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Digest Paper

Carbon–fluorine bond activation for the synthesis of functionalized molecules

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ABSTRACT

The synthesis of fluorinated compounds as well as the use of these products as building blocks for the preparation of complex molecules are fast growing research areas. Herein we highlight recent progress in the activation of allylic and benzylic C–F bonds for the synthesis of functionalized molecules. S_N2' reactions of allylic difluoro and trifluoro compounds as well as transition-metal-catalyzed (nickel, palladium, platinum and copper) processes are described. The C–F bond activation of 3-fluoropropenes was achieved with platinum- or organocatalysis. Benzylic C–F bond activation was realized with magnesium by deprotonation leading to the formation of reactive quinone methide intermediates and with hydrogen bond donors by forming strong F···H interactions.

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Introduction

The incorporation of fluorine to organic molecules can dramatically alter the reactivity, chemical and biological properties, and physiological activity. Fluorine can have a large influence on the acidity or basicity of functional groups by shifting the pK_a value by several orders of magnitude.[1] It may also change the molecular conformation[2] and generally increases the stability of hydrocarbons.[3] For instance, fluorine substituents have shown to affect the metabolic stability, lipophilicity, and the binding affinity of many drugs.[4] These unique properties that fluorine substitution can achieve in pharmaceuticals, agrochemicals, and materials have led to an increased interest in fluorine chemistry.[5] It is therefore not surprising that the synthesis of fluorine containing molecules as well as the selective activation or cleavage of C–F bonds has emerged as a lively research area.

Fluorine is the most electronegative element in the periodic table and the C–F bond, which is the strongest bond in organic chemistry (CH_3–F: 115 kcal mol^{-1}; CH_3–H bond: 105 kcal mol^{-1}), is highly polarized with the electron density being located on fluorine.[6] Thus, the cleavage of C–F bonds often requires harsh reaction conditions. However, allylic and benzylic fluorides differ in that respect by having a lower activation barrier. For instance, geminal trifluoro allylic compounds react via a S_N2' pathway with hard and soft nucleophiles to form 3-substituted-1,1-difluoroalkenes under mild

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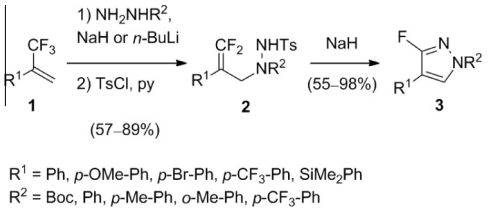
conditions.[7] The high reactivity of trifluoromethylated alkenes toward nucleophiles results from the electron-withdrawing resonance effect ($\sigma_R = 0.16$) and the inductive effect ($\sigma_I = 0.38$) of a trifluoromethyl group attached to an alkene. The low LUMO of the double bond facilitates the nucleophilic attack. In 3,3-difluoropropenes ($\sigma_I = 0.29$, $\sigma_R = 0.03$) and 3-fluoropropenes ($\sigma_I = 0.15$, $\sigma_R = -0.04$) the inductive and resonance effects are less pronounced.[8] Therefore, reactions of 3,3-difluoropropenes are restricted to metal-catalyzed reactions,[9] the addition of soft nucleophiles (e.g., organocopper and organoaluminum reagents),[10] and reductions with organocopper or aluminum reagents,[11] samarium diiodide[12] or *N*-heterocyclic carbenes.[13] In this digest we will focus on recent advances in allylic and benzylic C–F bond activation. A general review on C–F bond activation by Uneyama[14] and reviews on aromatic C–F bond activation by Perutz[15] and Weaver[16] are available.

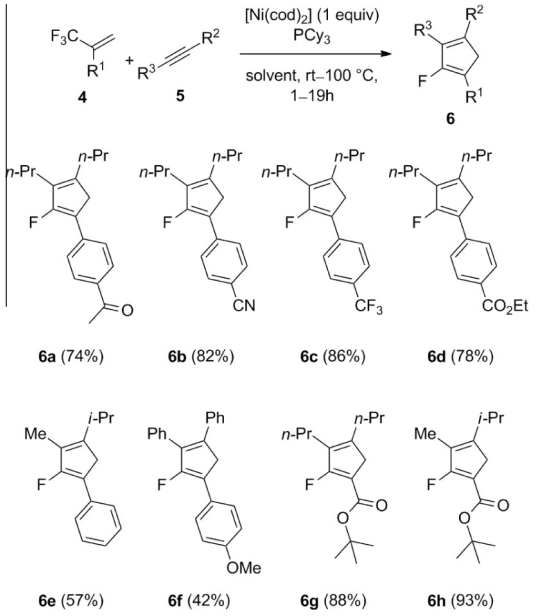
Activation of allylic trifluoromethyl groups

