Transition Metal Fluoride Complexes in Asymmetric Catalysis

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Abstract: The phenomenal progress of catalytic asymmetric synthesis has been realized, in part, through the search for and subsequent identification of catalysts with unusual reactivity profiles. Several reaction processes recently reported feature a fluoride counterion as a critical structural component of the catalyst or procatalyst. In this *Concept* we describe the unique structural and bonding characteristics that fluoride engenders in metal complexes, which have been exploited in enantioselective catalytic reactions of little precedence.

Keywords: asymmetric catalysis · bridging ligands · fluorine · transition metals

Introduction

Catalytic asymmetric synthesis is an intense area of investigation advancing at breathtaking pace at the interface of inorganic and organic chemistry. The phenomenal progress has been realized in part through the search for and subsequent identification of unusual reactivity associated with novel transition metal complexes. Ligand design and syntheses play an indispensable role in the discovery process. Moreover, incremental modifications of the steric and electronic characteristics of ligands and the associated metal complexes can lead to optimization of desired reaction profile (product selectivity and yield, reaction rate) and mechanistic insight. A survey of the coordinating functionalities that have been utilized as ligands in successful catalytic processes for asymmetric synthesis reveals that the common donors employed are primarily chalcogenide as well as pnictogen or cyclopentadienyl derived ligands. It is interesting to note that the nature of the counterions that may constitute an integral component of the active complex is typically considered as secondary in catalyst design. When counterion effects are investigated, most efforts in asymmetric catalysis have been to minimize their interaction with the metal center. This is particularly the case when Lewis acidic catalysts are sought and the use of triflate, hexafluorostibnate, or hexafluorophosphate is preferred.[1]

Recently, several reaction processes have been reported wherein a catalyst precursor (procatalyst) or a putative catalyst possesses a fluoride counterion as a critical structural feature. The unique structural and bonding characteristics of this halogen engender distinctive electronic and structural properties to the associated transition metal complex that have only lately been appreciated in asymmetric catalysis. Although a number of excellent reviews exist on structural and solution properties of transition metal fluoride coordination complexes,[2, 3] few have outlined the unique properties of these complexes for enantioselective catalysts. In this *Concept* we detail some recent advances in the preparative and structural chemistry of transition metal fluoride complexes as well as their use as catalysts that mediate reactions with little precedence.[4, 5]

Background

Structural and bonding characteristics of fluorides: The Van der Waals radius of fluorine of 1.35 Å renders this element only slightly larger (12.5%) than hydrogen (1.20 Å), a property well appreciated in medicinal chemistry. Its size also imparts some interesting features to the structural inorganic chemistry of the corresponding complexes. Thus, it is not unusual for fluorides to function as bridging ligands between metal centers. With a covalent radius of 0.64 Å, the fluorine 2p valence electrons can participate in secondary π-bonding interactions. In this regard, fluorine lone-pair electrons that are symmetrically equivalent have been postulated to donate electron density to available metal-centered orbitals through p(π) back-bonding. One of the earliest expostulations on this effect is found in Pauling's classic treatise "*The Nature of the Chemical Bond*".[6] The contributions of canonicals **1–3** were discussed in considering the ground-state structure of boron halogenides. The presence of the empty p orbital on boron and the fluorine lone-pairs is postulated to result in
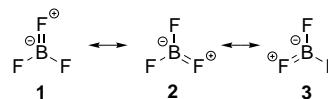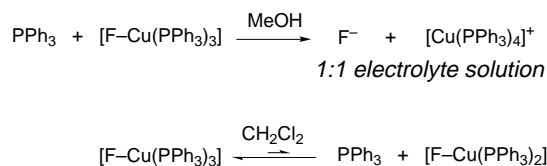
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resonance stabilization (cf. **1–3**). The stabilization gained is suggested to sufficiently compensate for the energetic costs incurred by the accompanying charge separation. Pauling hypothesized that the observed differences between the calculated B–F single-bond distance (1.37 Å) and the observed B–F bond distance in BF_3 (1.29 Å) was a consequence of 33% double-bond character for each of the three B–F bonds in BF_3. In support of this model, the B–F bond lengths in complexes in which the orbital on boron is not available for π-bonding interactions were discussed. For example, the observed B–F bond length in $H_3N \cdot BF_3$ (1.37 Å) is in agreement with the calculated value (1.37 Å). The structural phenomena of B–X π bonding and the resulting effect on reaction chemistry is suggested to be manifest in practice by the often cited trend of decreasing Lewis acidity along the series $BBr_3 > BCl_3 > BF_3$.[7] It has been suggested that the larger more diffuse p orbitals of the heavier halides (Br, Cl) progressively interact less effectively with the empty boron-centered p orbital, leading to an increase in Lewis acidity for BBr_3 and BCl_3. However, some caution is warranted in the application of this rule-of-thumb: the problems with categorizing the behavior and properties of an electron-deficient center as a Lewis Acid in the absence of the Lewis base partner has been highlighted by a number of investigators. In this regard, calculations have revealed that Me_3N forms a stronger complex with BCl_3 than BF_3 ($Me_3N \cdot BCl_3$ $\Delta G_f = 40.5$ kcal mol^{-1} versus $Me_3N \cdot BF_3$ $\Delta G_f = 32.9$ kcal mol^{-1}); by contrast BF_3 forms a stronger complex with MeCN than BCl_3 (MeCN $\cdot BCl_3$ $\Delta G_f = 6.4$ kcal mol^{-1} versus MeCN $\cdot BF_3$ $\Delta G_f = 9.1$ kcal mol^{-1}).[8]

