C–O Bond Formation

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Inherent Oxygen Preference in Enolate Monofluoromethylation and a Synthetic Entry to Monofluoromethyl Ethers**

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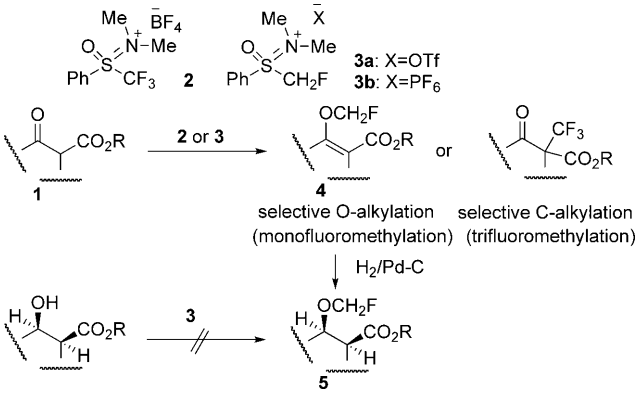
The control of regioselectivity in the alkylation of enolates is one of the oldest research areas in organic chemistry.[1] The ratio of regioisomers formed by C/O-alkylation is sensitive to the extent of substrate enolization, which is highly dependent on the structure of the carbonyl compound, but also on the nature of the alkylating reagent and the reaction conditions, in particular the solvent and base. It has been shown that more C-alkylation tends to be observed with softer nucleophiles, whereas O-alkylation is favored with harder electrophiles.[2,3] However, the complete control of C/O regioselectivity is still a challenge, for example, the regioselective O-methylation of β-ketoesters **1**.[3,4] In 2008, we reported that the trifluoromethylsulfoxinium salt **2** was very effective for the electrophilic trifluoromethylation of carbon-centered nucleophiles.[5]

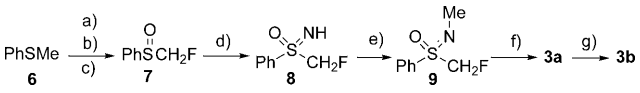
As an extension of our interest in the synthesis of organofluorine compounds,[6] we reveal herein that the electrophilic monofluoromethylation of 1,3-dicarbonyl compounds by the novel monofluoromethylsulfoxinium salts **3** occurs selectively at the oxygen atoms of enolates, rather than at the corresponding carbon atoms, to provide **4**, whereas trifluoromethylation by enolate alkylation with **2** takes place at the carbon centers. The resulting previously unknown monofluoromethyl enol ethers **4** of β-ketoesters[7] can be conveniently transformed into monofluoromethyl ethers **5** in high yield by a reduction system based on Pd/C catalysis (Scheme 1). As a consequence, the approach not only constitutes one of the scarce examples of the selective O-alkylation of enolates, but also provides a new synthetic entry to biologically relevant monofluoromethyl ethers, which are of interest to the pharmaceutical and agrochemical industries, and which are difficult to obtain by the direct electrophilic fluoromethylation of alcohols.[8,9] We also described the monofluoromethylation of other oxygen-centered nucleophiles, such as carboxylic acids, phenols, naphthols, alcohols, and sulfonic acids, with the self-stable monofluoromethylating reagents **3**. Thus, this approach provides access to a great



Scheme 1. Monofluoromethylation versus trifluoromethylation: inherent O or C selectivity in the alkylation of enolates and a new synthetic entry to monofluoromethyl ethers. Tf = trifluoromethanesulfonyl.

number of biologically relevant monofluoromethyl esters, ethers, and sulfonates.

The novel electrophilic monofluoromethylation reagents **3** were synthesized by the procedure shown in Scheme 2. Phenyl monofluoromethyl sulfoxide (**7**),[10a,b] prepared from thioanisole (**6**) in three steps, including nucleophilic substitution of chloride with KF, was converted into sulfoximine **8** under conventional conditions by treatment with NaN_3/H_2SO_4. (Caution! This step involves the generation of explosive hydrogen azide). The stepwise methylation of **8** with Me_3OBF_4/K_2CO_3 followed by methyl trifluoromethanesulfonate gave *N*,*N*-(dimethylamino)-*S*-phenyl-*S*-monofluoromethyloxosulfonium trifluoromethanesulfonate (**3a**) via **9**[10c] as a viscous oil. The trifluoromethanesulfonate **3a** was transformed into the hexafluorophosphate **3b** as colorless crystals with KPF_6 in CH_2Cl_2 in 88% yield.



