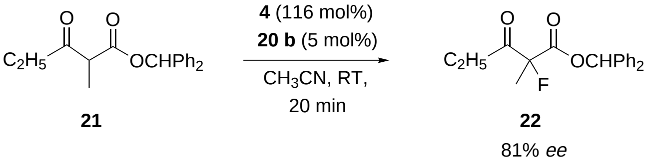
Scheme 2. First nucleophilic enantioselective epoxide opening with enantiopure transition metal Lewis acid **16**.

In the stoichiometric reaction the low extent in which chloride-promoted ring opening occurs is noteworthy. In a stoichiometric ARO of **17** with **16** and TMSN$_3$, Jacobsen reported complete incorporation of the chloride atoms,[17a] which indicates that under the reaction conditions no anion exchange takes place at the metal complex prior to ring opening. Since in the present case $Cl^-$ displays a much higher nucleophilicity than $F^-$, an identical product distribution should have been expected. The fact, however, that this is not the case, leads to the conclusion that the chromium complex acts as a conventional Lewis acid that activates the epoxide for ARO by $F^-$. The amount of chloride incorporation is likely to be the consequence of competing ring opening by free chloride ions generated under the reaction conditions. One can almost assume that the present catalytic system cannot be operating by the cooperative mechanism[17a,b] that has been so successful in the related AROs described by Jacobsen.[17c] Furthermore, the dramatic drop in enantioselectivity in the catalytic reaction suggests that the fluoride source does not allow for rapid release of the catalyst after the ARO has occurred, which thus results in uncatalyzed, unselective ring opening. Final conclusions will have to await further detailed mechanistic investigation.[18]

A first real breakthrough in transition metal catalyzed fluorination has recently been achieved by Hintermann and Togni.[19] In their work, monosubstituted $\beta$-keto esters such as **21** were chosen as starting materials and focus was placed on Lewis acid activation. It was anticipated that the necessary enolization of the $\beta$-keto esters would be accelerated by catalytic amounts of metal complexes. From kinetic screening, complexes based on titanium emerged as the most suitable catalysts, and TADDOL-modified[20] titanium complexes **20a** and **20b** were the most successful ones in terms of asymmetric induction. Isolation of these complexes, which during the course of this work[19] was achieved for the first time, was necessary to guarantee reproducibility and enantioselectivity. In the presence of 5 mol% of catalyst and a slight excess of the fluorinating agent **4**, conversion into fluorinated products such as **22** occurred smoothly in acetonitrile at room temperature (Scheme 3). Not surprisingly, the sterically more elaborated complex **20b** gave rise to higher enantioselectivities than **20a** (62–90% *ee* versus 28–59% *ee* for the given examples) but it is interesting to see that it also represents the more reactive catalyst: for example, in the presence of **20b** the reaction time for conversion of **21** is 20 minutes, while with **20a** it is 2 hours!



**20** **a**: R = Ph, $L_2 = (CH_2OCH_3)_2$
**b**: R = 1-Nph, $L_2$ = 2 $NCCH_3$



Scheme 3. First enantioselective electrophilic fluorination reaction catalyzed by enantiopure Ti-TADDOLates **20a,b**. The absolute configuration of the product is unknown.

Current understanding of the reaction suggests that an unprecedented mechanism is operating. Unlike classical Lewis acid catalyzed reactions,[21] the metal complex does not activate the carbonyl moiety but is thought to enhance the degree of enolization and thus create the necessary nucleophilic enol structure for reaction with the fluorinating agent.[22]

Regarding enantioselectivities this new catalytic fluorination can readily compete with the results from stoichiometric reactions with chiral N–F compounds, and the fact that both the TADDOL ligands and the fluorine source *Selectfluor* are commercially available makes it the most convenient method presently at hand. Since the reaction is so far limited to $\beta$-keto esters, it will be interesting to see whether this catalyst system can be transferred successfully to other substrate classes. Clearly the enantioselective synthesis of fluorinated stereogenic centers other than quaternary ones remains a huge challenge. Future work could also aim to combine the two novel fluorination procedures. Especially where reaction rate is concerned, combined use of (achiral) transition metal catalyst and substoichiometric amounts of cinchona alkaloids might give rise to successful complementary catalytic systems.

