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Synthesis of Seven-membered Ring Containing Difluoromethylene Unit by $Sc(OTf)_3$-catalyzed Activation of Single C–F Bond in CF_3 Group

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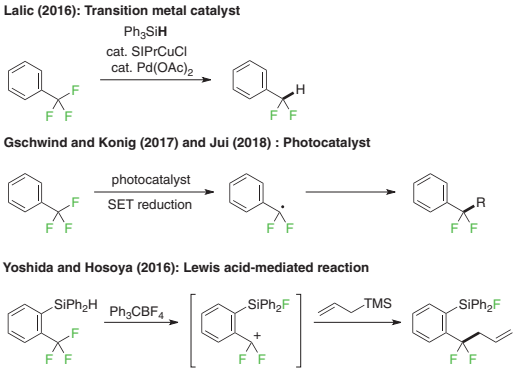
A $Sc(OTf)_3$-catalyzed activation of a single C–F bond in a CF_3 group is described. This reaction has two interesting features: (1) the synthesis of difluoromethylene compounds through Lewis acid-catalyzed activation of a single C–F bond in a CF_3 group, and (2) the selective formation of a seven-membered ring over a five-membered ring.

Keywords: C–F bond activation | Seven-membered ring | Difluoromethylene compound

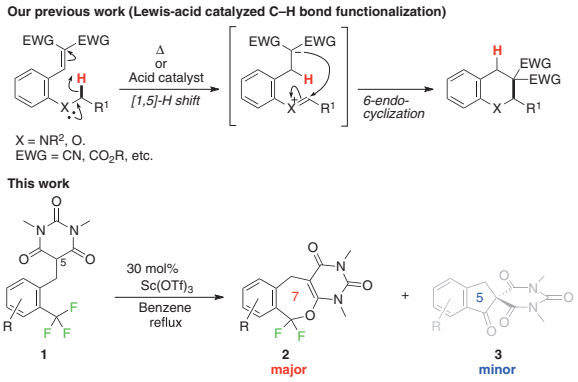
Recently, many organic chemists have shifted their attention to organic fluorine compounds. The main reason for this trend is the important effects fluorine has on pharmaceuticals, that is, the introduction of a fluorine atom to organic molecules significantly enhances their biological activities compared to a non-fluorine molecule.[1] Among the known organic fluorine molecules, those with a difluoromethylene unit have attracted much attention due to their prominent biological activities, such as Tafluprost, Gemcitabine, and Docetaxel analog.[2]

To access the target structure, the mono functionalization of a C–F bond[3–5] in a CF_3 group would be a reliable choice because of the high accessibility of compounds with the CF_3 group. Most of the successful methods reported so far have relied on the cleavage of a C–F bond with the aid of an adjacent activating group, such as a carbonyl group[6] or a vinyl group.[7] Reports of the single C–F bond functionalization of a simple CF_3 group, particularly an aromatic CF_3 group, are scarce.[8] This is difficult to achieve because the C–F bond dissociation energy gradually decreases as the number of fluorine atoms decreases, that is, the activation of a C–F bond in a CF_2 group is easier than that in a CF_3 group. Leckta and co-workers, in a pioneering work in 1997,[9] accomplished the synthesis of a fluorine containing difluoromethylene unit through an intramolecular fluorine transfer from a CF_3 group to a vinyl cation generated from a diazonium salt. However, the chemical yield was quite low (20%). After almost 20 years, four research groups independently reported effective methods. The key reaction in three of the four groups was a single-electron transfer by a transition metal (Pd-Cu catalysis by the Lalic group)[10] and a photoredox catalyst (*fac*-Ir(ppy)$_3$ by Gschwind and König groups,[11a] and *N*-phenylphenothiazine by the Jui group) (Scheme 1).[11b] A Lewis acid version was developed by the Yoshida and Hosoya group, in which installation of an *ortho*-silyl group relative to a CF_3 group was essential.[12] The achievement of a simple Lewis acid-catalyzed single C–F bond activation is not a trivial issue, and the development of a novel and simple method is strongly desired.

Recently, our group has been interested in the hydride shift triggered C(sp^3)–H bond functionalization, namely, internal redox reaction (Scheme 2).[13] In the course of development of new transformations by way of group transfer instead of hydride



Scheme 1. Strategies for activation of single C–F bond in an aromatic CF_3 group.

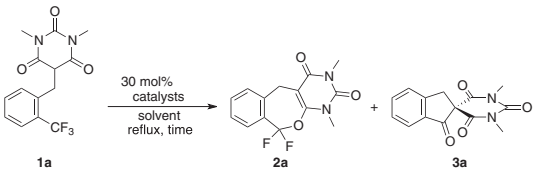


Scheme 2. Formation of difluoromethylene-containing seven-membered ring by single C–F bond activation.

shift,[13l] we examined fluorine group transfer. Instead of achieving the desired reaction, we found a Lewis acid-catalyzed activation of a single C–F bond in an aromatic CF_3 group starting from 1,3-dimethyl barbituric acid **1** having an *ortho*-CF_3 benzyl group at 5-position. This reaction has two interesting features: (1) the synthesis of difluoromethylene compounds through Lewis acid-catalyzed activation of a single C–F bond in a CF_3 group, and (2) the selective formation of a seven-membered ring over a five-membered ring. We report herein the details of this unique reaction.

