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Regioselective 1,4-trifluoromethylation of α,β-enones using '*protect-in-situ*' methodology

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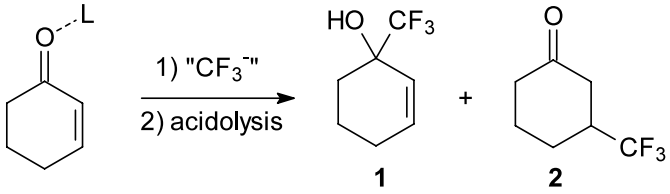
Abstract—In a convenient and efficient procedure, the nucleophilic 1,4-trifluoromethylation of several α,β-enones using (trifluoromethyl)trimethylsilane was achieved. The high regioselectivity of the reaction has been reached by blocking the carbonyl moiety of the electrophile with a bulky aluminum-centered Lewis acid.

The direct nucleophilic introduction of perfluoroalkyl and, especially, trifluoromethyl moieties is a very important route to synthesize compounds with applications in agrochemistry, the pharmaceutical industry and material sciences.[1,2] Numerous methods for trifluoromethylation have been reported previously,[2] with one of the most useful reagents being (trifluoromethyl)trimethylsilane.[3,4] A number of electrophiles (carbonyl compounds,[5,6] imines,[7] alkyltriflates,[8] aromatics,[9] acyl halides,[5b,10] esters[6,11] and amides[4a]) have been successfully trifluoromethylated using (trifluoromethyl)trimethylsilane under nucleophilic initiation.[4] However, the selective nucleophilic introduction of CF_3 into the β-position of α,β-unsaturated compounds remains a challenging problem in synthetic organic chemistry. To the best of our knowledge, only 1,2-addition products have been obtained using different reagents (CF_3SiMe_3/Nu, the *O*-silylated adduct of CF_3H and *N*-formylmorpholine/CsF or $CF_3H/N(SiMe_3)_3$/DMF/Me_4NF).[4a,5,6,11–13]

The only examples of α,β-enones successfully 1,4-perfluoroalkylated by R^FSiMe_3 reagents ($R^F = CF_3$, C_2F_5) under Me_4NF catalysis are the 2-perfluoroalkylchromones, as recently reported by us.[14] The reason for such an anomalous behavior of 2-perfluoroalkylchromones is possibly the additional $-I$ activation of the β-position of the α,β-unsaturated systems by the R^F moiety. This 1,4-perfluoroalkylation reaction thus provides an access to 2,2-bis(perfluoroalkyl)chroman-4-one derivatives representing fluorinated analogs of natural products. As a logical development and continuation of this work we report here a new method for the highly regioselective 1,4-trifluoromethylation of α,β-enones with CF_3SiMe_3 using the '*protect-in-situ*' methodology.

In his pioneering work Prakash has already reported[5] that the reaction of cyclohex-2-enone with CF_3SiMe_3 in the presence of a catalytic amount of Bu_4NF proceeds predominantly via 1,2-addition, yielding a 90:10 mixture of compounds **1** and **2** (total yield 60%) after hydrolysis. The same reaction carried out in the presence of CsF was even more regioselective, furnishing the 1,2-addition product in 96% isolated yield.[12c] Thus, we chose cyclohex-2-enone as a model in the search for a general method for 1,4-trifluoromethylation.



Scheme 1.

Keywords: nucleophilic addition; (trifluoromethyl)trimethylsilane; trifluoromethylation; regioselectivity.

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Organocopper derivatives have been extensively studied and are extremely useful reagents for selective 1,4-alkylation.[15] In particular, it has been reported,[16] that Michael acceptors react with EtOOC–CF_2Cu to form 1,4-addition products. Therefore we started our investigation using CF_3Cu as the source of the trifluoromethyl moiety. Unfortunately, attempts with this reagent generated in situ (CF_3SiMe_3/Me_4NF/CuI_{cat}/THF system) as well as with pre-generated 'CF_3Cu' (DMF/NMP solution) were unsuccessful. In the first case, only the 1,2-adduct **1** was obtained. The last reaction resulted in a mixture of unidentified compounds, where no products **1** or **2** were detected—both at ambient and at elevated temperature (Scheme 1, Table 1, entries 1–3).

