mass spectrometer source with a syringe pump (Harvard type 551111: Harvard Apparatus Inc., South Natick, MA, USA) with a flow rate of 4 µL min^{-1}. Calibration was performed using protonated horse myoglobin. Scanning was performed in the MCA (multichannel analyzer) mode, and several scans were combined to obtain the final spectrum. Electrochemical studies were made by cyclic voltammetry with a conventional three-electrode system using a BAS CV-50 W voltammetric analyzer equipped with a Pt microdisk or a Hg Kemula hanging electrode as working electrode and a Ag wire counter electrode. Ferrocene ($E_{1/2} = +0.65$ V) or paraquat ($E_{1/2} = -0.23$ and -0.60 V) were used as an internal standard with the Pt and Hg electrodes, respectively. Solutions contained the electrode-active substrate (ca. 5×10^{-4} mol dm^{-3}) in deoxygenated and anhydrous DMF containing tetra-*N*-butylammonium tetrafluoroborate (0.2 mol dm^{-3}) as supporting electrolyte. The quoted half-wave potentials were reproducible within 15 mV.

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[14] Crystal data for $[Cu_4L_4](PF_6)_4$: $C_{124}H_{96}Cu_4N_{16}P_4F_{24}$, $M_r = 2644.21$; deep-orange diamond-shaped microplates ($0.2 \times 0.2 \times 0.02$ mm^3), obtained by slow evaporation of an acetonitrile solution. $\mu = 0.778$ mm^{-1}, $F(000) = 5376$, monoclinic, space group $C2$, $a = 26.645(4)$, $b = 16.607(3)$, $c = 29.359(4)$ Å, $\beta = 91.7(1)^\circ$, $V = 13065.1$ Å^3, $Z = 4$, $\rho_{calcd} = 1344$ kg m^{-3}. Data collection at 277(2) K on the wiggler line DW32 (R. Fourme, P. Dhez, J. P. Benoit, R. Kahn, P. Dubuisson, J. Frouin, *Rev. Sci. Instrum.* **1992**, *63*, 982 – 987) at the DCI synchrotron, LURE (Orsay-France) at $\lambda = 0.964$ Å, on a MAR-Research 345 image plate system. Image plate distance: 10 cm. A total of 100 frames, each 3° in rotation, were recorded and processed with the *hkl* package of the program (Z. Otvinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307 – 326). As one of the twins was in greater percentage, it was possible to integrate only one component at the indexing level. $3.74 < \theta < 26.26^\circ$, $-24 \leq h \leq 24$, $0 \leq k \leq 15$, $0 \leq l \leq 27$. A total of 23225 reflections was obtained of which 5490 were independent and used to refine 809 parameters. 5462 observed reflections with $I > 2\sigma(I)$. $R = 0.0961$, $wR_2 = 0.2578$ (observed), $R = 0.0964$, $wR_2 = 0.2580$ (all data). The structure was solved by direct methods (SHELXS86) and refined on F^2 for all reflections by least-squares method (SHELXS93). Hydrogen atoms were introduced at their theoretical positions and refined with constraints on bond distances and angles. Isotropic thermal factors were kept at 1.2 times that of the bonded atom. Only copper, nitrogen, and phosphorus atoms were refined anisotropically to limit the number of parameters versus the number of data. Largest difference peak and hole are 0.82 and -0.57 e Å^{-3}, respectively. CCDC-170600 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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The Mechanism of Catalytic Enantioselective Fluorination: Computational and Experimental Studies

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Despite the undisputed importance of organofluorine compounds, for example, in biomedical applications, the generation of fluorinated carbon stereocenters by C–F bond-forming reactions remains rare and particularly challenging.[1, 2] Recently, the first catalytic, enantioselective fluorination of β-ketoesters with F-TEDA (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane; TEDA = triethylenediamine) in the presence of 5 % of $[TiCl_2(TADDOLato)]$ (TADDOL = $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol) catalysts was reported.[3, 4] We have shown that the reaction proceeds smoothly in acetonitrile at room temperature and the obtained enantioselectivity reaches 90 % *ee* using a (*R*,*R*)-TADDOL bearing 1-naphthyl substituents.[4] We assume, as a first mechanistic hypothesis, that