Table 1 summarizes the results of screening for the reaction conditions. When **1a** was treated with 30 mol % of $Yb(OTf)_3$ in refluxing $ClCH_2CH_2Cl$, the reaction did not proceed, and **1a** was completely recovered (Entry 1). Both $Gd(OTf)_3$ and $La(OTf)_3$ were also ineffective (Entries 2 and 3). Gratifyingly, $Hf(OTf)_4$ exhibited excellent catalytic performance, and C–F bond activation followed by hydrolysis occurred to give indanone derivative

Table 1. Examination of reaction conditions.[a]



Run	Catalyst	Solvent	yield (%)[b]		
			2a	**3a**	**1a**
1	$Yb(OTf)_3$	$ClCH_2CH_2Cl$	0	0	98
2	$Gd(OTf)_3$	$ClCH_2CH_2Cl$	0	0	98
3	$La(OTf)_3$	$ClCH_2CH_2Cl$	0	0	94
4	$Hf(OTf)_4$	$ClCH_2CH_2Cl$	0	66	0
5	$Sc(OTf)_3$	$ClCH_2CH_2Cl$	42	20	0
6	$TiCl_4$	$ClCH_2CH_2Cl$	7	7	52
7	$SnCl_4$	$ClCH_2CH_2Cl$	0	0	98
8	$BF_3 \cdot OEt_2$	$ClCH_2CH_2Cl$	0	0	71
9	$B(C_6F_5)_3$	$ClCH_2CH_2Cl$	0	0	94
10	TfOH	$ClCH_2CH_2Cl$	0	0	94
11	$Sc(OTf)_3$	Benzene	45	8	Trace
12	$Sc(OTf)_3$	Toluene	0	35	0
13	$Sc(OTf)_3$	$C_6H_5CF_3$	0	24	0
14	$Sc(OTf)_3$	CH_3CN	0	0	98
15	$Sc(OTf)_3$	THF	0	0	98
16	$Sc(OTf)_3$	Pyridine	0	0	93

[a]Unless otherwise noted, all reactions were conducted with 0.10 mmol of **1a** in the presence of 30 mol % of catalyst in solvent (1.0 mL) at refluxing temperature. [b]Isolated yield.

3a in good chemical yield (66%, Entry 4). $Sc(OTf)_3$ also showed high catalytic ability, but a slightly different result was observed. Not only indanone **3a** (five-membered ring), but also seven-membered ring adduct **2a** with a difluoromethylene unit was obtained, and the latter one was the major product (**3a**: 20%, **2a**: 42%, respectively, Entry 5). The structures of **2a** and **3a** were determined by X-ray analysis.[14] As described above, careful substrate design and special setting of the reaction conditions were required to activate a single C–F bond in an aromatic CF_3 group.[10–12] The present reaction realized this difficult transformation without special precautions. Another interesting feature of this reaction was the selective formation of a seven-membered (middle-sized) ring over a five-membered ring. To improve this abnormal product selectivity (**2a**/**3a**), further screening for the reaction conditions was conducted. Examination of the acid catalysts suggested that $Sc(OTf)_3$ was the catalyst of choice. Some strong Lewis acids, such as $TiCl_4$, $BF_3 \cdot OEt_2$, $B(C_6F_5)_3$, and Brønsted acid (TfOH), did not promote the reaction at all (Entries 6–10). Then, solvent screening was conducted with $Sc(OTf)_3$ as the optimal catalyst, and it was revealed that the choice of solvent had a significant effect on the selectivity of the two products (**2a**/**3a**). Selectivity was improved in benzene, and seven-membered ring **2a** was obtained in 45% yield (Entry 11). In sharp contrast, indanone **3a** was furnished exclusively in the case of toluene and $C_6H_5CF_3$ (35% and 24%, respectively, Entries 12 and 13). Polar solvents, such as CH_3CN, THF, and pyridine, completely inhibited the reaction, and **1a** was recovered (Entries 14–16).

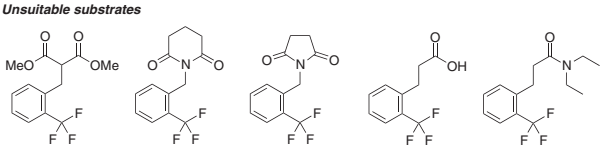


Figure 1. Importance of the 1,3-dimethyl barbituric acid moiety.

