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Developing Catalytic Enantioselective Fluorination

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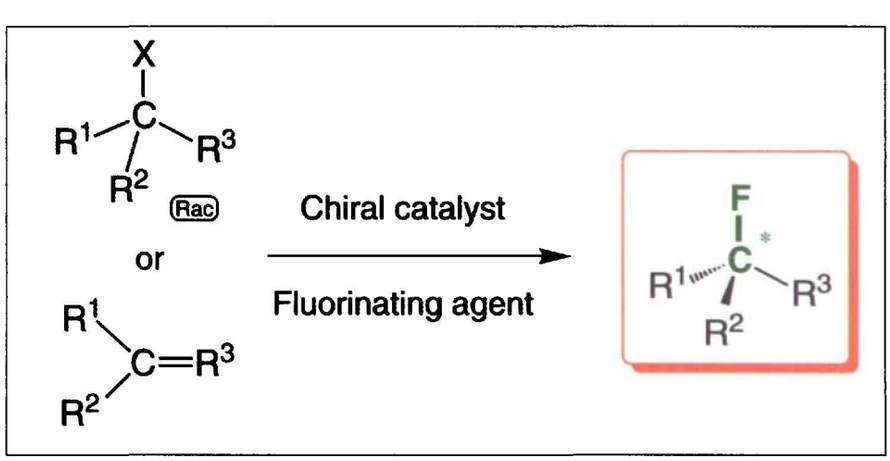
Abstract: The background that led to the development of the first catalytic and enantioselective carbon-fluorine bond-forming reaction is presented. Two different approaches, *i.e.* the use of nucleophilic and electrophilic fluorinating agents, respectively, have been pursued. Well-defined Ru(II) 16-electron systems of the type $[RuF(PP)_2]^+$ (where PP is a chelating diphosphine), as well as analogous complexes containing tetradentate PNNP ligands, were found to catalyze the halogen exchange reaction of activated alkyl chlorides, bromides, and iodides in the presence of TlF as the fluorine source. Isolable crystalline $[TiCl_2(TADDOLato)]$ complexes are efficient catalysts in the enantioselective fluorination of 2-substituted 1,3-dicarbonyl compounds with Selectfluor® (also called F-TEDA; 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis{tetrafluoroborate}). Levels of enantioselectivity up to 90% ee were obtained.

Keywords: Asymmetric catalysis · Enantioselective chlorination · Enantioselective fluorination · Ruthenium fluoro complexes · Titanium TADDOLato complexes

Introduction

Although in nature organic molecules containing fluorine are extremely rare [1], it is not exaggerated to say that fluoroorganic compounds are nowadays ubiquitous among biologically active derivatives [2][3]. Many of them contain fluorine substituents at aromatic rings or perfluoroalkyl groups. Somewhat underrepresented, though no less important, are derivatives displaying a single fluorine atom attached to a stereogenic center. A wide collection of reagents and synthetic methods is currently available for the selective introduction of fluorine into organic molecules [4]. These also include stereoselective procedures which, however, rely upon sources of chirality used in stoichiometric amounts [5–7]. In other words, no catalytic reaction was known before we started this work that would lead to the formation of a new carbon–fluorine bond under concomitant control of the absolute stereochemistry of the newly generated stereogenic C–F center. We felt that this state of affairs constituted a problem of sufficient fundamental relevance to embark in a project aimed at finding suited combinations of substrates, fluorinating agents, and chiral catalysts for a successful asymmetric fluorination, as illustrated in Scheme 1.

From an organometallic and coordination-chemical point of view, the observation that transition metal complexes have been actually neglected as possible catalysts for processes in which a new carbon–fluorine bond is formed constituted a further incentive towards our goal. In fact, organometallic chemists have been rather concerned with the activation, *i.e.* the cleavage of the C–F bond. A great number of reactions typically involving the oxidative addition of a C–F fragment to an electron-rich transition



Scheme 1. What are the combinations of substrates, fluorinating agents, and chiral catalysts leading to a successful asymmetric fluorination?

