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Difluoromethylation

Direct α-Siladifluoromethylation of Lithium Enolates with Ruppert-Prakash Reagent via C–F Bond Activation

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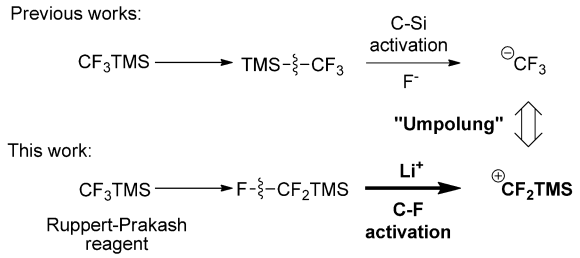
Abstract: The direct α-siladifluoromethylation of lithium enolates with the Ruppert–Prakash reagent (CF_3TMS) is shown to construct the tertiary and quaternary carbon centers. The Ruppert–Prakash reagent, which is versatile for various trifluoromethylation as a trifluoromethyl anion (CF_3^-) equivalent, can be employed as a siladifluoromethyl cation ($TMSCF_2^+$) equivalent by C–F bond activation due to the strong interaction between lithium and fluorine atoms.

Recently, great attention has been focused on trifluoromethylated compounds in view of their important applications in biological and material science.[1] Synthetic methods for these compounds are generally classified into three types for nucleophilic, electrophilic, and radical trifluoromethylations. In particular, in the nucleophilic case, stable and commercially available trifluoromethyltrimethylsilane (CF_3TMS; Ruppert–Prakash reagent)[2] as a nucleophilic trifluoromethyl anion (CF_3^-) equivalent has played a key role in the development of trifluoromethylations (Scheme 1, top).[3] On the other hand, synthesis of



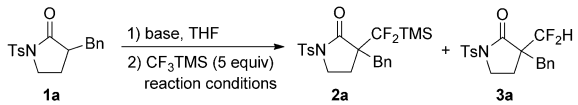
Scheme 1. Umpolung of CF_3TMS by C–F bond activation

gem-difluorinated cyclopropanes and cyclopropenes from alkenes and alkynes by using CF_3TMS as a difluorocarbene (CF_2:) equivalent has recently been reported by Hu and Prakash.[4] However, C–C bond-forming reactions directly by using CF_3TMS as an electrophilic reagent have never been reported.

C–F bond activation has also attracted current interest, in view of the challenge of activating the inert C–F bonds.[5,6] However, only limited examples have so far been reported even by using transition-metal-catalyzed cross-coupling reactions on sp^2 carbon.[7] Based on this background, we have developed direct difluoromethylation and iododifluoromethylation of lithium enolates with CF_3H and CF_3I as electrophilic reagents through C–F bond activation by strong interaction between lithium and fluorine atoms.[8] Herein, we report the C–F bond activation of CF_3TMS based on a polarity inversion approach, namely, the umpolung[9] of CF_3TMS, to a siladifluoromethyl cation ($TMSCF_2^+$) from the trifluoromethyl anion (CF_3^-) equivalent (Scheme 1, bottom). In this approach, the direct α-siladifluoromethylation of lithium enolates with CF_3TMS gave α-siladifluoromethylated carbonyl compounds with tertiary and quaternary carbon centers, which can be converted to various derivatives with difluoromethylene (-CF_2-) group by C–C bond-forming reactions. The difluoromethylene group is regarded as a bioisostere for an ether functionality in biological science.[1d,10] The introduction of the difluoromethylene group into organic compounds[11] is thus biologically and synthetically important,[10,12] as typically shown in difluoromethylenated analogues of nucleosides.[10c]

Initially, the α-siladifluoromethylation of lithium enolates prepared from γ-lactam **1a** and lithium hexamethyldisilazide (LHMDS; 1 equiv) was found with CF_3TMS (5 equiv) to provide

Table 1. Effect of the base in siladifluoromethylation.[a]