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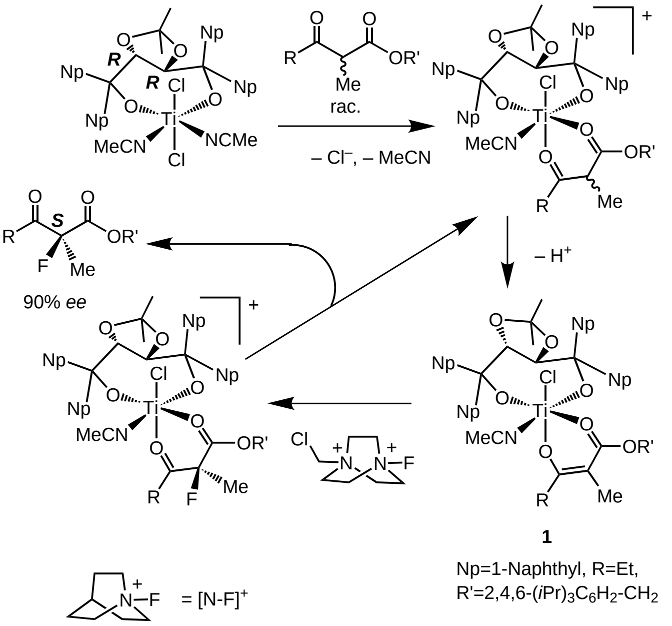
the β-ketoester coordinates to the catalyst as an enolate and substitutes one of the two chlorides and one of the acetonitrile molecules (Scheme 1). Thus, the octahedral monochloro Ti(enolato) complex **1** is the reactive species and is fluorinated by F-TEDA in the crucial C−F bond-forming step,[4] the mechanistic details of which are still poorly appreciated.[5–8]



Scheme 1. Simplified mechanistic hypothesis for the Ti-catalyzed asymmetric fluorination reaction. The $[N{-}F]^+$ ion reagent used in the computational studies is also shown.

To understand the origin of enantioselectivity and to elucidate the detailed mechanism of the actual fluorination step, we performed density functional theory (DFT) based mixed quantum mechanical/molecular mechanical (QM/MM) calculations on complex **1**. Using the program ADF2000[9] in combination with a suitably modified version of the classical force-field AMBER95,[9–11] we found that the eight possible stereoisomeric forms of complex **1** represent local minima on the energy hypersurface. In particular, the four most stable stereoisomers **1a–d** (Figure 1) have the chloride ligand in axial position, the equatorial plane being defined by the Ti center and the two coordinated TADDOL oxygen atoms. Each of the corresponding equatorial counterparts, obtained by exchanging the coordination positions of chloride and acetonitrile, are 4–6 kcal mol^{-1} less stable. The bonding parameters[11] of the calculated structures **1a–d** are in excellent agreement with those reported recently for an analogous complex that contained a 1,3-diketonato ligand and was characterized by X-ray crystallography.[12] For the species **1a** and **1c** the enolate fragment and one of the two face-on oriented naphthyl groups are almost perfectly parallel (Figure 2). As a consequence, the *Re*-face of the enolate in **1a** (the *Si*-face in **1c**, respectively) is completely shielded and a fluorine atom can only be delivered from the opposite side. For the other two isomers **1b** and **1d** similar considerations apply to an edge-on oriented naphthyl group, but the effect appears to be less pronounced. The shielding situation in the most stable isomer **1a** correctly predicts the observed absolute configuration of the product.