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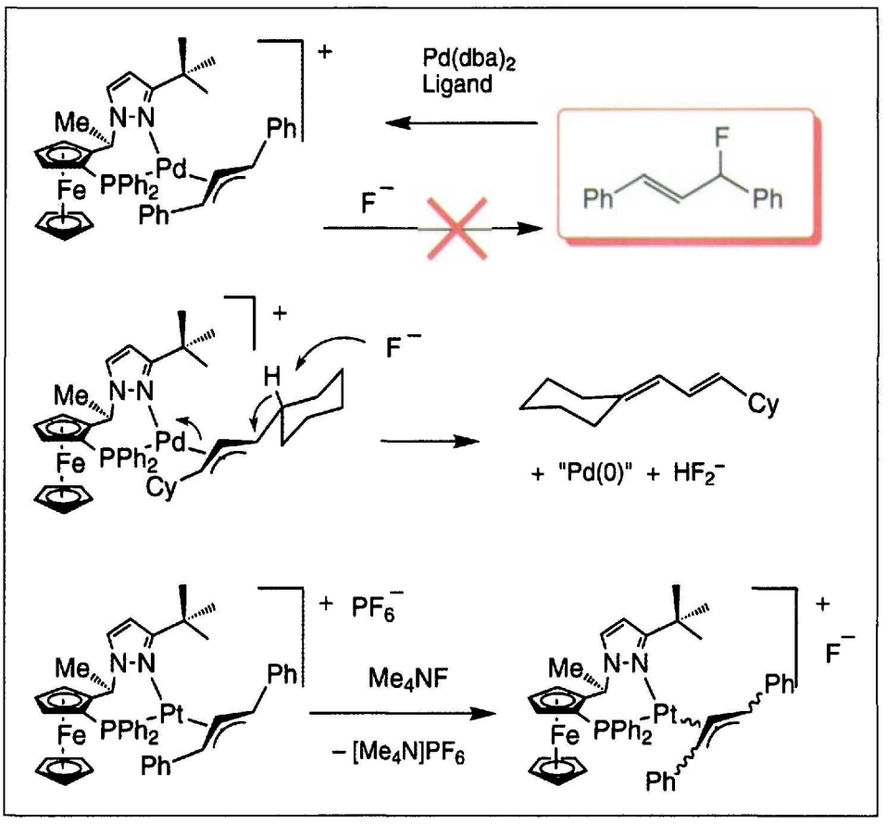
metal compound have been reported in the literature [8–11], although the C–F bond has been recognized as inert toward oxidative addition [12]. This research area led to the discovery of the first catalytic process for C–F bond activation [13]. On the other hand, the participation of organometallic and coordination compounds as mediators for the formation of a new C–F bond is documented only by rare examples [14–16], although the catalytic action of simple first-row nitrates in the direct fluorination (*i.e.* with F_2) of malonates has recently been reported [17].

