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Fluoride-Promoted Oxidation of Fischer Alkoxy Carbene Complexes: Stoichiometric and Catalytic Conditions

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Abstract: The utility of fluoride anion as promoter of the oxidation of Fischer carbene complexes is presented. Two different and complementary methods that allow the fast and convenient preparation of carbene-derived esters in good yields have been developed using stoichiometric or catalytic quantities of fluoride ion.

The utility of Fischer carbene complexes (FCCs) as intermediates in organic synthesis has been widely demonstrated, and it is today commonly accepted.[1] Among the new chemistry originated by Fischer carbene complexes, the Dötz benzannulation[2] reaction appears to be a unique tool for the construction of substituted and functionalized phenol derivatives, while Hegedus photochemical ketene generation represents also a remarkable synthetic contribution.[3] In these reactions, the carbene carbon is incorporated as part of the skeleton of the newly formed products and a further step to remove the metal is not necessary. In other reactions, such as the Diels−Alder reaction[4] or 1,3-dipolar cycloadditions,[5] the cycloadducts are obtained with high regioselectivity, high diastereoselectivity, and/or increased reaction rates. For those reasons, Fischer carbene complexes can be termed as "superesters" or "superamides"; however, to free the organic portion in the cycloadducts, the development of procedures to remove the metal moiety is necessary.

In this sense, aldehydes can be obtained by reacting FCCs with hydrobromic acid or triflic acid,[6] and enoleters can be accessed by treatment with a base (i.e., pyridine) when the carbene complex bears acidic hydrogens in the α-position.[6b,7] Other transformations include methylenation with diazomethane,[6b,8] Wittig reagents,[9] chloromethyllithium[10] or ethylvinyl ether,[11] hydrogenation leading to saturated compounds,[6b,12] and reduction of amino carbenes to amines and alkoxy carbenes to alcohols or enol ethers by metal hydrides.[13]

In most cases, alkoxy FCCs are converted into their analogous esters by treatment with oxidants such as pyridine *N*-oxide (PNO),[14] dimethyl sulfoxide,[6b,c,15] dimethyldioxyrane,[16] ceric ammonium nitrate (CAN),[14b,17] PhIO,[14b] NaOCl,[18] KOCl,[18] iodine,[18] silica and air,[19] air alone,[20] or lamp or sunlight exposition.[5b] However, the strong reaction conditions sometimes required or the slow reaction rates, resulting in long reaction times, including weather dependence for the sunlight exposition, as well as the unpredictable and/or low reaction yields often caused by the formation of byproducts, encourages the development of new methodologies for the oxidation of

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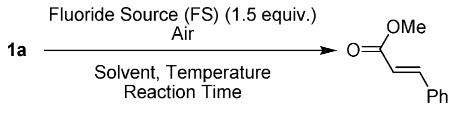
TABLE 1. Fluoride-Promoted Oxidation of Carbene Complex 1a



4a

entry[a]	FS	solvent	reaction time	yield[b] (%)
1	NBu_4F	THF	17 min	43[c,d]
2[e]	NBu_4F	THF	5 min	27
3	NBu_4F	CH_2Cl_2	12 min	61[c]
4	NBu_4F	DME	35 min	68
5[f]	NBu_4F	DME	2 h	79
6	CsF	THF	22 h	86[c,d]
7	CsF	DME	48 h	80
8	KF	THF	36 h	78[c,d]
9	KF	CH_3CN	40 h	68
10	KF	CH_2Cl_2	nr	
11	KF	CH_3OH	2 h	33[g]
12	KF	DME	24 h	76
13[h]	KF	DME	24 h	77
14[i]	KF	DME		[j]

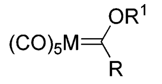
[a] All reactions were carried out at room temperature unless otherwise stated. [b] Yield of isolated product after flash chromatography unless otherwise stated. [c] The reaction product was not completely purified after flash chromatography; this number represents the combined yield of the isolated mixture (assuming that all the products have the same molecular weight). [d] Products resulting from THF ring opening and/or polymerization were also detected. [e] Reaction performed with solid NBu_4F at a 5-fold concentration. [f] Reaction carried out at 0 °C. [g] A 16% yield of methyl 3-phenylpropanoate **5d** (resulting from double-bond reduction) was also isolated. [h] Reaction carried out at 40 °C. [i] Reaction carried out at reflux. [j] DME polymerization products were observed; no carbene-derived products were identified.

carbene complexes. During the course of our research in 1,3-dipolar cycloadditions of Fischer carbene complexes with azomethine ylides,[5b] we found that, under certain conditions, high yields of carbene oxidation products were obtained instead of the desired cycloadducts. A close examination led us to conclude that the oxidation was being promoted by the fluoride anion used to in situ generate the 1,3-dipole, and we then decided to optimize the conditions in order to develope a new and mild carbene oxidation methodology. The following alkoxy FCCs **1**−**3** have been oxidized in this work.