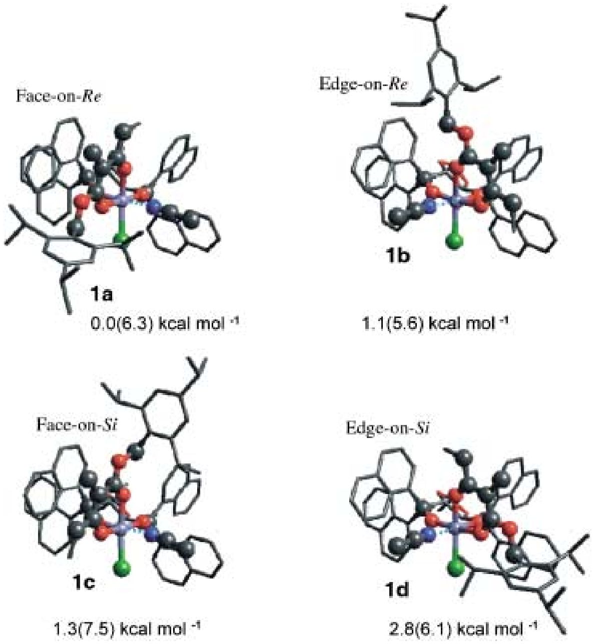


Figure 1. Structure and relative energies of the four most stable Ti(enolato) complexes with the chloro ligand (green) in axial position with respect to the plane of the Ti(TADDOLato) chelate. Hydrogen atoms are omitted for clarity. The energies of the corresponding stereoisomers with an equatorial chloride ligand are given in parenthesis. All the groups directly bound to the titanium were treated at the DFT level and are represented as balls and sticks. All other atoms are shown as sticks and were accounted for by a classical force field.[10]

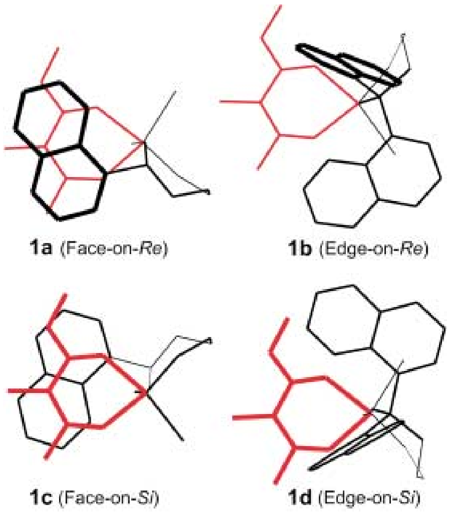


Figure 2. Schematic projections on enolate plane (red) for the calculated structures **1a–d** showing the shielding of one of the enolate enantiofaces by either a face-on or an edge-on naphthyl group (for a definition of face-on and edge-on orientations of aryl groups in TADDOLs, see ref. [3]).

There is a long-standing debate about the reaction mechanism for the electrophilic fluorination reaction with N–F reagents. In particular, it is controversial whether the reaction proceeds by a single-electron transfer (SET) or is a simple nucleophilic substitution (S_N2) at the fluorine atom.[5–8] Two experimental observations have oriented our investigation. Firstly, a small amount (1–4%) of chlorinated by-product is

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formed in the case of slow reacting substrates,[13] with the source of chlorine being the catalyst. Secondly, the extent of chlorination can be enhanced up to 12–15% by the addition of one equivalent of a chloride salt (NH_4Cl or NaCl). The enantioselective formation of the chlorinated product demonstrates the involvement of the catalyst in the side reaction. However, since F-TEDA is inert towards chloride,[14] the origin of an electrophilic chlorinating agent under reaction conditions is not clear.

To further investigate these points we carried out QM/MM first-principles molecular dynamics[15] studies of the fluorination step in vacuo and in acetonitrile solution.[16] All the simulations were performed for a temperature of 300 K. The lowest energy complex **1a** was taken as a starting point and 1-fluoro-1-azonium-[2.2.2]bicyclooctane ($[N{-}F]^+$ ion, which models F-TEDA, see Scheme 1) was added to the system.

The in vacuo simulations were started at a distance d_{C-F} of 3.5 Å between the C_α atom of the β-ketoester and the fluorine atom of the $[N{-}F]^+$ ion. After a few femtoseconds, one electron is transferred from the Ti complex to the $[N{-}F]^+$ ion. As a consequence, an antiferromagnetic diradical species is formed that is stable throughout the investigated time scale of a few picoseconds and no further spontaneous reaction is observed. This result is an indication that in vacuo the reaction proceeds by a SET involving the formation of a $[N{-}F]^\bullet$ radical, that however, does not automatically lead to product formation.