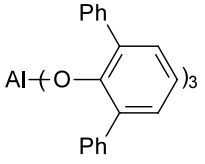
Over the last 15 years Yamamoto's group has developed a new approach for selective 'discrimination' of a carbonyl moiety in the presence of other electrophilic centers. The central point of this method is an intermediary complexation of the C=O group with a bulky aluminum-centered Lewis acid preventing addition of the nucleophile at this position (Fig. 1).[17] The derived complex can be easily decomposed after the addition step to give the desired product. The importance of this '*protect-in-situ*' methodology can be demonstrated by the reaction of cyclohex-2-enone with C_2F_5Li. Under 'normal' conditions, that is without Lewis acid protection, 1,2-pentafluoroethylation occurs exclusively.[18] In contrast, the intermediary complexation with a bulky aluminum-centered Lewis acid gave the 1,4-adduct.[19] However, due to the instability of CF_3Li[2] the most intriguing and important problem—selective β-trifluoromethylation—has not been solved.[19]

Thus, we have attempted to incorporate this '*protect-in-situ*' methodology to trifluoromethylation via CF_3SiMe_3. Reactions of complexed cyclohex-2-enone with the CF_3SiMe_3/Nu system were investigated, where the bulkiness of the aluminum phenoxide (L) and the nature and stoichiometry of the nucleophilic initiator (Nu) were varied (Scheme 1, Table 1, entries 4–12). Dichloromethane was chosen as the solvent, as it was earlier found to be the optimal reaction medium for such Al-mediated transformations.[17,19] From the aluminum phenoxides investigated, ATPH proved to be the best in our case. As for the nucleophilic initiator,

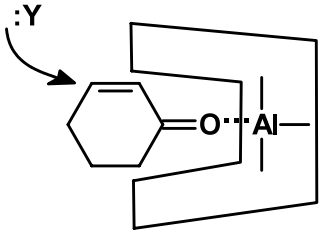
Table 1. Trifluoromethylation of cyclohex-2-enone

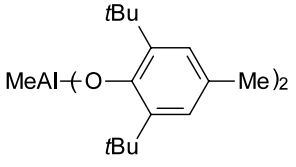
Entry	'CF_3^-'[a]	Nu[b]	L	Solvent	Reaction time (h)	Yield[c] of **1** (%)	Yield[c] of **2** (%)
1	CF_3SiMe_3 (2)/Nu[b] (1)/CuI (0.1)	Me_4NF	–	THF	4	84	–
2	'CF_3Cu'[d]	–	–	DMF/NMP (1:1)	12 (at 20°C)	–	–
3	'CF_3Cu'[d]	–	–	DMF/NMP (1:1)	16 (at 65°C)	–	–
4	CF_3SiMe_3 (3)/Nu (2.5)	Me_4NF	MAD[e,f]	CH_2Cl_2	18	3	5
5	CF_3SiMe_3 (3)/Nu (0.02)	Me_4NF	ATPH[e,f]	CH_2Cl_2	4	–	–
6	CF_3SiMe_3 (3)/Nu (1)	Me_4NF	ATPH	CH_2Cl_2	4	–	25
7	CF_3SiMe_3 (3)/Nu (2)	Me_4NF	ATPH	CH_2Cl_2	4	–	48
8	CF_3SiMe_3 (3)/Nu (3)	Me_4NF	ATPH	CH_2Cl_2	5 (at −35°C)	3	53
9	CF_3SiMe_3 (3)/Nu (3)	Me_4NF	ATPH	CH_2Cl_2	4	1	55
10	CF_3SiMe_3 (2)/Nu (3)	*t*BuOK	ATPH	CH_2Cl_2	19	–	56[g]
11	CF_3SiMe_3 (2)/Nu (1)	2,6-$Ph_2C_6H_3ONa$	ATPH	CH_2Cl_2	22	–	–
12	CF_3SiMe_3 (3)/Nu (2.5)	Me_4NF	$(PhO)_3Al$[f]	CH_2Cl_2	4	59	–

[a] In brackets: equivalents of compound *per* 1 equivalent of cyclohex-2-enone.
[b] Nucleophilic initiator.
[c] Yield based on cyclohex-2-enone, determined by ^{19}F NMR with $PhCF_3$ as internal standard.
[d] Pre-generated by reaction of CF_3SiMe_3 with CuBr in the presence of KF according to ref.[21]
[e] See Figure 1.
[f] Aluminium phenoxides were prepared from the corresponding phenols and Me_3Al according to known procedures: MAD,[22] ATPH and $(PhO)_3Al$.[19]
[g] Isolated yield 46%.