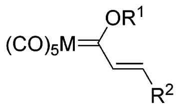
α,β-Unsaturated FCC **1a** was used as the model system; several conditions were evaluated, and some of them are listed in Table 1. In all cases, 1.5 equiv of a fluoride source were employed, and 1,2-dimethoxyethane (DME) proved to be by far the optimum solvent among all the solvents examined (entries 1, 3, 4, and 8−12). KF, CsF, and Bu_4NF were tested as fluoride sources, and the oxidation with all of them led to similar yields; however, in terms of kinetics, the reactions proceeded faster with KF than with CsF (entry 7 vs 12), *with Bu_4NF as the fluoride source that allowed the best results* (entry 4) when 1,2-DME was used as solvent. The use of a higher concentration caused a faster although low-yielding oxidation. The reaction worked well at room temperature, and the employment of higher temperatures did not result in appreciable increases of the reaction rate, producing similar or even lower yields (entries 12−14). Decreasing the reaction temperature was appropriate for carbene complex **1a** (entry 5 vs 4), but the reaction rate was almost 4-fold diminished, which resulted inconvenient for the oxidation of other carbene complexes (vide infra).

We tried to extend the methodology to other alkoxy FCCs, using KF or Bu_4NF as fluoride sources.[21] Thus, when menthol-derived carbene **1b** was employed, the rate differences in using KF or Bu_4NF as fluoride source increased (Table 2, entry 1 vs 2); the increment is spectacular for the *more stable tungsten carbene complex* **1e** (entry 6 vs 7), *which is also oxidized under those conditions.*

General Formula for Fischer Alkoxy Carbene Complexes



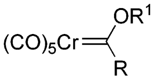
1-3



Fur = Furyl
Fc = Ferrocenyl

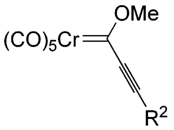
Alkenyl Carbene Complexes

1a M = Cr; R^1OH = MeOH; R^2 = Ph
1b M = Cr; R^1OH = Menthol; R^2 = Ph
1c M = Cr; R^1OH = 8-Phenylmenthol; R^2 = 2-Fur
1d M = Cr; R^1OH = 8-Phenylmenthol; R^2 = Fc
1e M = W; R^1OH = Menthol; R^2 = Ph



Alkyl and Aryl Carbene Complexes

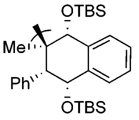
2a R = Me; R^1OH = 8-Phenylmenthol
2b R = Ph; R^1OH = MeOH
2c R = 3-Fur; R^1OH = Menthol



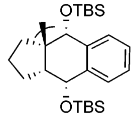
Alkynyl Carbene Complexes

3a R^2 = Ph
3b R^2 = 1-Cyclopentenyl

3c R^2 =



3d R^2 =



As expected, the steric hindrance surrounding the carbene carbon played a decisive role in the reaction rate. In this sense, 8-phenylmenthol-derived alkenyl carbenes were oxidized much more slowly than menthol-derived alkenyl carbenes when using KF as fluoride source

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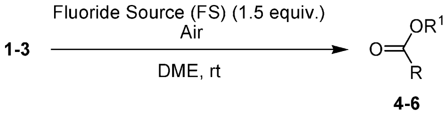
(21) CsF was discarded as it was more expensive and led to the slowest reaction rates.