There is a considerable amount of spectroscopic and experimental data in the coordination chemistry of transition metal fluorides that implicate fluoride as a π donor. Thus, in a series of halo metal-carbonyl complexes $[MX(CO)L_2]$ spectral data suggest that the fluoride complex exhibits the most electron-rich metal center. Additionally, the C≡O stretching frequencies for $[RhX(CO)(PPh_3)_3]$ are observed to increase along the series $F > Cl > Br > I$.[9] Although the data is the telltale signature of back-bonding effects by symmetrically equivalent fluorine nonbonding electrons, the magnitude of the effect, however, is a matter of debate. In contrast to the these spectroscopic observations, ab initio quantum mechanical calculations and ^{13}C NMR spectroscopic interpretations by Frenking and Grutzmacher suggest the opposite trend.[10] Thus, p(π) population at the central atom of a YX_3 molecule (Y = B, Al, Ga, In, Tl, and X = F, Cl, Br, I) increases along the series $F < Cl < Br < I$. The suggested ability of iodide to stabilize electron deficient centers is in contrast to the models discussed earlier. It is hypothesized that iodide, as the least electronegative halide, leads to the most stable canonical structures **1–3**, in which the halogens bear partial positive charge. The energetic consequences of halogen substitution on carbocation stability has also been studied experimentally and computationally. A ^{13}C NMR spectroscopic study of halo-substituted methyl carbocations has led Olah to postulate that the ability of halogens to stabilize positive charge on carbon decreases along the series $F > Cl > Br > I$.[11] A related theoretical study by Schleyer examined the stabilization of the halomethyl cation as a function of the halide. In contrast

to Olah's studies, it is found that the stability of CH_2X^+ increases along the series $F < Cl < Br < I$.[12]