ATPH [**Al** **T**ris(2,6-di**PH**enyl**p**henoxide)]





MAD [**M**ethyl **Al** bis(2,5-**D**i-*tert*-butyl-4-methyl**p**henoxide)]

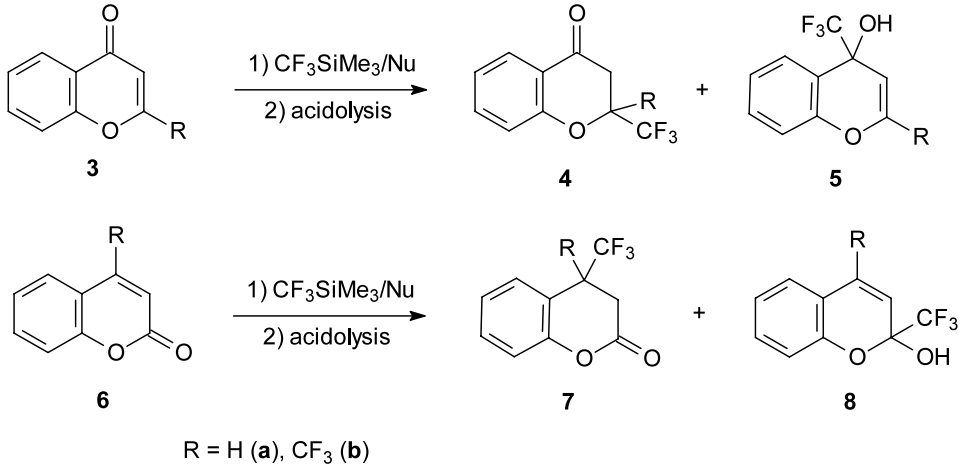
Figure 1.

anhydrous Me_4NF,[20] *t*BuOK and sodium 2,6-diphenylphenoxide were tested. The latter seemed to be the most suitable initiator when ATPH was used as the Lewis acid, but it did not result in CF_3 addition (Table 1, entry 11). The best yield and 1,4-regioselectivity were obtained using *t*BuOK as the nucleophilic initiator. It is notable that the best results were obtained using 3 equivalents of Me_4NF or *t*BuOK (Table 1, entries 9, 10). Hence, the optimized conditions for 1,4-trifluoromethylation of cyclohex-2-enone were: CH_2Cl_2/ATPH (1 equiv.)/CF_3SiMe_3 (2 equiv.)/*t*BuOK (3 equiv.), −78→20°C (entry 10, Table 1), which resulted in the ketone **2** regioselectively 56% yield (by ^{19}F NMR, isolated yield 46%, Table 1).

The behavior of other α,β-enones—chromones **3** and coumarins **6**—towards the CF_3SiMe_3/Nu system was also studied. Compounds **3a**, **6a** and **6b** did not undergo satisfactory 1,4-addition under the usual trifluoromethylation conditions. Treatment of unsubstituted chromone **3a** with (trifluoromethyl)trimethylsilane in the presence of a catalytic amount of Me_4NF (2 mol%) gave no reaction even at 20°C.[23] The use of 1 equiv. of Me_4NF (DME, −30→20°C) resulted in the formation of a complicated mixture of products, in which neither the 1,2- nor the 1,4-adduct could be identified. In the case of coumarins **6**, mixtures of 1,2- and 1,4-adducts were generated, and were significantly enriched with the former (^{19}F NMR yields: 53% versus 8% for **6a**, and 44% versus 1% for **6b**).[24] On the other hand, the pre-complexation of compounds **3a** and **6** with ATPH[25] in CH_2Cl_2 resulted in the products of 1,4-addition **4a**[26] and **7** with good regioselectivity and in satisfactory yields (Scheme 2, Table 2, entries 1, 3, 4).

It was previously found[14] that the reaction of 2-trifluoromethyl substituted chromone **3b** with CF_3SiMe_3 carried out in the presence of Me_4NF (2 mol%) without intermediary complexation also led to a mixture of 1,2- and 1,4-addition products in 9 and 77% yields, respectively. In contrast, applying the '*protect-in-situ*' protocol during the trifluoromethylation of **3b** resulted in the formation of the 1,4-adduct **4b** as the only product of trifluoromethylation (Scheme 2, Table 2, entry 2).[28]

In summary, we have developed a novel method for the regioselective 1,4-trifluoromethylation of α,β-enones by treating the substrate protected with a bulky aluminum Lewis acid using (trifluoromethyl)trimethylsilane and a threefold excess of the nucleophilic initiator. This '*protect-in-situ*' protocol is currently the sole synthetic method for obtaining some type of β-trifluoromethylated carbonyl compounds on a preparative scale, and may provide a useful route to otherwise inaccessible fluorinated molecules for synthetic and practical applications. Further studies on the scope and applicability of this method to regio- and stereoselective 1,4-polyfluoroalkylation of α,β-unsaturated substrates using R^FSiMe_3 reagents ($R^F = CF_3$ and higher homologues) and chiral phenoxides as well as Lewis acid



Scheme 2.