1a **2a** **3a**

Entry	Base ([equiv])	T [°C]	t [h]	Yield [%][b] **2a**/**3a**
1	LHMDS (1)	−78	0.5	18/3
2	KHMDS (1)	0	2	0/0
3	NHMDS (1)	0	2	0/0
4	LTMP (1)	−78	0.5	<1/0
5	LDA (1)	−78	0.5	0/0
6	*n*BuLi (1)	−78	0.5	0/0
7	LHMDS (2)	−78	0.5	68[c]/15[c]
8[d]	LHMDS (2)	−78	0.5	27/24
9	LHMDS (2)	RT	5	41/14

[a] Conditions: after the addition of base (0.1 or 0.2 mmol; ≈1.0 M in THF or Et_2O) to **1a** (0.1 mmol) in THF (0.1 mL), CF_3TMS (0.5 mmol) was added to the mixture at −78 °C. [b] Yields were determined by using ^{19}F NMR spectroscopy analysis with benzotrifluoride as an internal standard. [c] Isolated yields. [d] Two equivalents of CF_3TMS were used.

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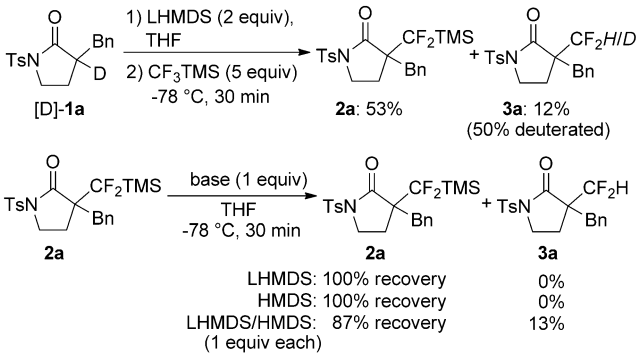
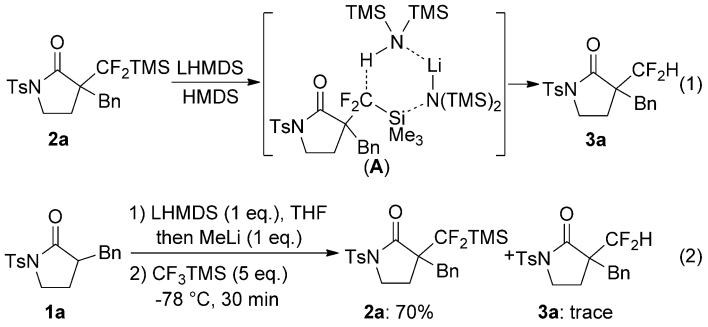
α-siladifluoromethylated product **2a** along with desilylated product **3a** in yields of 18 and 3%, respectively (Table 1, entry 1). The structure of the all-carbon quaternary center attached to siladifluoromethyl was confirmed by X-ray analysis of **2a**; the bulky trimethylsilyl group is oriented far from benzyl group due to steric repulsion.[13] In sharp contrast to lithium, the enolates with other alkaline metals (K and Na) could not mediate the reactions even at higher temperature because of their lower affinity with the fluorine atom (Table 1, entries 2 and 3). The reactions with other lithium bases, LTMP (lithium 2,2,6,6-tetramethylpiperidine), LDA (lithium diisopropylamide), and *n*BuLi, did not proceed at all (Table 1, entries 4–6). Significantly, lithium enolates prepared from two equivalents of LHMDS, namely mixed aggregate (see below, Scheme 8),[8b] dramatically enhanced the reactivity to afford product **2a** in 68% yield, whereas undesired **3a** still appeared in 15% yield (Table 1, entry 7). Decreasing the amount of CF_3TMS or increasing the reaction temperature decreased yields (Table 1, entries 8 and 9). Of the coordinating solvents examined, THF was found to be the best solvent for this reaction.