The M–F bond strength spans a large range of energies, with strong bonds observed with hard-metal partners (Ti–F in $TiF_4 = 140$ kcal mol^{-1}) and weaker bonds with soft metals (Cu–F in $CuF_2 = 88$ kcal mol^{-1}). The ability of fluoride to participate in strong hydrogen-bonding has substantial effects on the kinetic lability of transition metal fluorides. In this regard, at 13.5 kcal mol^{-1}, the hydrogen bond between H_2O and F^- is one of the stronger H-bonding interactions known.[13] Thus, the presence of even minute quantities of a protic solvent can render transition metal fluorides quite kinetically labile, which leads to facile ionization.[14] By contrast, in rigorously aprotic solvents, for a number of metal complexes, the fluoro derivative may be the most stable in the halogen series; this has been observed for $[(Ph_3P)_2PdX(Ph)]$.[15] As an additional example, the stable complex $[CuF(PPh_3)_3]$ has been characterized crystallographically and displays a Cu(I)–F bond of 2.06 Å. An investigation of the solution properties revealed that in methanol the complex completely dissociates to give a 1:1 electrolyte solution; by contrast, in a polar aprotic solvent such as CH_2Cl_2 a more complicated dynamic process is observed that involves the reversible dissociation of the PPh_3 ligand.[16]

$$PPh_3 \; + \; [F\text{–}Cu(PPh_3)_3] \xrightarrow{\text{MeOH}} F^- \; + \; [Cu(PPh_3)_4]^+$$
1:1 electrolyte solution

$$[F\text{–}Cu(PPh_3)_3] \xrightarrow{\text{CH}_2\text{Cl}_2} PPh_3 \; + \; [F\text{–}Cu(PPh_3)_2]$$

Coordination Chemistry

Structural inorganic chemistry of metal fluoride coordination compounds continues to provide an exciting array of novel, intriguing structures. This is exemplified by the pioneering work of Roesky in the preparation and characterization of Group 4 metallocene fluorides. Examination of these structures reveals the rich coordination chemistry of fluoride that leads to a multitude of bonding arrangements. Remarkably, Roesky has demonstrated that titanocene fluorides may encapsulate Group 1 or 2 metal cations. This work highlights the potential role of fluoride as a bridging ligand for various metal fragments (Figure 1). Thus, for example, complexes in which titanium and aluminum centers are bridged by one or two fluorides ligands ($[Ti^1\text{–}F^1\text{–}Al(R)_2\text{–}F^2\text{–}M^2]$ and $[\{Cp_2Ti(\mu_2\text{-}F)_2AlEt_2\}_2]$) have been well characterized by X-ray crystallography.[17, 2a] Collectively these studies highlight the diversity of structures that may be prepared which may have great potential as catalysts for organic synthesis.

The relatively limited number of studies on transition metal fluorides as catalysts for organic synthesis probably stems from the difficulties that have been traditionally associated with the preparation of metal fluoride complexes or their perceived instability relative to analogues of the heavier halogens. The experimental difficulties associated with handling anhydrous gaseous HF or elemental fluorine complicates the de novo synthesis of coordination complexes of
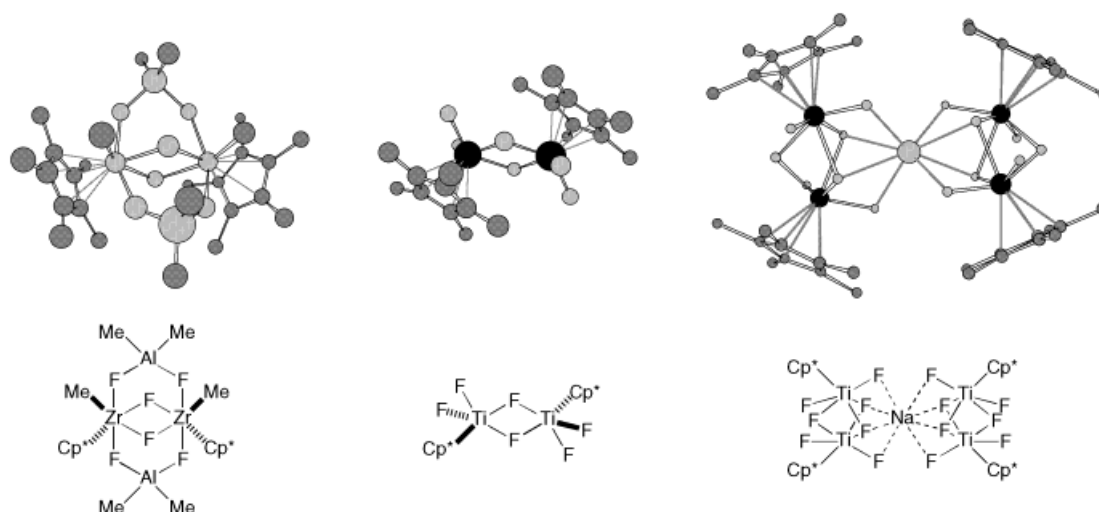
Figure 1. Representative X-ray structures of transition metal fluorides.