Scheme 2. a) NCS, CCl_4, room temperature, 11 h (98%); b) KF, [18]crown-6, CH_3CN, reflux, 7 days; c) NBS, MeOH/H_2O, room temperature, 30 min (83%, for 2 steps); d) NaN_3, concentrated H_2SO_4, $CHCl_3$, room temperature, 11 h (93%); e) Me_3O/BF_4, K_2CO_3, CH_2Cl_2, room temperature, 3 h (90%); f) MeOTf, neat, room temperature, 11 h (94%); g) saturated aqueous KPF_6, CH_2Cl_2 (88%). NBS = *N*-bromosuccinimide.

We began our investigation with methyl 1-indanone-2-carboxylate (**1a**) as a test substrate for the monofluoromethylation reaction with **3a** and **3b** under the conditions

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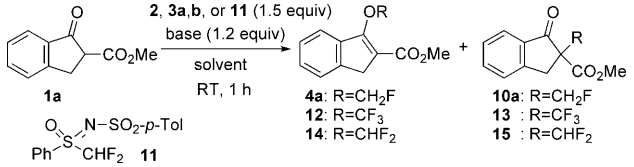
previously described for trifluoromethylation with **2**; that is, the reaction was carried out in the presence of DBU in CH_2Cl_2.[5] Surprisingly, monofluoromethylation with **3a** took place at the oxygen atom rather than at the expected carbon center of the β-ketoester **1a** to provide the previously unknown monofluoromethyl ether **4a** in 24% yield (Table 1, entry 1).[7] The low yield of **4a** was significantly improved to 71% by the use of the hexafluorophosphonium salt **3b** instead of **3a** under the same reaction conditions (Table 1, entry 2). In both cases, none of the C-monofluoromethylated product **10a** was detected. For comparison, tri- and difluoromethylation were attempted under the same reaction conditions. Interestingly, whereas the trifluoromethylation of **1a** with reagent **2** provided the C-trifluoromethylated product **13** regioselectively in 93% yield (Table 1, entry 3), the difluoromethylation of **1a** proceeded nonselectively at both the carbon and oxygen atoms with **11**, a similar type of reagent developed by Hu and co-workers,[9f] to yield a 37:63 O/C-alkylated mixture of **14** and **15** in 38% yield (Table 1, entry 4). We next investigated the effects of the base and the solvent on the O-selective monofluoromethylation of **1a** with **3**. Although the chemical yield varied depending on the reaction conditions, complete O selectivity was observed in all cases (Table 1, entries 5–9). The reaction of **1a** with **3b** in the presence of the phosphazene base P_1-*t*Bu in MeCN gave the best result, with the selective formation of **4a** in excellent yield (97%; Table 1, entry 10).

These results highlighted the uniqueness of the inherent selectivity for O-alkylation in the monofluoromethylation of β-ketoesters. To explore the generality of the regioselective O-monofluoromethylation of β-ketoesters, we carried out experiments with a variety of substrates, including indanone carboxylates, tetralone carboxylates, and other β-ketoesters (Table 2). The distribution of O/C-alkylation products did not depend on the substrate structure, and selective O-monofluoromethylation was observed in all cases. The less reactive acyclic β-ketoester **1k** underwent the reaction to furnish monofluoromethyl enol ether **4k** in 64% yield as an *E/Z* mixture (Table 2, entry 10). However, the reaction of the much less reactive substrate benzyl 2-methyl-3-oxopentanoate did not proceed well. A further, related substrate class, oxindole carboxylates **1l–o**, underwent O-selective monofluoromethylation to provide the corresponding O-monofluoromethyl indole ethers **4l–o** in high yields in 1 hour (Table 2, entries 11–14).