Nucleophilic Fluorination

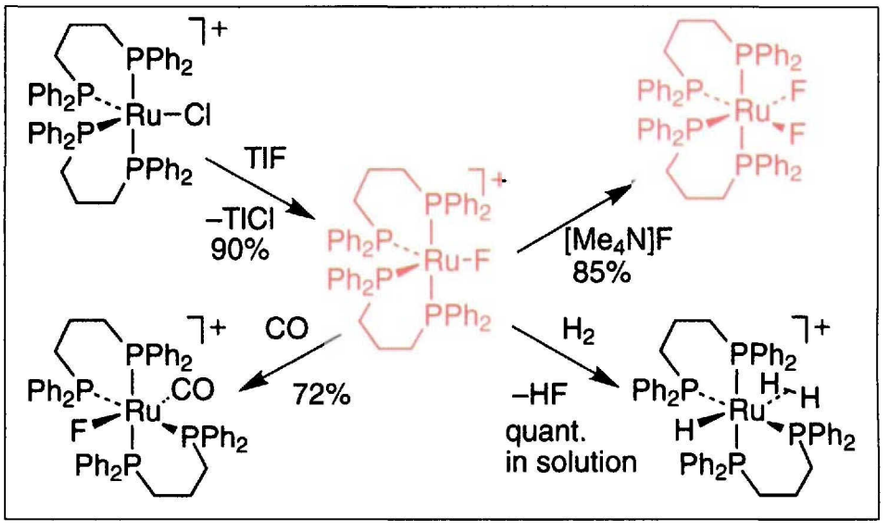
Our involvement with fluorine started by serendipity. Thus, in the enantioselective Pd-catalyzed allylic amination of 1,3-diphenylallyl ethyl carbonate with benzylamine, a strong dependence of the enantioselectivity on the type of anions present in solution was observed [18]. A co-catalytic amount of fluoride was found to improve the selectivity significantly, also when deleterious anions such as PF_6^- were present. Similarly, the first highly enantioselective intermolecular hydroamination reaction catalyzed by Ir(I) complexes, in which added fluoride had a beneficial effect on both selectivity and catalyst activity was discovered in our laboratories [19]. The former observation led to the question whether fluoride could attack cationic Pd(II) (or Pt(II)) π-allyl complexes as a nucleophile, thus leading to allylic fluorination. However, as shown in Scheme 2, no such reaction could ever be realized, and fluoride either did not react at all, or catalyzed other processes. On the contrary, 1,3-diphenylallyl fluoride was found to smoothly undergo an oxidative addition to Pd(0) complexes [20]. According to a recent computational study [21] the nucleophilic attack of fluoride onto a Pd-π-allyl complex appears to be a strongly endothermic process, this being in line with our observations.

At this point, we started a systematic study concerning the synthesis and reactivity of isolated Ru(II) fluoro complexes, as well as their use as catalysts in the nucleophilic fluorination of molecules containing activated carbon–halide bonds (halide metathesis). The first complexes we investigated are cationic, pentacoordinate 16-electron Ru(II) systems, containing a FP_4 donor set. The rationale behind this choice – a coordination-chemical approach to catalysis – derived mainly from two considerations. Firstly, by virtue of its π-donor ability, fluoride is able to stabilize coordinatively unsaturated systems, that still remain sufficiently reactive to undergo binding of organic substrates. Secondly, the tetraphosphine ligand set, and therefore the absence of any strong π-accepting ligand, ensures a high reactivity of the Ru–F bond. These new complexes are thus predestined as fluoride-transfer agents. The preparation and some examples of reaction of a new Ru fluoro complex are shown in Scheme 3 [22].



Scheme 2. Unsuccessful attempts toward a Pd-catalyzed allylic fluorination.

As expected, these complexes were found to efficiently exchange the halide with activated alkyl bromides, chlorides, and iodides displaying S_N1-type reactivity [23]. These stoichiometric reactions can be very rapid and quantitative, depending on the substrate. Indeed, 1,3-diphenylallyl bromide, for instance, reacts instantaneously at room temperature with the fluoro complex to the corre-



Scheme 3. Synthesis and examples of reactivity of a new 16-electron Ru(II) fluoro complex.