fluorides. Moreover, although simple metal fluoride salts are readily available and quite inexpensive, their insolubility in commonly utilized organic solvents precludes their ready use in the laboratory.[18] However, a number of recent reports provide practical preparative methods for the synthesis of transition metal fluorides.[19] Roesky has pioneered the use of Me_3SnF and AsF_3 for the synthesis of a wide variety of transition metal fluoride complexes that are otherwise not easily accessed. Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) has found use as an anhydrous fluoride source in the preparation of Ir^I and Rh^I fluoride complexes.[2d, 20] Other water-free fluoride sources such as Me_4NF [21] and Schwesinger's phosphinium fluoride salt $[(Me_2N)_3P_2N]F$ [22] have been utilized as well. Carreira has documented the use of $[Bu_4N][Ph_3SiF_2]$ (TBAT) and $[Bu_4N][Ph_3SnF_2]$ as sources of anhydrous fluoride for the in situ preparation of transition metal fluorides. Both salts are easily prepared as crystalline solids, are easily handled in the laboratory, and are readily soluble in common organic solvents.[23]

Catalytic Chemistry

A number of catalytic, asymmetric organic reaction processes have been reported in which the use of a metal fluoride complex has been shown to lead to substantial benefits over other metal halides. These reactions can be classified into two broad categories on the basis of the putative role of metal fluoride. In the first type, the metal fluoride complex serves only as a procatalyst, or catalyst precursor. In these cases, the active catalyst is unmasked by treatment of the metal fluoride complex with a suitably reactive fluorophile, typically a silane. The silylfluoride byproducts generated during the initiation step are generally unreactive. In the second category of reactions, at least one fluoride ligand remains bound

or intimately associated with the active transition metal catalyst.

Asymmetric ketimine reduction: One of the more successful processes developed for the enantioselective, catalytic reduction of ketimines has been reported by Buchwald. A chiral *ansa*-titanocene(III) catalyst[24] in combination with a stoichiometric silane efficiently delivers amines in high yields and superb enantioselectivity.[25] A common method for the generation of titanocene(III) complexes is the treatment of the titanocene dichloride with two equivalents of *n*BuLi.[26] Using such a catalyst formulation, Buchwald initially reported the enantioselective hydrogenation of ketimines. However, the *n*BuLi protocol gave lower enantioselectivity in the corresponding imine hydrosilylation reactions. In subsequent investigations, Buchwald documented the use of the crystalline and air stable bis(indenyl)titanium difluoride **4** as a practical, highly enantioselective procatalyst (Figure 2).[25] Upon treatment of **4** with excess silane, in situ reduction is suggested to occur to form the active Ti^{III} hydride catalyst **5**. As little as 0.02 mol % of this catalyst mediates the imine reduction to the corresponding chiral, secondary amines **6** in up to 99 % *ee* at ambient temperatures and pressures. Buchwald has postulated that a key benefit to the use of the fluorotitanium procatalyst **4** rests in the fact that unlike the procedure that utilizes *n*BuLi with concomitant generation of LiCl, the procedure commencing with compound **4** is salt free.