We proposed that desilylated product **3a** could be derived by protonation with hexamethyldisilazane (HMDS), which was generated in situ by deprotonation of **1a** with LHMDS. Indeed, when starting from α-deuterated [D]-**1a**, deuterated α-difluoromethyl product [D]-**3a** was obtained under the optimized conditions ([H]-**3a**: 6% yield, [D]-**3a**: 6% yield; Scheme 2, top). However, α-siladifluoromethylated product **2a**, with one equivalent of LHMDS or HMDS separately, did not provide any α-difluoromethyl product **3a**, and **2a** was thus completely recovered (Scheme 2, bottom). Only in the presence of one equivalent each of LHMDS and HMDS, which were derived from deprotonation of **1a** with two equivalents of LHMDS, α-siladifluoromethylated **2a** was converted into desilylated **3a** in 13% yield (Scheme 2, bottom).



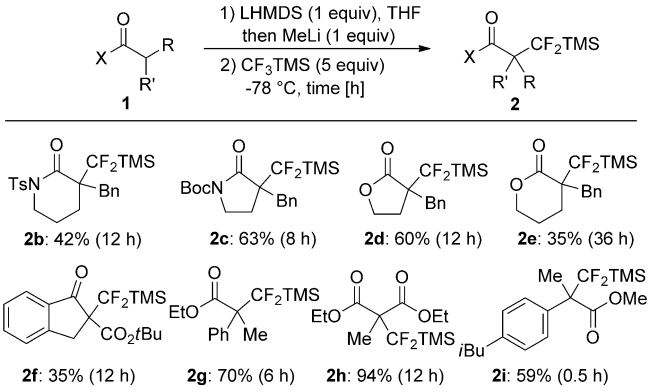
Scheme 2. Effect of additional lithium base.

The results shown in Scheme 2 imply that the undesired protodesilylation presumably proceeds via a six-membered cyclic chelate (**A**) that involves both LHMDS and HMDS in a ratio of 1:1 with **2a** (Scheme 3, top). To retard the protodesilylation with HMDS, deprotonation of the resulting HMDS was thus executed with further addition of alkyllithium because the stable mixed aggregate could be generated without HMDS (see below; Scheme 8).[8] After investigation of various additional alkyllithium species, it was found that methyllithium (MeLi) selectively gave α-siladifluoromethylated product **2a** in 70% yield without formation of protodesilylation product **3a** (Scheme 3, bottom).



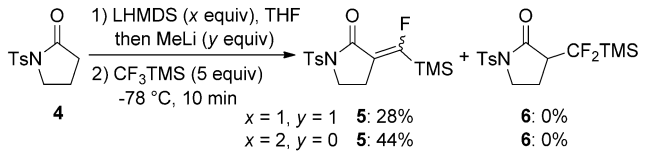
Scheme 3. Control of protodesilylation by mixed lithium base.

α-Siladifluoromethylation of the lithium enolates generated from several lactams, lactones, and esters was performed under optimized reaction conditions by using LHMDS (1 equiv) and then MeLi (1 equiv; Scheme 4). Six- and five-membered lactams, irrespective of the protecting group, gave α-siladifluoromethylated products **2b**, **c** in 42 and 63% yields. This is in sharp contrast to our iododifluoromethylation,[8a] of which the ratio with respect to trifluoromethylation is critically dependent on the nature of the lactam protecting group. The reactions of lactones also led to corresponding products **2d**–**f**. As compared with lactones, esters showed high reactivity to afford products **2g**–**i** in good to high yields. In particular, ibuprophene methyl ester **1i** provided α-siladifluoromethyl ibuprophene derivative **2i** in 59% yield.



Scheme 4. Siladifluoromethylation of α-disubstituted carbonyl compounds. Conditions: After addition of LHMDS (1.0 M in THF; 0.1 mmol, 100 μL) followed by MeLi (1.1 M in Et_2O; 0.1 mmol, 91 μL) to **1** (0.1 mmol) in THF (0.1 mL), CF_3TMS (0.5 mmol) was added to the mixture at −78 °C. Isolated yields are given.