The oxindole monofluoromethyl ethers **17a**,**b** were obtained from the reaction of oxindoles **16a**,**b** with **3b** under the same reaction conditions in 85 and 36% yield, respectively (Scheme 3b). The structure of **17a** is of interest as an isosteric analogue of the antifungal oxindole alkaloids isatinone A and costinone B (Scheme 3a).[11] The amino acid derivative **18**, with an aldehyde moiety, was also transformed into the monofluoromethylated dehydroserine derivative **19** in high yield under the same conditions (Scheme 3c).

The series of O-monofluoromethylated enol ethers prepared in this study can be transformed into primary and

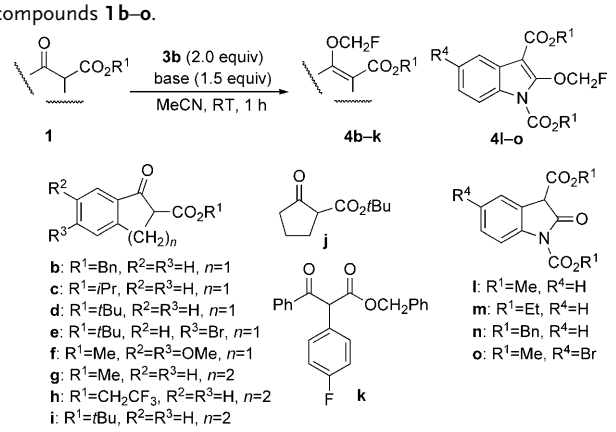
Table 1: Regioselectivity for O/C-alkylation in the fluoromethylation of β-ketoester **1a**.



Entry	Reagent	Base	Solvent	Product	Yield [%]	O/C-alkylation
1	**3a**	DBU	CH_2Cl_2	**4a**	24	100:0
2	**3b**	DBU	CH_2Cl_2	**4a**	71	100:0
3	**2**	DBU	CH_2Cl_2	**13**	93	0:100
4	**11**	DBU	CH_2Cl_2	**14/15**	38	37:63
5	**3a**	TMG	CH_2Cl_2	**4a**	42	100:0
6	**3a**	P_2-Et	CH_2Cl_2	**4a**	39	100:0
7	**3a**	P_1-*t*Bu	CH_2Cl_2	**4a**	55	100:0
8[a]	**3a**	P_1-*t*Bu	CH_2Cl_2	**4a**	96	100:0
9	**3b**	P_1-*t*Bu	MeCN	**4a**	77	100:0
10[a]	**3b**	P_1-*t*Bu	MeCN	**4a**	97	100:0

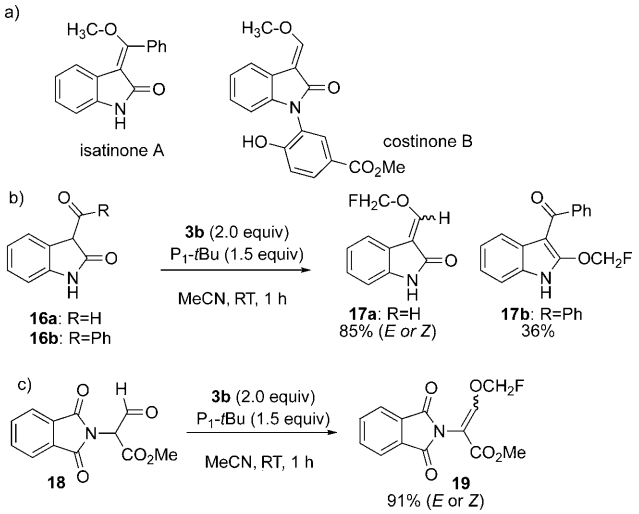
[a] The reaction was carried out with 2.0 equivalents of the reagent and 1.5 equivalents of the base. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMG = tetramethylguanidine, P_2-Et = tetramethyl(tris(dimethylamino)-phosphoranylidene)phosphorictriamid-Et-imin, P_1-*t*Bu = *tert*-butyliminotris(dimethylamino)phosphorane.