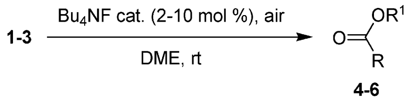
TABLE 2. Fluoride-Promoted Oxidation of Alkoxy FCCs 1−3



entry	**1−3**	FS	reaction time	**4−6**	yield[a] (%)
1	**1b**	KF	100 h	**4b**	67
2	**1b**	Bu_4NF	45 min	**4b**	65
3	**1c**	KF	7 d	**4c**	61
4	**1c**	Bu_4NF	18 min	**4c**	65
5	**1d**	KF	13 d	**4d**	62
6	**1e**	KF	15 d	**4b**	44
7	**1e**	Bu_4NF	15 min	**4b**	63
8	**2a**	Bu_4NF	[b]	**5a**	69
9	**2b**	Bu_4NF	10 min	**5b**	76
10	**2c**	Bu_4NF	10 min	**5c**	55
11	**3a**	KF	27 h	**6a**	84
12	**3a**	Bu_4NF	5 min	**6a**	15[c]
13	**3b**	KF	84 h	**6b**	41

[a] Yield of isolated product after flash chromatography unless otherwise stated. [b] The reaction is instantaneous. [c] A 15% yield of partially reduced product **4a** was also isolated.

TABLE 3. Catalytic Fluoride-Promoted Oxidation of Alkoxy FCCs 1−3



entry	**1−3**	cat. (%)	reaction time (h)	**4−6**	yield[a] (%)
1	**1a**	10	1.5	**4a**	84
2	**1a**	5	6	**4a**	88
3	**1a**	2	8	**4a**	89
4	**1a**	1	36	**4a**	80
5	**1a**	0.5	36	**4a**	83
6	**1b**	10	36	**4b**	86
7	**2a**	10	12	**5a**	86
8	**2b**	5	5	**5b**	85
9	**2c**	10	12	**5c**	88
10	**3a**	5	8	**6a**	61
11	**3a**	2	24	**6a**	63
12	**3b**	2	24	**6b**	33[b]
13	**3c**	5	14	**6c**	87
14	**3d**	5	14	**6d**	91

[a] Yield of isolated product after flash chromatography unless otherwise stated. [b] For this substrate, higher fluoride loading (5%) resulted in an even lower yield.

(entries 3, 5 vs 1), and the latter were oxidized more slowly than the less hindered methanol-derived alkenyl carbenes either using KF or Bu_4NF as fluoride sources (see Table 2, entries 1, 2 vs Table 1, entries 11, 3). In these slow transformations *there is a background oxidation by air to some extent*, but there is indeed a fluoride effect that accelerates the reaction; for example, the oxidation of carbene complex **1b** was incomplete in DME after 120 h in the absence of any fluoride source (compare to Table 2, entry 1).

In general, when 1.5 equiv of Bu_4NF is used, the oxidation is complete within minutes. The methodology allowed also the oxidation of alkyl (Table 2, entry 8), aryl (entries 9, 10), and alkynyl (entries 11−13) carbene complexes.

We have performed other experiments to determine the stability of FCCs *in the absence of air* but in the presence of stoichiometric amounts of fluoride anion. We can conclude that FCCs *can tolerate fluoride in the absence of air at low temperature.* In fact, they are fairly stable at temperatures below −10 °C, while they decompose at low but noticeable rates at 0 °C and the decomposition becomes faster above that temperature.

We have also explored the possibility of an alternative catalytic fluoride-promoted (Bu_4NF) oxidation of Fischer alkoxy carbene complexes, and the results are summarized in Table 3. The oxidation, under catalytic conditions, usually led to higher yields of isolated products. The catalyst loading, for carbene complex **1a**, could be reduced to 0.5% (entry 5), although the reaction time increased considerably as the amount of catalyst was reduced (entries 1−5). Most of the oxidations were fast enough with 2−5% of catalyst loading, but menthol-derived carbenes required a 10% of catalyst to be oxidized in useful times (entries 6, 7, and 9), probably for steric reasons. Consequently, 8-phenylmentol-derived carbene complexes were not tested under these conditions. This procedure allowed also the oxidation of alkyl, aryl and alkynyl carbene complexes (entries 6−14), even when the latter bear bulky triple bond substituents (entries 13, 14).[22] Catalytic fluoride-promoted oxidation of tungsten carbene complex **1e** was very slow; most of the starting material remained unreacted after 72 h for a 10% of catalyst loading.

In summary, we have developed two easy-to-work, convenient, low-cost, and complementary procedures to remove the metal moiety of Fischer alkoxy carbene complexes by fluoride-promoted (KF or Bu_4NF) oxidation to the analogous esters. When 1.5 equiv of Bu_4NF in 1,2-DME was used, moderate to good yields of the oxidized products were obtained in a few minutes. Depending on both the steric demand of the carbene carbon and the nature of the metal, catalytic amounts of fluoride may be employed, which usually produces higher yields. Research to uncover the mechanistic insights of this transformation is currently underway, and it will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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