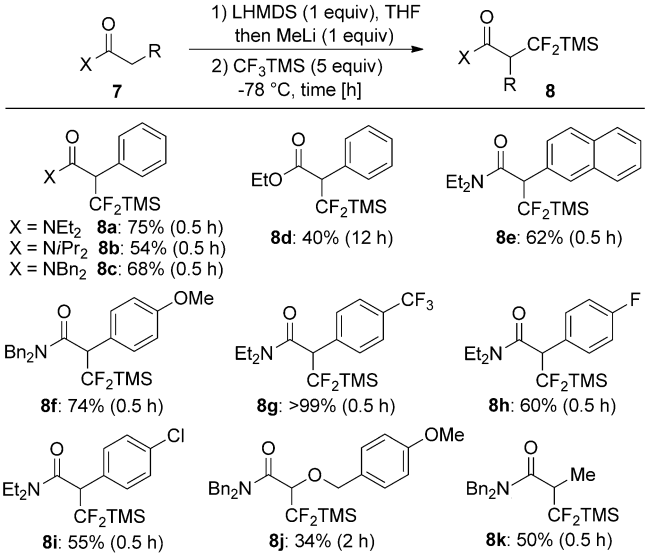
To extend the substrate scope, we decided to construct tertiary carbon centers even with acidic α-protons (Scheme 5). The



Scheme 5. Defluorination of a cyclic compound

use of tosyl (Ts)-protected cyclic lactam **4** under the optimized reaction conditions did not lead to desired product **6** but to monofluoroenone **5** in 28% yield, which could be obtained through α-deprotonation of **6** by the parent enolate or base followed by β-F elimination. In the presence of two equivalents of LHMDS, **5** was obtained as the sole product in 44% yield.

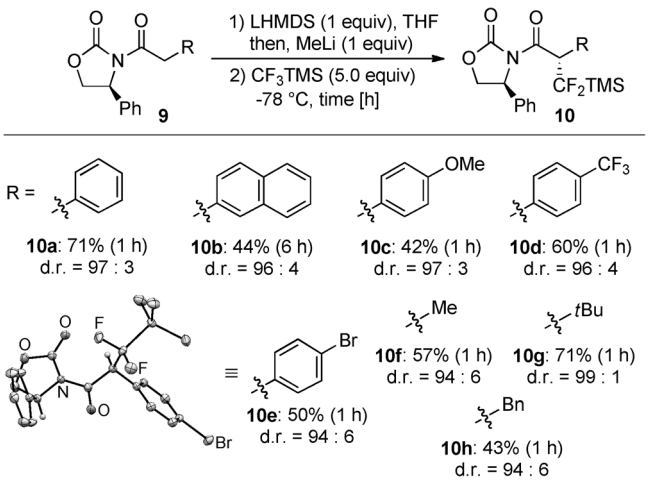
After evaluation of various carbonyl compounds, it was found that the reactions of acyclic amides and ester **7** under optimized conditions led to α-siladifluoromethylated products **8**, which suppresses β-F elimination during the course of the reaction (Scheme 6). Optimization of N-substituents on amides



Scheme 6. Siladifluoromethylation of α-monosubstituted amide compounds. Conditions: After addition of LHMDS (1.0 M in THF; 0.1 mmol, 100 μL) followed by MeLi (1.1 M in Et_2O; 0.1 mmol, 91 μL) to **7** (0.1 mmol) in THF (0.1 mL), CF_3TMS (0.5 mmol) was added to the mixture at −78 °C. Isolated yields are displayed. Due to the low solubility of **7f**, 0.5 mL THF was used.

7a–c showed that the ethyl group gave the best yield (75% yield). Esters also afforded corresponding product **8d** with slight decrease in reactivity. Various α-aryl amides **7e–i** can be employed in this reaction, regardless of the electron density on the aromatic ring. Significantly, amide **7g** with *p*-trifluoromethyl benzene gave an almost quantitative yield. α-Methyl and -oxy amides also provided the desired products (**8j** and **k**). The reactions of *N*,*N*-diethyl amides instead of the *N*,*N*-dibenzyl counterpart (**7f** and **j**, **k**) resulted in decomposition of the lithium enolates.