Fuchibe et al. described a simple method for the construction of fluorinated ring systems such as fluoropyrazoles using hydrazines as bifunctional nucleophiles.[17] The S_N2' reaction of 2-trifluoromethyl-1-alkenes **1** with hydrazines and sodium hydride or *n*-butyl lithium as the base gave 1,1-difluoro-1-alkenes **2** which were cyclized in an addition–elimination sequence (S_NV reaction) to the corresponding 3-fluoropyrazoles **3** in good to excellent yield (Scheme 1).

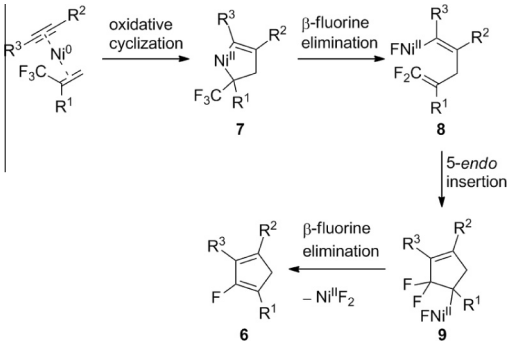
The group of Ichikawa[18] reported the synthesis of substituted cyclopentadienes via a nickel-mediated [3+2] cycloaddition. The



Scheme 1. Synthesis of 3-fluoropyrazoles **3** from 2-trifluoromethyl-1-alkenes **1** and hydrazines.



Scheme 2. Nickel(0) mediated synthesis of substituted cyclopentadiene rings from 2-trifluoromethyl-1-alkenes **4** and alkynes **5**.

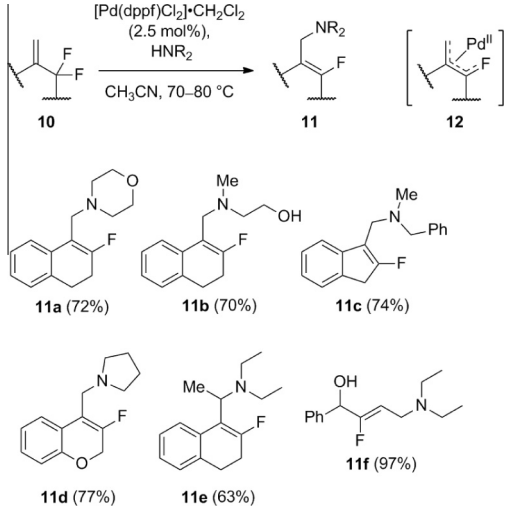


Scheme 3. Proposed mechanism of the nickel(0) mediated synthesis of substituted cyclopentadiene rings.

cyclopentadienes were obtained from the reaction of α-trifluoromethylstyrenes or *tert*-butyl α-trifluoromethylacrylate with symmetrical and unsymmetrical alkynes (Scheme 2). It was proposed that the reaction proceeds via double C–F bond activation of the trifluoromethyl group. The suggested mechanism involves an oxidative cyclization of 2-trifluoromethyl-1-alkenes **4** and alkynes **5** with a nickel(0) species. β-Fluorine elimination affords the alkenyl nickel species **8** which can undergo a 5-*endo* insertion. The second β-fluorine elimination then generates the 2-fluoro-1,3-cyclopentadienes **6** (Scheme 3).

Activation of allylic difluoromethyl groups

In 2010, Paquin and co-workers[19] developed a palladium-catalyzed allylic amination reaction of 3,3-difluoropropenes. Allylic C–F bond activation first leads to an intermediate palladium π-allyl complex **12** (Scheme 4). Nucleophilic attack at the less strongly bound allylic site,[20] and also more sterically accessible carbon atom, affords β-aminofluoroalkenes **11**, which are important non-hydrolyzable peptide isosters.[21] Cyclic and acyclic 3,3-difluoropropenes and various secondary amines could be employed in the reaction scope, including morpholine, pyrrolidine, diethylamine, and *N*-methylbenzylamine. Furthermore, unprotected 2-(methylamino)ethanol and amine hydrochloride salts could be used with the standard reaction conditions. To circumvent the problem of dialkylation when primary amines were employed, a large excess



Scheme 4. Palladium-catalyzed allylic amination of 3,3-difluoropropenes via C–F bond activation.