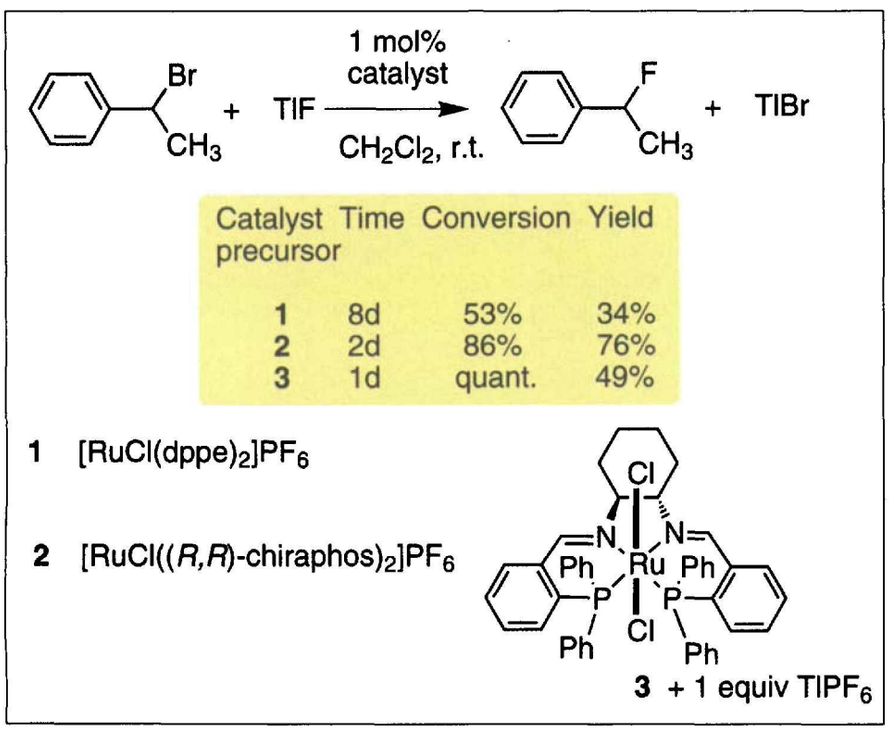
sponding allyl fluoride and the Ru bromo derivative. Rigorous exclusion of humidity and good experimental skills are however required when working with the highly reactive fluoro complexes. We were able to turn the halide metathesis reaction into a catalytic process by using TlF as a fluoride source and halide scavenger. Because of this dual role of TlF it is no longer necessary to use the isolated fluoro complexes as catalyst precursors, as these will be formed *in situ* from the more stable cationic monochloro or neutral dichloro systems, thus extending the range of possible catalysts also to complexes containing ligands of different types [24]. A selection of results concerning the fluorination of racemic 1-phenylethyl bromide is shown in Scheme 4. The observation of a modest but significant asymmetric induction of 16% ee after 1–2% conversion in the case of a complex containing a chiral tetradentate PNNP ligand is most intriguing, and is taken as an indication that the Ru complex is indeed involved in the fluoride-transfer step. However, the fact that the enantioselectivity decays toward 0% ee when the substrate is completely consumed, also indicates that a kinetic resolution process is probably operating. The encouraging results obtained so far are for us impetus toward a further improvement of this chemistry in view of new practical fluorination reactions.

Electrophilic Fluorination

Since the pioneering work by Differding and Lang who reported in 1988 the first enantioselective electrophilic fluorination reaction of an enolate with a chiral N-fluoroamine (N-F) reagent derived from camphor [25], this particular area of organofluorine chemistry has flourished [7][26–28]. However, progress has taken place in an incremental way by improving upon the original finding [29–33], and no conceptually new approach has been reported. In other words, more reactive N-F reagents, including chiral ones, have become available and can be used in the stereoselective fluorination of various types of enolates or silyl enolethers. The corresponding carbonyl compound is usually unreactive, thus the necessity of the enol/enolate formation step. However, carbonyl compounds that are strongly enolized undergo slow fluorination without the addition of a base. Moreover, as reported by Umemoto in 1990, the addition of the Lewis acid $ZnCl_2$ to a β-ketoester existing in equilibrium with the corresponding enol form brought a significant acceleration of the fluorination reaction with N-fluoropyridinium salts [34]. This very observation led to our simple working hypothesis for the development of the first catalytic enantioselective fluorination reaction: *The enol form of a β-ketoester is much more reactive than the keto form in electrophilic fluorination reactions. A Lewis acid catalyzes fluorination because it triggers enolization. If fluorination occurs on the coordinated enol (or enolate), then asymmetric induction should be possible using chiral Lewis acids.*