Table 2: Regioselective O-monofluoromethylation of 1,3-dicarbonyl compounds **1b–o**.



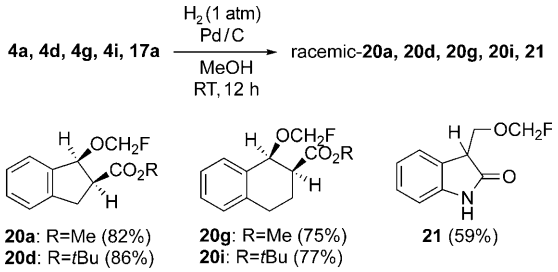
Entry	**1**	Base	**4**	Yield [%]
1	**1b**	P_1-*t*Bu	**4b**	96
2	**1c**	P_1-*t*Bu	**4c**	91
3	**1d**	P_1-*t*Bu	**4d**	85
4	**1e**	P_1-*t*Bu	**4e**	88
5	**1f**	P_1-*t*Bu	**4f**	96
6[a]	**1g**	P_2-Et	**4g**	85
7[a]	**1h**	P_2-Et	**4h**	83
8[a]	**1i**	P_2-Et	**4i**	81
9	**1j**	P_1-*t*Bu	**4j**	80
10[a]	**1k**	P_1-*t*Bu	**4k**[b]	64
11	**1l**	P_1-*t*Bu	**4l**	96
12	**1m**	P_1-*t*Bu	**4m**	95
13	**1n**	P_1-*t*Bu	**4n**	93
14	**1o**	P_1-*t*Bu	**4o**	86

[a] The reaction was carried out with 1.5 equivalents of **3b** and 1.2 equivalents of the base. After 1 h, the solvent was evaporated, and the residue was purified by column chromatography to give the products. [b] The product was obtained as a mixture of *E* and *Z* isomers (61:39 or 39:61). Bn = benzyl.

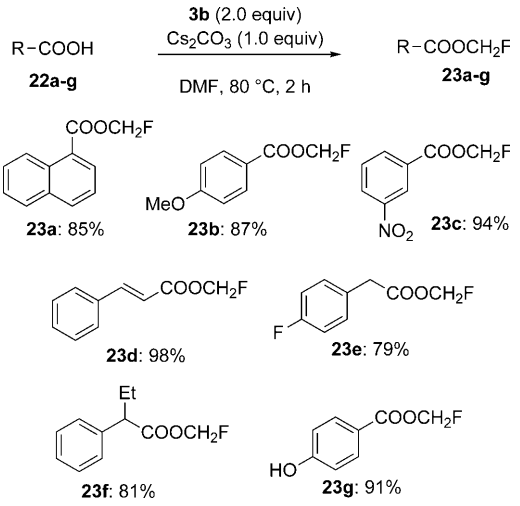


Scheme 3. a) Structures of the antifungal oxindole alkaloids isatinone A and costinone B (the configuration of the double bond of the enol ether is unknown). b) Monofluoromethylation of the 2-oxindole derivatives **16a**,**b**. c) Monofluoromethylation of the amino acid derivative **18**.

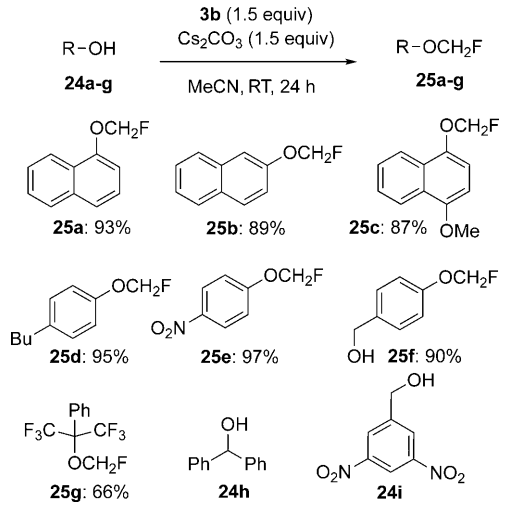
secondary monofluoromethyl ethers in high yields by reduction under Pd/C catalysis (Scheme 4). All of these ethers were difficult to obtain by direct electrophilic monofluoromethylation of the corresponding alcohols with **3** (see Scheme 6).[9]



Scheme 4. New synthetic approach to secondary and primary monofluoromethyl ethers. (The yield of **21** was determined by NMR spectroscopy.)