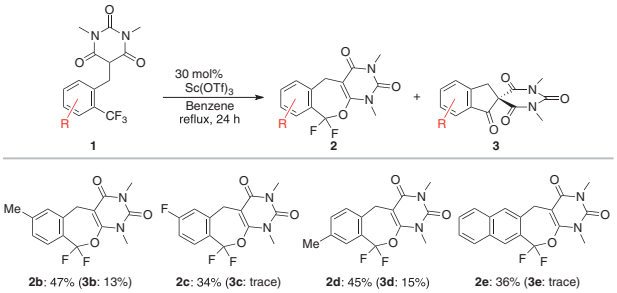


Figure 2. Substrate scope.

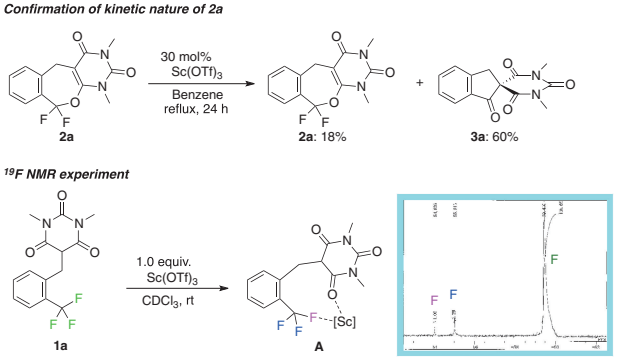


Figure 3. Confirmation of kinetic control and ^{19}F NMR experiment.

The employment of 1,3-dimethyl barbituric acid was indispensable to achieve the reaction (C–F bond activation) (Figure 1). Various 1,3-dicarbonyl moieties, such as dimethyl malonate, piperidine-2-6-dione, and pyrolidine-2-5-dione, and carboxylic acid and amide moiety resulted in the recovery of the starting materials.

The substrate scope of this seven-membered ring formation is illustrated in Figure 2. The selective formation of seven-membered rings was observed when substrates **1b–d** with methyl and fluorine groups on the aromatic ring were used, and corresponding difluoromethylene compounds **2b–d** were obtained in moderate chemical yields (34–47%). The construction of a tetracyclic adduct was also attainable from a naphthyl-type substrate (**2e**: 36%).

To obtain some insights into the reaction mechanism, additional experiments were conducted (Figure 3). Exposure of seven-membered ring adduct **2a** to the optimized reaction conditions resulted in the formation of indanone **3a** (60%). This suggests that seven-membered ring adduct **2a** was the kinetic product. Although the strengths of each peak were quite weak due to the low solubility of $Sc(OTf)_3$, two new peaks with 1:2 ratio were observed in the ^{19}F NMR spectrum by mixing **1a** and

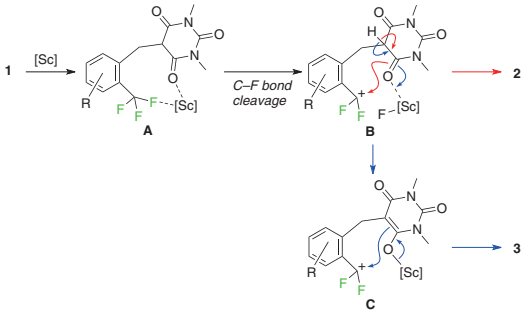


Figure 4. Proposed reaction mechanism.

$Sc(OTf)_3$ in $CDCl_3$ (**1a**:$Sc(OTf)_3$ = 1:1 molar ratio), indicating some interaction taking place between one of the fluorine atoms and $Sc(OTf)_3$.[15] The absence of any changes of the fluorine peaks upon mixing $C_6H_5CF_3$ and $Sc(OTf)_3$ (1:1 molar ratio) suggests that one of the carbonyl oxygens of barbituric acid supported the formation of a complex of **1a** and $Sc(OTf)_3$, like **A** in Figure 3.

Based on the above experiments, the proposed reaction mechanism is illustrated in Figure 4. At first, one of the fluorine atoms in the CF_3 group and a carbonyl oxygen in barbituric acid coordinate to $Sc(OTf)_3$, resulting in the activation of a C–F bond. The preferential formation of a seven-membered ring over a five-membered ring could be explained on the basis of the principle of least motion.[16] From cationic intermediate **B**,[17] the seven-membered ring formation (red arrow) would occur in one step while maintaining the structure of **B**. On the other hand, a two-step sequence (enolization followed by intramolecular nucleophilic addition, blue arrow) would be required for the formation of **3**. As a result, seven-membered ring adducts **2** were obtained in a highly selective manner.

In summary, we have developed a direct route to heterocycles having a difluoromethylene unit via the activation of a single C–F bond in the CF_3 group. Although it is not clear why the single C–F bond activation occurred even with strong Lewis acid catalysis, the reaction described herein offers a new entry in the C–F bond activation field. Mechanistic studies based on theoretical calculations are under way in our laboratory, and will be reported in due course.

Supporting Information is available on https://doi.org/10.1246/cl.190280.

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