Table 2. Trifluoromethylation of compounds **3**, **6**

Entry	Starting compound	Products	Yield[a] of 1,4-addition product (**4**, **7**) (%)	Yield[a] of 1,2-addition product (**5**, **8**) (%)	Nu[b]	Reaction time (h)
1	**3a**	**4a**, **5a**	48 (30)[c]	–	*t*BuOK	12
2	**3b**[27a]	**4b**, **5b**	72	–	Me_4NF	16
3	**6a**	**7a**, **8a**	35 (20)[c]	–	*t*BuOK	11
4	**6b**[27b]	**7b**, **8b**	61	6	Me_4NF	6

[a] Yield based on α,β-enone, determined by ^{19}F NMR with $PhCF_3$ as internal standard.
[b] Nucleophilic initiator (3 equivalents per 1 equivalent of α,β-enone).
[c] Isolated yield in brackets.

protection of other types are currently in progress in our group and will be published elsewhere.

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25. 2,6-Diphenylphenol used for ATPH synthesis was recovered after hydrolysis of the complex and work up of the reaction mixture in all cases.
26. **2-Trifluoromethylchroman-4-one** (**4a**). A 2 M heptane solution of Me_3Al (1.14 mL, 2.26 mmol) was added dropwise to a stirred solution of 2,6-diphenylphenol (1.67 g, 6.79 mmol) in CH_2Cl_2 (15 mL) at room temperature and the resulting solution was stirred for 30 min to furnish ATPH in heptane/CH_2Cl_2. The solution was cooled to −55°C and chromone **3a** (0.33 g, 2.26 mmol) was added at this temperature to give the **3a**·ATPH complex. The solution was cooled to −78°C, stirred for 5 min, then CF_3SiMe_3 (0.64 g, 4.51 mmol) was added followed by *t*BuOK (0.76 g, 6.79 mmol) portionwise at −78°C. The mixture was allowed to warm (ca. 4 h) to room temperature and stirred for 8 h. The reaction mixture was treated with 5% hydrochloric acid (ca. 20 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined extracts were washed with water (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The oily residue was dissolved in methanol (3 mL) resulting in the formation of colorless crystals of 2,6-diphenylphenol (0.97 g). The mother liquor was evaporated and isohexane (3 mL) was added to the residue to precipitate a further portion of 2,6-diphenylphenol (0.25 g). The filtrate was then evaporated and purified by column chromatography (silica gel, isohexane:$CHCl_3$) to afford 2,6-diphenylphenol (0.10 g; the overall amount of 2,6-diphenylphenol recovered was 1.32 g) and **4a** as colorless crystals (0.15 g, yield 30%), mp 84–85°C. ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ: 2.92 (dd [A part of ABX pattern], 1H, 3-H, $J_{AB}=16.8$, $J_{AX}=4.8$ Hz), 3.00 (dd [B part of ABX pattern], 1H, 3-H, $J_{BX}=11.4$ Hz), 4.81 (m, [X part of ABX pattern], 1H, 2-H), 7.08-7.17 (m, 2H, 6-H, 8-H), 7.57 (ddd, 1H, 7-H, $^3J_{H-H}=8.3$, $^3J_{H-H}=7.3$, $^4J_{H-H}=1.8$ Hz), 7.92 (ddd, 1H, 5-H, $^3J_{H-H}=7.7$, $^5J_{H-H}=0.6$ Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ: −79.07 (d, $^3J_{F-H}=5.8$ Hz).

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28. Control of the regiochemistry of the studied reactions was performed using ^{19}F NMR spectroscopy. The δ_F values of **1**, **2**,[5b] **4b**,[14] and **7a**[27b] were known. A characteristic feature of the 1,4-adducts **2**, **4a** and **7a** is the splitting of the CF_3 group signal into a doublet ($^3J_{F-H} = 6–8$ Hz). The ^1H, ^{13}C, ^{19}F NMR and MS data of all synthesized compounds are in accordance with proposed structures.