Encouraged by the construction of a tertiary carbon center without defluorination, we also examined the diastereofacial

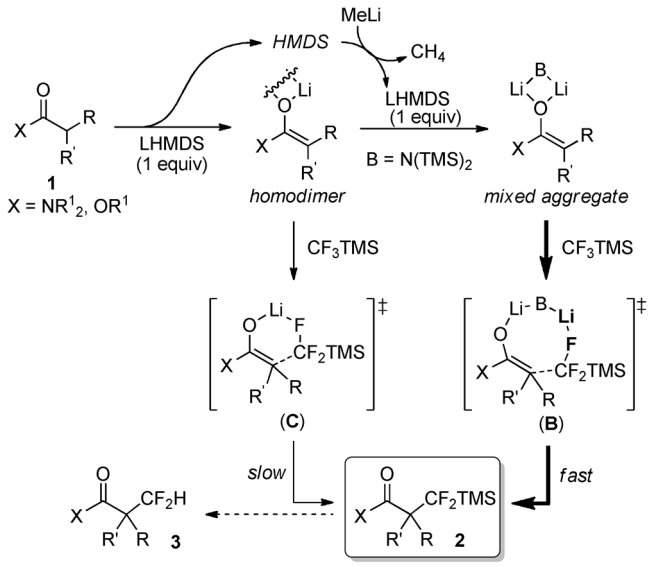


Scheme 7. Synthesis of chiral siladifluoromethylated compounds. Conditions for **10a**, **c**, **d**, **f**, and **h**: After addition of LHMDS (1.0 M in THF; 0.1 mmol, 100 μL) followed by MeLi (1.1 M in Et_2O; 0.1 mmol, 91 μL) to **9** (0.1 mmol) in THF (0.1 mL), CF_3TMS (0.5 mmol) was added to the mixture at −78 °C. Conditions for **10b**, **e**, and **g**: LHMDS (2 equiv) was used instead of LHMDS and MeLi (1 equiv each). Isolated yields of major diastereomers are displayed.

α-siladifluoromethylation of α-monosubstituted carbonyl compounds **9** with a chiral oxazolidinone auxiliary (Scheme 7). As the substituent on chiral carbon center, the phenyl group exhibited the best diastereoselectivity. Under optimized reaction conditions, oxazolidinone substrates **9a–e** with not only electron-rich but also electron-deficient aryl groups led to corresponding products **10a–e** in high diastereoselectivities (dr > 94:<6). The structure of **10e** was determined by X-ray analysis of the single crystal and consequently the chiral center of the major diastereomer at the α-position was found to be *S*-configuration. Oxazolidinone substrates **9f–h** with alkyl groups, such as methyl, *tert*-butyl, and benzyl, were also amenable to the highly diastereoselective α-siladifluoromethylation.

To gain an insight into the mechanism of our novel reaction, we initially investigated whether difluorocarbene (CF_2:), generated by decomposition of CF_3TMS, is a reactive species for α-siladifluoromethylation of lithium enolates. The addition of electron-rich alkenes (e.g., tetramethylethylene) was examined under these reaction conditions, but found not to provide *gem*-difluorocyclopropanes even at room temperature.[4] After one equivalent of LHMDS was added to the solution of CF_3TMS in THF at −78 °C, more than 95% of CF_3TMS remained, which implies that the difluorocarbene mechanism is highly unlikely in the present α-siladifluoromethylation, although only a trace amount of CF_3H was observed in ^{19}F NMR spectroscopy.