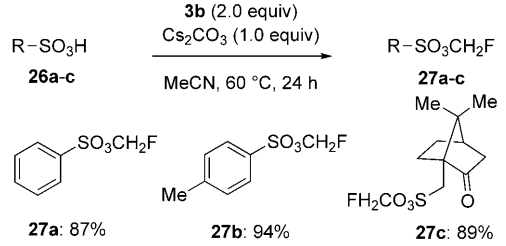
Scheme 5. Monofluoromethylation of carboxylic acids **22a–g**. DMF = *N*,*N*-dimethylformamide.



Scheme 6. Monofluoromethylation of naphthols **24a–c**, phenols **24d–f**, and phenylhexafluoro-2-propanol (**24g**). For the synthesis of **25g**, 2.0 equivalents each of **3b** and Cs_2CO_3 were used.

To further exploit the inherent preference of the CH_2F cation for the oxygen atom, we investigated the monofluoromethylation of other O nucleophiles. Thus, the aryl carboxylic acids **22a–c** and **22g**, conjugated carboxylic acid **22d**, and benzyl carboxylic acids **22e** and **22f**, underwent facile monofluoromethylation to afford the monofluoromethyl esters **23a–g** in high yields (Scheme 5). Naphthols **24a–c**, phenols **24d–f**, and phenylhexafluoro-2-propanol (**24g**) also reacted with **3b** to provide the corresponding monofluoromethyl ethers **25a–g** in high yields. However, conventional alcohols, such as **24h** and **24i**, did not react with **3b** under the same reaction conditions (Scheme 6).[9] 4-Hydroxybenzoic acid (**22g**) and 4-(hydroxymethyl)phenol (**24f**) underwent successful chemoselective monofluoromethylation to provide fluoromethyl 4-hydroxybenzoate (**23g**) and (4-(fluoromethoxy)phenyl)methanol (**25f**), respectively (Schemes 5 and 6). The aryl and aliphatic sulfonic acids **26a–c** were also converted efficiently into the corresponding monofluoromethyl sulfonates **27a–c** in 87–94% yield (Scheme 7).

In conclusion, we have developed novel self-stable reagents, monofluoromethylsulfoxinium salts **3a** and **3b**, for an electrophilic monofluoromethylation reaction and examined their reactivity. We observed unique inherent preference



Scheme 7. Monofluoromethylation of sulfonic acids **26a–c**.

of the CH_2F cation for the oxygen atom in the alkylation of enolates. This approach not only constitutes one of the scarce examples of the selective O-alkylation of enolates, but also provides a new synthetic entry to biologically relevant monofluoromethyl ethers of interest to the pharmaceutical and agrochemical industries.[9] This strategy might offer a possible solution for the direct electrophilic trifluoromethylation of alcohols.[9] Our findings on the selective O-alkylation of enolates by monofluoromethylsulfoxinium salts **3** also provides significant insight into the unusual reactivity of fluorinated sulfoximines,[10c,12] as exemplified by the important discovery by Hu and co-workers that monofluorosulfoximines react with simple nitrones to give monofluoroalkenes with excellent *E*/*Z* stereoselectivity.[13] Although the mechanisms of O-selective monofluoromethylation and C-selective trifluoromethylation are unclear, these results should shed more light on the mechanism of the electrophilic trifluoromethylation reaction, including details regarding the CF_3 cation, the CF_3 radical, and the mechanism of single-electron transfer.[14,15] Molecular-mechanical and molecular-orbital calculations, which should provide further insight into the mechanisms of O-monofluoromethylation and C-trifluoromethylation, are now under way.

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