



INSTITUTIONEN FÖR KEMI OCH MOLEKYLÄRBIOLOGI

Lanthanide-mediated C-F Bond Activation Method Development and Mechanistic Investigations

Mario Janjetovic

Institutionen för kemi och molekylärbiologi
Naturvetenskapliga fakulteten

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Abstract

The use of transition-metals and main-group Lewis acids has proven to be an outstanding source for activation and subsequent functionalization of fluorinated compounds. However, the first is mainly limited to C(sp²)-F bonds which partially are activated by an adjacent heteroatom, and the latter is limited to simple C(sp³)-F bonds due to particularly strong Lewis acid character.

The main focus of this thesis has been directed towards development of mild and chemoselective lanthanide mediated C-F bond activation of simple and functionalized alkyl fluorides from a synthetic point of view.

The first part of the thesis covers a solvent dependent reductive HDF of alkyl fluorides by employing Sm(HMDS)₂ as a single-electron transfer reagent. The Sm(II)-reagent, assisted by microwave heating, is capable of reductive cleavage of primary, secondary, and tertiary alkyl fluorides to the corresponding hydrocarbons in excellent yields

The second part of the thesis describes the utilization of YbI₃(THF)₃ as a superior Lewis acid for the selective iodination of primary, secondary, and tertiary alkyl fluorides in presence of various common functional groups. The mechanism of the reaction was distinctively studied by the means of substrate reactivity, stereochemical analysis, and initial rate measurements. The reaction was further elaborated into a catalytic process in the presence of TMSI as a stoichiometric fluoride-trapping agent. ¹H and ¹⁹F NMR spectroscopy demonstrated a two-step catalytic cycle where TMSI regenerates the active YbI₃(THF)₃.

The third and final part of the thesis involves the development of a facile and efficient protocol of direct amination of alkyl fluorides employing La[N(SiMe₃)₂]₃. The method was shown to tolerate various secondary nucleophilic amines as well as functionalized alkyl fluorides. A concerted transition state was proposed for the reaction based on ¹H NMR spectroscopy, initial rate measurements, KIE, and steric effects. It was also found that La[N(SiMe₃)₂]₃ promoted instantaneous and subsequent substitution of β-amino fluorides. ¹H NMR spectroscopy revealed that the reaction appears to proceed via an aziridinium ion. Consequently, the reactive intermediate was prone to undergo ring-opening by various nucleophiles, yielding the corresponding β-substituted amines in high to excellent yields.

Keywords: C-F bond activation, fluorine chemistry, lanthanides, single-electron transfer reagent, Lewis acid, chemoselectivity, synthetic method, catalysis