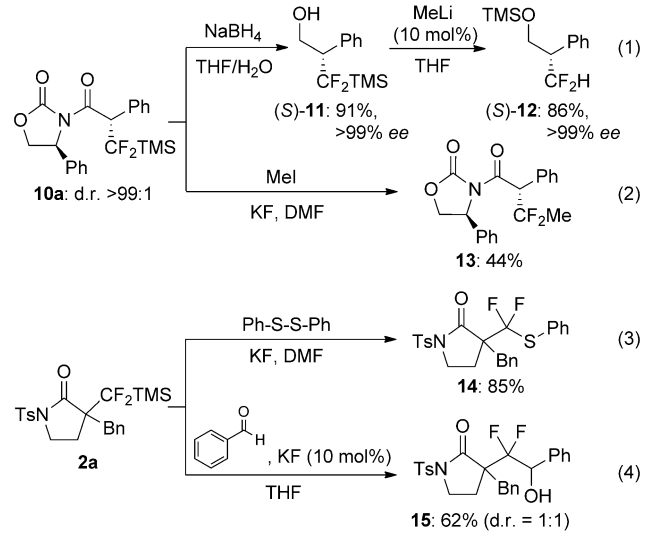
Based on the results above, we proposed that the reaction does not involve difluorocarbene mechanism but a C–F bond activation mechanism as shown in Scheme 8.[8b] Additions of one equivalent of LHMDS followed by MeLi to α-carbonyl compounds give the mixed aggregate without generation of HMDS as a proton source. Subsequently, the reaction of CF_3TMS with the mixed aggregate leads to eight-membered **B** to form α-siladifluoromethylated products **2** selectively by C–F bond activation based on the strong Li–F interaction. The S_N2-



Scheme 8. Proposed mechanism of α-siladifluoromethylation

type pathway[14] via eight-membered **B** is faster than the pathway via six-membered **C** from homo-dimer with CF_3TMS because the addition of one more equivalent of LHMDS for lithium enolate significantly accelerates the α-siladifluoromethylation (Table 1, entries 1 vs. 7).[8] Only in the presence of HMDS and LHMDS (1 equiv each) without further addition of MeLi does protodesilylation of **2** leading to difluoromethylated products **3** take place via chelate (**A**; see above: Schemes 2 and 3).

Diastereomer mixture **10a** (dr 97:3) could easily be separated by using silica-gel column chromatography to give the diastereopure **10a** (dr > 99:1). The reduction of **10a** in the presence of $NaBH_4$ (4 equiv) provided the corresponding alcohol (*S*)-**11** in 91% yield without racemization. Treatment of (*S*)-**11** with a catalytic amount of MeLi led to difluoromethylated (*S*)-**12** through a Brook rearrangement (Scheme 9, reaction 1). The



Scheme 9. Applications to C–C bond-forming reactions

methylation with MeI also proceeded by virtue of the reactive silyl functionality (Scheme 9, reaction 2). Additionally, **2a** with an adjacent quaternary carbon center was transformed to corresponding thioether **14** and alcohol **15** with disulfide and benzaldehyde, respectively, by using spray dry potassium fluoride (Scheme 9, reactions 3 and 4).

In summary, we have described the first examples of C–F bond activation of the Ruppert–Prakash reagent (CF_3TMS) as an electrophile through polarity inversion to a siladifluoromethyl cation ($TMSCF_2^+$). This direct α-siladifluoromethylation of lithium enolate with CF_3TMS proceeded by C–F bond activation and C–C bond formation and led to construction of α-siladifluoromethyl-attached quaternary and tertiary carbon centers with high synthetic and biological potential. Additionally, the reaction of carbonyl compounds with a chiral oxazolidinone auxiliary produced chiral α-siladifluoromethylated compounds in high diastereoselectivities.

Experimental Section

General procedure for α-siladifluoromethylation of α-disubstituted carbonyl compounds (Scheme 3, bottom)

Lithium hexamethyldisilazide (LHMDS; 1.0 M in THF, 0.10 mL, 0.10 mmol) was added dropwise to a solution of 3-benzyl-1-tosylpyrrolidin-2-one (**1a**; 32.9 mg, 0.10 mmol) in THF (0.1 mL) at −78 °C under argon. The solution was stirred at 0 °C for 30 min, and then MeLi (1.1 M in Et_2O, 91 μL, 0.1 mmol) was added at −78 °C. After the solution was stirred for 10 min, CF_3TMS (74 μL, 0.50 mmol) was added at −78 °C. After stirring for 30 min at −78 °C, the reaction mixture was quenched with a mixture of H_2O and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined layers were washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexane) to afford difluoro(trimethylsilyl)-methylated product **2a** (70% yield). The structure of **2a** was clarified by X-ray analysis of the single crystal.

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Keywords: C–F activation · difluoromethylation · lithium enolate · Ruppert–Prakash reagent · umpolung

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