Enantioselective aldol addition reactions: The use of a fluoro transition metal complex as a putative catalyst has also been
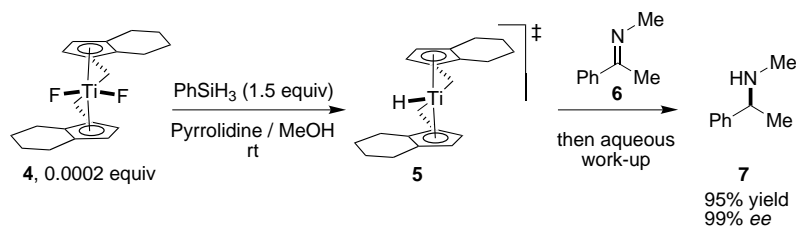

Figure 2. Buchwald's asymmetric imine reduction.

documented in C−C bond-forming reactions, namely, the enantioselective addition reaction of enol silanes to aldehydes. To date most workers in this area have relied on the design and synthesis of chiral Lewis acid complexes that activate the electrophilic reaction partner,[27] as first reported by Mukaiyama.[28] A complementary catalytic process can be envisioned for the addition of enolsilanes and aldehydes in which the nucleophilic partner, or the enolsilane, undergoes transmetalation to give a reactive metalloenolate intermediate.[29] In this regard, Carreira and co-workers have recently demonstrated that a chiral Cu[I] enolate complex functions exceedingly well as the active species in the enantioselective, catalytic addition of silyl dienolate 10 (Figure 3). Mechanistic investigations suggest that a catalytically active copper(ı) species results from reaction of the bisphosphine · CuF$_2$ complex 9 with silyl dienolate 10 (Figure 3).[30] Thus, a small amount of the dienol silane equivalent to the amount of catalyst utilized is consumed in reducing the Cu[II] complex to the active Cu[I] species. The process is convenient to carry out in the laboratory by generation of the active catalyst in situ from pTol-BINAP, [Cu(OTf)$_2$], and the anhydrous fluoride
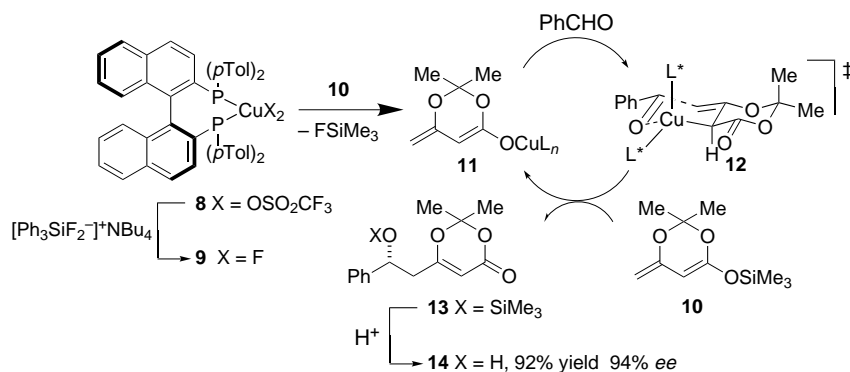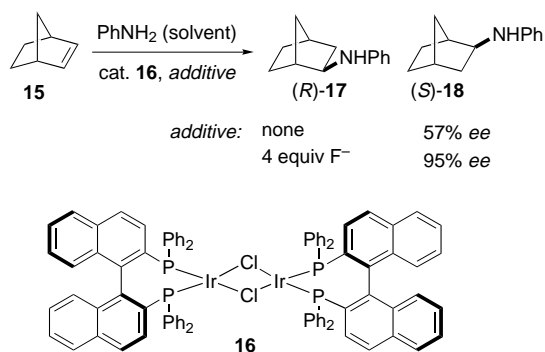

Figure 4. Togni's norbornene catalytic, enantioselective hydroamination reaction.

strong hydrogen bonds result in enhanced reactivity in the oxidative addition of N−H across norbornene.