Searching for a suited Lewis acid required a fluorination reaction that would not occur without the intervention of a catalyst. The β-ketoester ethyl 2-methyl-3-phenyl-3 oxopropionate does not react with Selectfluor® (also called F-TEDA; 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2]octane bis{tetrafluoroborate}) [35], one of the most powerful electrophilic fluorinating agents, over prolonged periods of time in acetonitrile even at elevated temperatures. From a wide selection of Lewis acids tested it was soon clear that classical Ti Lewis acids are by far the best suited catalysts for this reaction [36]. It is important to realize that for $[TiCl_2(diolato)]$ complexes, for which of course chiral derivatives are easily accessible, the oxygen ligand atoms must be attached to sp^3 centers. This restriction, clearly shown by the poor catalytic activity displayed by Ti binaphthol derivatives, led to the use of TADDOLs, ligands that have been developed by Seebach and co-workers at ETH [37]. Among different TADDOLs that have been tested in the catalytic fluorination reaction – some of which have been kindly provided by A.K. Beck – the one bearing 1-naphthyl groups proved so far to be superior. We were also pleased that the corresponding catalyst precursors could be isolated in crystalline form in high yield. Moreover, these isolated complexes gave more reproducible and reliable results than the compounds generated *in situ*. The crystal and molecular structures of two representatives mononuclear complexes are shown in Fig. 1. In both cases, the Ti atoms display a distorted octahedral coordination geometry with solvent molecules occupying mutual *cis* positions and the chloro ligands in *trans* axial orientation [38], as very recently reported for similar derivatives [39–41].

Thus, for α-methyl-β-ketoesters enantioselectivities up to 90% ee were obtained, ranging among the highest stereoselectivities ever observed for a fluorination reaction. In the case of slow reacting substrates, the formation of small amount



Scheme 4. Ru(II) complexes as catalysts in the nucleophilic fluorination (halide metathesis) with TlF.

of the *chlorinated* product was observed. The source of chlorine is free chloride liberated from the catalyst. The addition of a chloride salt to the reaction mixture leads to a significant increase of the extent of chlorination. Since chloride does not react with F-TEDA under catalytic reaction conditions, the exact origin and nature of an electrophilic chlorinating agent is not yet clear, however it cannot be chloride itself. These aspects are intimately connected with the detailed mechanism of the actual C–F(Cl) bond-forming step (*vide infra*). However, enantioselective chlorination can be successfully conducted using N-chlorosuccinimide (NCS) [42]. Whereas the enantioselectivities of fluorination and chlorination are often comparable, the analogous bromination with NBS is much less selective (< *ca.* 25% ee). The results of fluorination and chlorination are summarized in Scheme 5.

Concomitantly with the extension of this new halogenation reaction to other 1,3-dicarbonyl substrates – β-ketoamides, ketolactones, 1,3-diketones have been found to react affording, however, lower enantioselectivities than α-methyl-β-ketoesters – we are very much interested in understanding the reaction mechanism. A first hypothesis involving a cationic Ti monochloro complex as the catalyst is illustrated in Scheme 6. The key intermediate is a neutral Ti enolato complex for which eight diastereoisomeric forms are possible. QM/MM calculations [43] have identified the one illustrated in Fig. 2, for the case of the β-ketoester giving the highest enantioselectivity, as the most stable. It is clearly recognizable that one enantioface of the coordinated enolate is completely shielded by one face-on naphthyl group. External attack by F-TEDA can only occur from the opposite side. Besides predicting the correct absolute configuration of the product, this model also identifies a major problem with respect to an improvement of the selectivity: The four most stable diastereoisomeric forms of the intermediate have the chloro ligand in axial position, lie within an energy range of *ca.* 3 kcal/mol, and lead pairwise to opposite enantiomers. The key for selectivity appears, therefore, to be the channeling of the system into the formation of possibly only one diastereoisomeric enolato complex. Finally, the carbon–fluorine bond-forming step appears to consist in a single-electron transfer process from the coordinated enolate to the N-F unit, followed by rapid fluorine radical transfer, according to ongoing computational studies [43]. A fluorine radical could be trapped by chloride, thus giving rise to competing chlorination (*vide supra*).