To summarize, the development of novel enantioselective fluorination methods with the aid of either chiral *N*-fluoroammonium salts or transition metal catalysts has established truly practical routes towards chiral fluorinated compounds. Despite the current mechanistic uncertainties it appears that a door has been opened for exciting and promising further development of asymmetric (catalytic) fluorination reactions in the near future.[23]

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# Versatile Scorpionates—New Developments in the Coordination Chemistry of Pyrazolylborate Ligands

**Frank T. Edelmann***

More than 30 years after their discovery poly(pyrazolyl)borate ligands (scorpionates) still belong to the work horses in coordination chemistry.[1] These anions, normally associated with the name Trofimenko, are among the most often used complex ligands.[2, 3] This is true for various main group elements as well as numerous transition metals, lanthanoids, and actinoids. These ligands are so popular due to their reliability and accountability as spectator ligands, which normally do not interfere with the reaction scenarios occurring at the metal centers. Tris(pyrazolyl)borates ($Tp \equiv HB(pz)_3$) generally coordinate as tridentate ligands through three nitrogen atoms of the pyrazole rings ($\kappa^3N,N',N''$), thereby providing effective steric shielding of the metal center.[3, 4] By introducing suitable substituents (e.g. Me, $CF_3$, *t*Bu, Ph) particularly in the 3-position of the pyrazolyl rings this effect can be tuned to a large extent. Cone angles much larger than 180° can be achieved with the use of such sterically demanding scorpionate ligands, which, for example, have been utilized to realize unusual bonding (e.g. monomeric zinc hydroxides).[3] Besides the very common $\kappa^3N,N',N''$ coordination mode the tridentate $\kappa^3N,N,B\text{-}H$ type[5] and the bidentate $\kappa^2N,N'$ coordination[6] are also known. Higher hapticities could thus far only be achieved in cases where the substituents in 3-position of the pyrazole rings contained additional donor atoms. For example, the three pyridyl substituents of the ligand $Tp^{py}$ make it potentially hexadentate.[7] Due to their identical charge, facial coordination, and the fact that both may formally act as six-electron donors, the $Tp^-$ ions have often been compared to the cyclopentadienyl ligands.[3]

Several recent contributions have demonstrated that the coordination modes of tris(pyrazolyl)borate ligands can be far more versatile than hitherto anticipated. In addition to new findings concerning the electronic properties of the scorpionates, unknown coordination modes as well as novel reaction patterns have been discovered.

## 1. *Electronic Effects*

With respect to its steric bulk the hydrotris(3,5-dimethylpyrazolyl)borate anion $(Tp^{Me_2})^-$ is regarded as a steric equivalent of the pentamethylcyclopentadienyl (Cp*) ligand.[3d] However, conflicting reports can be found in the literature on the electron-donating properties of hydrotris(pyrazolyl)borate (Tp) and $Tp^{Me_2}$ in comparison to $C_5H_5$ (Cp) and $C_5Me_5$ (Cp*).[8] Most researchers claim that the ligands Tp and $Tp^{Me_2}$ are stronger electron donors than Cp and Cp*. In a recent study on C–H activation reactions by $[(Tp^{Me_2})Ir]$ complexes Bergman et al. were able to show the opposite effect, that is that the $Tp^{Me_2}$ derivatives are *less electron rich* than the corresponding [Cp*Ir] complexes.[9] The starting point for this investigation was the known fact that the iridium(III) complexes $[Cp^*(PMe_3)Ir(Me)][OTf]$ (**1**, OTf = $OSO_2CF_3$) and $[Cp^*(PMe_3)IrMe(ClCH_2Cl)][BAr_f]$ (**2**, $BAr_f = B[3,5\text{-}(CF_3)_2C_6H_3]_4$) are capable of cleaving C–H bonds in a wide variety of hydrocarbons under extremely mild conditions.[10] As part of the search for robust ligands for the stabilization of the reactive cationic $Ir^{III}$ species the triflate **3** was synthesized as the first target molecule (Scheme 1).

The first evidence for a reverse electronic effect of the $Tp^{Me_2}$ ligand came from the finding that the Ir–O bond (212.8(5) pm) in **3** is shorter than that in the Cp* derivative **1** (221.6(10) pm).[10] In good agreement it was found that the reaction of $[Cp^*(PMe_3)Ir(H)_2]$ (**4**) with $[(Tp^{Me_2})(PMe_3)Ir(H)_2H][OTf]$ (**5**) results in quantitative formation of $[Cp^*(PMe_3)Ir(H)_3][OTf]$ (**6**) and $[(Tp^{Me_2})(PMe_3)Ir(H)_2]$ (**7**). Thus the equilibrium lies heavily in favor of the protonated (i.e. more strongly basic) Cp* complex. This result was further confirmed by a comparison of the IR stretching absorbances of $[(Tp^{Me_2})Ir(CO)_2]$ (**8**, 2039, 1960 cm$^{-1}$)[6a] and $[Cp^*Ir(CO)_2]$ (**9**, 2020, 1953 cm$^{-1}$) which were reported by Graham et al.[11] Here too it becomes clear that the metal center in the $Tp^{Me_2}$ compound is *less electron rich*.

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