Togni and co-workers have also observed a remarkable effect of fluoride on the enantioselectivity of a Pd-catalyzed allylic amination process.[35] Accompanying investigations have provided mechanistic insight on the effect of fluoride as a ligand for Pd[II]. Two important characteristics of this halogenide ligand are highlighted as contributing to the enhanced enantioselectivities of the allylic displacement reaction. Firstly, it is suggested that the presence of fluoride allows a fast equilibrium to be established between diastereomeric allyl-Pd complexes, which allows the enantioselective step to take place under Curtin–Hammet conditions. Secondly, on the basis of the fact that in the presence of added fluoride product isomerization was not observed, it is postulated that the fluoride serves effectively to block a coordination site on Pd, thereby preventing interaction with the allylic amine product. In this regard, in the absence of fluoride, when optically enriched allylic amine was subjected to [Pd(ferrocenyl)(η^3-PhCHCHCHPh)]PF$_6$ substantial enantiomerization was observed (99% ee to 60% ee in 24 h). Both the hydroamination and the allyl palladium work amply demonstrate the potential improvements that may be possible in catalyst selectivity by the judicious use of fluoride as a ligand.

Figure 3. The catalytic, enantioselective dienolate aldol addition reaction reported by Carreira.

source [Ph$_3$SiF$_2$]NBu$_4$.[31] Treatment of as little as 0.5 mol % of a bisphosphine · CuF$_2$ complex with 10 provides synthetically usefully aldolates in up to 96 % ee.[32] The successful demonstration of this asymmetric C−C bond-forming reaction opens up new opportunities for further design and discovery of non-Lewis acidic catalysts for C−C bond formation.

Olefin hydroamination: Togni has reported the use of Ir[I] complexes, such as 16, in the presence of excess fluoride as catalysts for the hydroamination reaction of norbornene by aniline (Figure 4).[33] Importantly, the parent chlorocomplex was found to be only moderately effective in yielding the product with modest enantioselectivity. The addition of excess of Schwesinger's reagent as a source of anhydrous fluoride gave a marked improvement in the optical purity of the product.[34] Thus, the enantioselectivity of the reaction was observed to increase from 57 % ee in the absence of fluoride to 95 % ee when the reaction was carried out in the presence of four equivalents of F$^-$. Although the structure of the active catalyst is unknown, these investigators speculated that the π-donating ability of fluoride coupled to its propensity to form

Addition of allyl trimethylsilanes to aldehydes: In contrast to the large number of Lewis acid catalysts that mediate the addition of ketone- or ester-derived enol silanes and aldehydes, there have only been few reports of addition reactions that involve allylsilanes.[36] This stems from the attenuated reactivity of ally silanes relative to allyl stannanes and silyl ketene acetals.[37] Thus, the Lewis acid complexes that effectively activate aldehydes towards addition by silyl enolates generally fail in aldehyde allyl silylation reactions. The asymmetric addition of allyl trimethylsilane 21 to

aldehydes with up to 94 % *ee* has recently been achieved utilizing a fluorotitanium catalyst prepared in situ from TiF$_4$ and either (*R*)- or (*S*)-(−)-1,1′-binaphthol (Figure 5).[5, 38] Although the structure of the catalyst is presently unknown, the unique role of fluoride is demonstrated by observation that the analogous complexes derived from the other halides
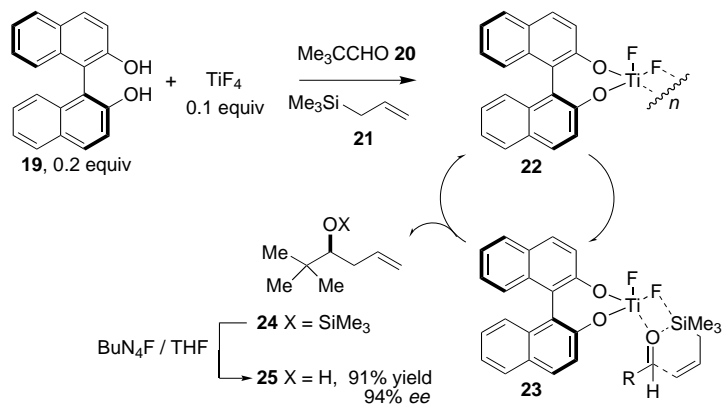

Figure 5. Carreira's allyl silane additions.