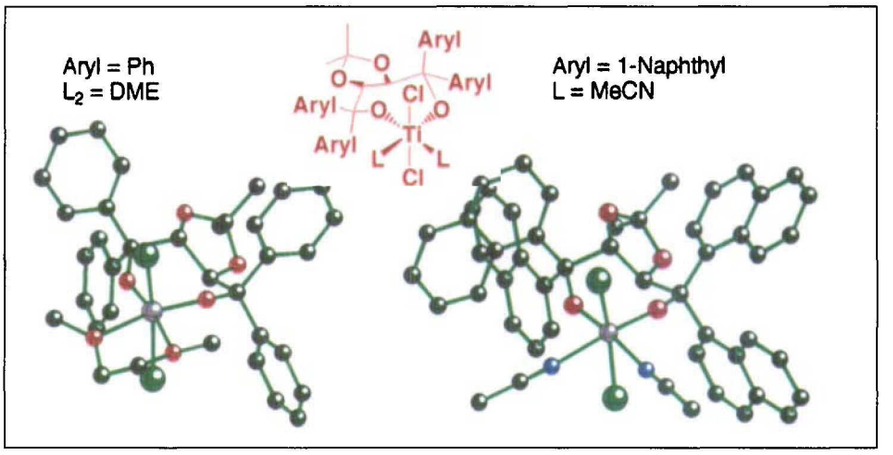
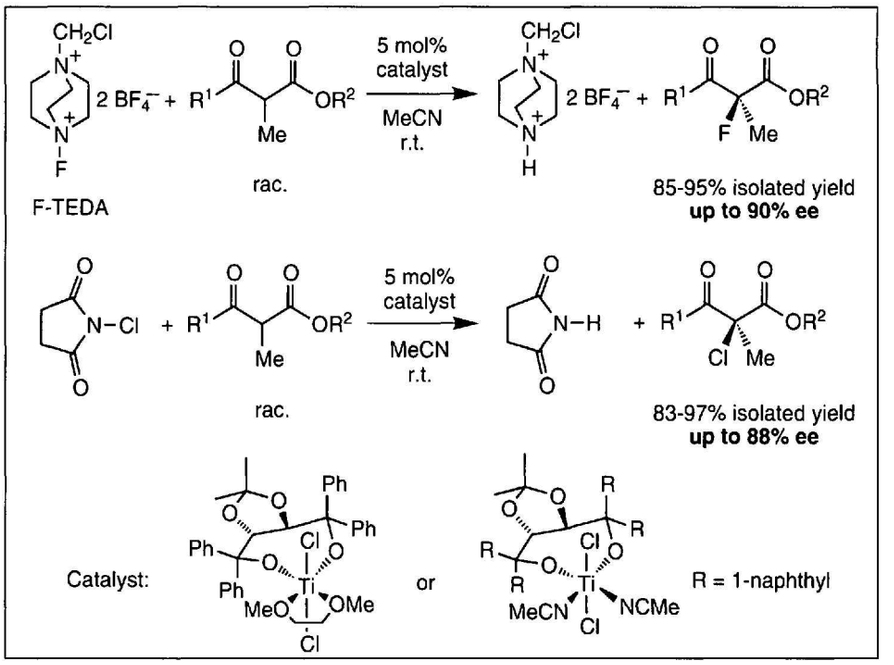


Fig. 1 Crystal and molecular structure of two $TiCl_2$((*R*,*R*)-TADDOLato) complexes. Hydrogen atoms are omitted for clarity.



Scheme 5. Catalytic enantioselective fluorination and chlorination of β-ketoesters.

Conclusion

We have demonstrated the feasibility of catalytic stereoselective fluorination. This has been recently termed, referring to electrophilic fluorination, '*a first real breakthrough in transition metal catalyzed fluorination*' [44]. However, this breakthrough was realized utilizing a well-known type of catalyst, a known fluorinating agent, to make known products from known starting materials. This is very much quintessential to synthetic chemistry: one needs the perception to find new and original combinations!