For the studies in acetonitrile solution, constrained molecular dynamics simulations were performed in which d_{C-F} was progressively reduced from 2.9 to 1.7 Å. This approach allowed the evolution of the system to be followed during the fluorination process and to eventually estimate the reaction free energy associated with this reaction step. In contrast to the in vacuo simulations, no spontaneous SET is observed even at $d_{C-F} = 2.6$ Å (Figure 3) as a result of the additional stabilization of the $[N{-}F]^+$ ion by the polar solvent. Upon further reduction of the constraint distance, the free energy increases and the average N−F distance elongates from 1.53(3) Å at $d_{C-F} = 2.9$ to 1.61(5) Å at $d_{C-F} = 2.2$ Å. At the latter distance, one electron is transferred from the Ti complex to the $[N{-}F]^+$ ion. Simultaneously, the N−F bond is broken and the force acting on the constraint changes its sign, thus indicating the crossing of the transition-state (Figure 3). Indeed, releasing the constraint at this point of the simulation leads to product formation within a few femtoseconds.

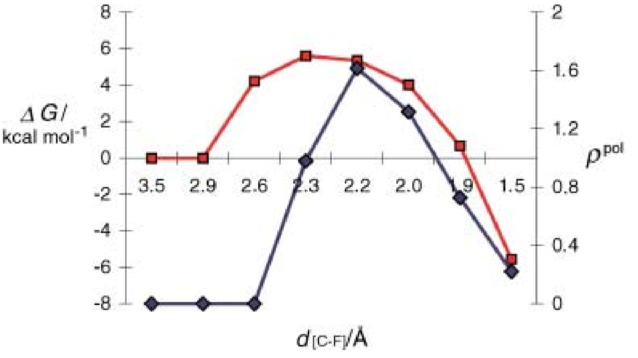

Figure 3. Approximate reaction free-energy profile for the catalytic electrophilic fluorination (red) as a function of the C−F distance [Å]. The integrated value of the absolute polarization spin density $\rho^{pol} = \int|\rho^{\alpha}(\vec{r}) - \rho^{\beta}(\vec{r})|\,dV$ is also indicated (blue). The total simulation time was 4.8 ps. After the simulation at $d_{C-F} = 1.9$ Å, the constraint was released and the system was simulated for another 0.3 ps.

The relative stability of cationic versus radical form of the intermediate species depends crucially on the interaction with the solvent. It is therefore conceivable that because of the thermal fluctuations in the solvation shell, an alternative reaction pathway could become available. The dipole–charge interaction of the $[N{-}F]^+$ ion with the solvent could eventually become small enough that, in analogy to the simulation in vacuo, a SET occurs before the transition state for the fluorine transfer is reached. In this case, an $[N{-}F]^\bullet$ radical would be formed. This radical could then react with the chloride present in solution leading to the formation of the relatively stable $Cl^\bullet$ radical, which is ultimately responsible for the formation of the chlorinated by-product. In this case, a radical scavenger should be able to quench the chlorination, while not affecting the fluorination reaction.

In fact, we have found that the addition of 2,2′,3,3′,4,4′,5,5′-octamethyl-1,1′-bis(*tert*-butylthio)ferrocene[17] to the reaction mixture has a drastic effect. The extent of ethyl 2-methyl-3-oxo-3-phenylpropanoate chlorination is reduced to 10–20% of the normal yield, while the fluorination is unaffected. Thus, by the addition of a one-electron donor it is possible to discriminate between the two halogenation processes. This result strongly supports the SET mechanism as a pathway for halogen transfer in these reactions.

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[11] A list of characteristic structural parameters for the $[Ti(TADDOL)Cl_2(CH_3CN)_2]$ and $[Ti(TADDOL)Cl(enolato)(CH_3CN)]$ complexes in comparison with experimental data is provided in the

Supporting Information. Calculations performed on a larger system that included the whole TADDOL ring in the QM part give essentially the same results in terms of geometry and relative configurational energies.

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[16] The system was immersed in a 46 × 49 × 44 Å box containing 557 acetonitrile molecules parametrized as reported (W. L. Jorgensen, J. M. Briggs, *Mol. Phys.* **1988**, *63*, 547–558). An initial equilibration was performed by 500ps of NPT classical molecular dynamics keeping the Ti(enolato)-complex and the $[\mathrm{N{-}F}]^+$ ions fixed to their starting positions.

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