(Cl, Br) fail to lead to product formation. The enhanced unique reactivity of this fluorotitanium complex has been suggested to arise from a combination of factors, which include the increased electronegativity of fluorine as a ligand as well as the strength of the Ti−F bond. The former property may lead to enhanced Lewis acidity at the metal center and the latter property ensures that nonproductive reaction of fluoride with the silylether product or the starting allyl silane is slow. Additionally, the known propensity of fluoride to form bridging structures has led to the suggestion by Duthaler that the halide may lead to activation of the nucleophilic component **23** (Figure 5).

Me$_3$Al addition to aldehydes: The asymmetric addition of dialkyl zinc reagents to carbonyl compounds has been well studied with a number of superb processes readily available to the synthetic chemist.[39] By contrast, the use of trialkylaluminum reagents in catalytic, enantioselective aldehyde additions has only recently been documented.[40, 41] Among the various catalysts employed in asymmetric dialkyl zinc additions to aldehydes, Ti^{IV} complexes have proven remarkably successful.[42, 43] The typical procedure prescribes the use of 5 – 10 mol % chiral Ti^{IV} catalyst along with excess [Ti(O*i*Pr)$_4$] and [R$_2$Zn] (> 1.0 equiv each).

Recently, the asymmetric addition of Me$_3$Al to aromatic aldehydes mediated by the putative titanium fluoride catalyst **29** was reported that obviates the use of excess [Ti(O*i*Pr)$_4$] additive (Figure 6).[44] Treatment of chiral diol ligand **24** (15 mol %) with Me$_3$Al, [TiF$_4$] (14 mol %) leads to the in situ formation of a catalyst that effects the addition of Me$_3$Al and aldehydes in up to 87 % *ee*. Unfortunately, there is no detailed information available about the starting complexes for these reactions. In analogy to the mixed Ti/Al fluoride complexes characterized by Roesky (cf. **30**), and the affinity of aluminum
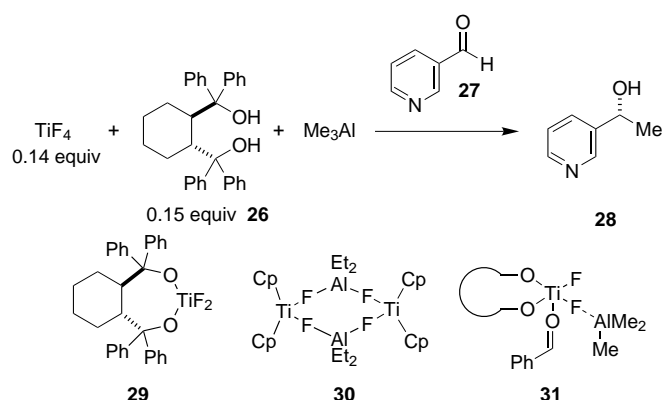

Figure 6. Carreira's Me$_3$Al additions.

for fluoride,[45] the intermediacy of complex **23** has been postulated. The study illustrates how the use of a transition metal fluoride complex can lead to unusual reactivity and the generation of unprecedented catalytic reaction processes.

Conclusion

The unique structural and bonding characteristics of fluoride impart unusual reactivity to the corresponding transition metal complexes. The examples discussed in this *Concept* constitute some of the more recent cases in which the use of a metal fluoride compound has resulted in complexes possessing useful properties that can be tapped for asymmetric catalysis. Thus, the use of metal fluoride complexes as initiators not only provides the preparation of novel species that result in higher selectivities (ketimine hydrosilylation), but also provides entrance to novel catalytic cycles (Mukaiyama aldol via metalloenolates). Moreover, the incorporation of transition metal fluoride catalysts in which the fluoride remains as an integral component of the catalyst permits entry to novel reaction processes with little precedence (allylsilane and alkyl aluminum additions to aldehydes, and olefin hydroamination). Further investigations of transition metal fluoride complexes in asymmetric catalysis should yield additional contributions in the evolution of this exciting field.

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