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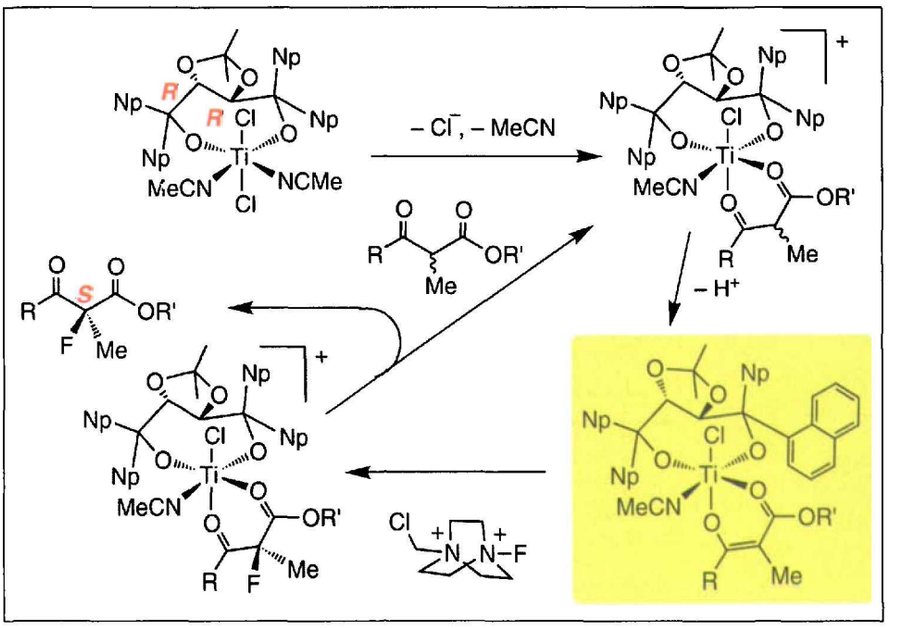

Scheme 6. A first mechanistic hypothesis for the Ti-catalyzed fluorination involving the formation of a Ti(enolato) complex.

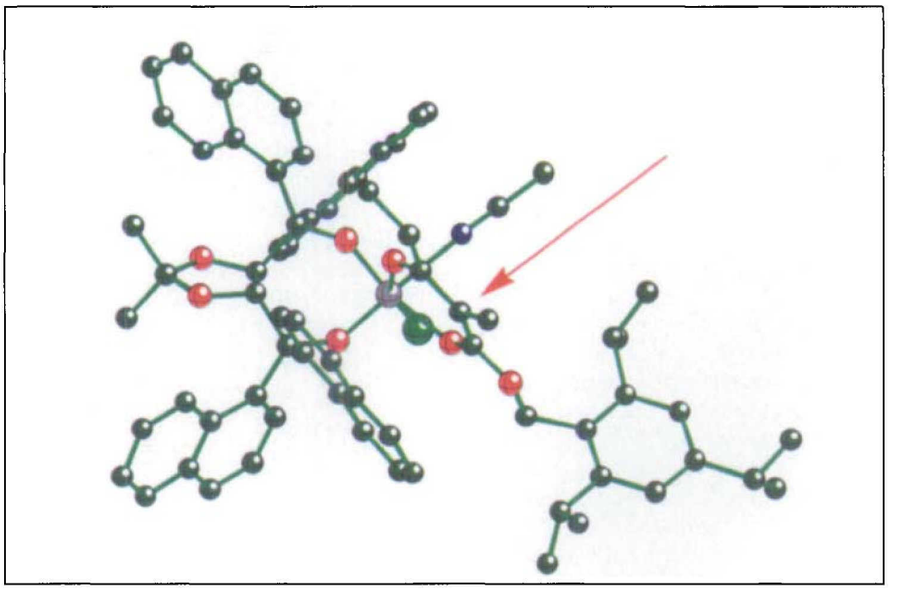

Fig. 2 Calculated structure of the preferred diasteroisomeric Ti(enolato) intermediate involved in catalytic fluorination [43]. The arrow shows the direction of the F-TEDA approach to the coordinated enolate (*si*-enantioface is accessible for (*R,R*)-TADDOL). Hydrogen atoms are omitted for clarity.

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