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New catalytic oxidation of trifluoromethyl carbinols by a ruthenium(II) complex

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Abstract

The first catalytic oxidation of trifluoromethyl carbinols has been accomplished by a novel ruthenium(II) complex using sodium periodate as an oxidant. Trifluoromethyl ketones were obtained under mild conditions and in excellent yields.

Fluorinated ketones, especially trifluoromethyl ketones, are of great interest because of their remarkable ability to function as enzyme inhibitors,[1] and because of their role as building blocks for trifluoromethyl heterocycles[2] and as monomers for novel polymeric materials.[3] Besides traditional methods involving the addition of Grignard or organo lithium reagents to trifluoroacetic acid,[4] other more recent methods such as the Wittig reaction with trifluoroacetamides,[5] or the reaction of acid chlorides with trifluoroacetic anhydride[6] brought great improvement to the access to trifluoromethyl ketones.

On the other hand, the facile addition of $TMSCF_3$ to aldehydes constitutes excellent access to trifluoromethyl carbinols.[7,8] However, their oxidation to ketones is not straightforward. Classical oxidation procedures such as the use of MnO_2,[9] $KMnO_4$[10] and CrO_3[1a] are often unsuccessful or require harsh conditions which are not suitable for some functional groups. Swern and modified Moffat oxidation methodologies very often fail or poorly succeed in the case of fluoroalkyl alcohols,[11] despite some described examples.[12] The only reliable procedure available in the literature is the oxidation by the Dess–Martin reagent.[13] However, its explosive nature and high air and moisture sensitivity limit its utility. To the best of our knowledge, no catalytic method for this oxidation has been reported so far. So there is still a need for a new methodology for the oxidation of trifluoromethyl carbinols. There has been considerable interest in recent years in the use of oxoruthenium complexes as catalysts for organic oxidation.[14] In this communication, we wish to report our successful efforts on the oxidation of

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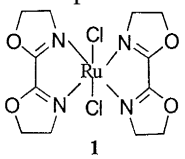
trifluoromethyl carbinols using a novel ruthenium(II) complex $RuCl_2(biox)_2$ **1** which is known to oxidise olefins to epoxides in very good yields in a stereospecific manner under aerobic conditions.[15]



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Initial studies focused on the oxidation of 5-phenyl-1,1,1-trifluoropentan-2-ol **2** under aerobic conditions: trifluoromethyl carbinol **2** was treated with 2.5 mol% of $RuCl_2(biox)_2$ **1** in dichloromethane using pivalaldehyde as the co-reductant in an atmosphere of oxygen. After 48 h at ambient temperature only a 30% conversion was observed. When the reaction was run at reflux temperature in dichloromethane, no change in the conversion was observed. With 1.5 equivalents of $NaIO_4$ and 2.5 mol% of **1**, a 45% conversion was observed at room temperature after 48 h. There was further optimisation to afford the corresponding trifluoromethyl ketone **3** in 84% yield after 32 h by performing the reaction at reflux temperature in dichloromethane.[16] We have checked that $NaIO_4$ acts as a co-oxidant and not as an active oxidant: when the reaction was performed without a ruthenium catalyst the starting alcohol **2** was recovered. A series of fluorinated carbinols have been prepared[18] and subjected to oxidation with $RuCl_2(biox)_2$ **1** under the optimised conditions. The results are summarised in Table 1.

With 1.5 equivalents of $NaIO_4$, 2.5 mol% of **1** at reflux in CH_2Cl_2, phenyl-substituted 1,1,1-trifluoropentan-2-ols could be oxidised to the corresponding ketones in good yields. 5-Phenyl-1,1,1-trifluoropentan-2-ol **2**, 5-(4-methoxyphenyl)-1,1,1-trifluoropentan-2-ol **4** and 5-(4-chlorophenyl)-1,1,1-trifluoropentan-2-ol **6** exhibited similar reactivity leading to the corresponding ketones **3**, **5** and **7** in good yields with no detectable influence of the substituents.

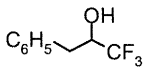
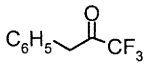
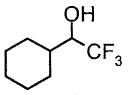
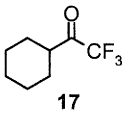
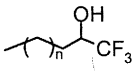
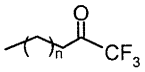
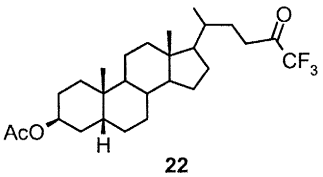
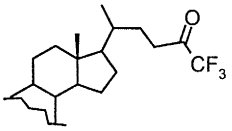
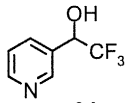
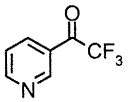
1-Phenyl-2,2,2-trifluoroethanol **8** could be easily and quantitatively oxidised to afford 2,2,2-trifluoroacetophenone **9**. Only 76% of the product could be isolated because of the volatility of ketone **9**. Under similar reaction conditions, 1-(4-methoxyphenyl)-2,2,2-trifluoroacetophenone **11** and 1-(3,4-dimethoxyphenyl)-2,2,2-trifluoroacetophenone **13** were obtained in excellent yields by oxidation of the corresponding alcohols **10** and **12**, respectively. As expected, the oxidation of these aromatic alcohols was easier than that of alkyl-substituted alcohols, with a shorter reaction time (8 h), and it could even been carried out at room temperature with a prolonged reaction time (24 h).

The efficiency of this methodology was proven in the oxidation of α,α-disubstituted alcohols: although the conversion of 1-cyclohexyl-2,2,2-trifluoroethanol **16** into ketone **17** was very slow (50 h) the reaction went to completion and the lower isolated yield was due to the volatility of ketone **17**. The reaction was also successful with long chain alcohols such as **18** and **20**, which are usually less reactive.[13] Thus, oxidation of 1,1,1-trifluoromethyl dodecan-2-ol **18** and 1,1,1-trifluoromethyl nonadecan-2-ol **20** afforded ketones **19** and **21** in quantitative yields. To oxidise these trifluoromethyl carbinols, only the CrO_3/pyridine mixture under severe conditions[1a] and the Dess–Martin reagent are described in the literature. The trifluoromethyl alcohol **22**[19] derived from lithocholic acid was selectively oxidised to the corresponding ketone **23**[20] in 90% yield after 22 h.

We have also shown, in the reaction with the pyridyl alcohol **24**,[21] that the oxidation is chemoselective. After 10 h, the trifluoromethyl ketone **25** was obtained as the only product and was isolated in an excellent yield (87%).

Thus, we have developed the first catalytic method for the oxidation of trifluoromethyl carbinols using sodium periodate and $RuCl_2(biox)_2$ **1** with high efficiency. Even alkyl trifluoromethyl carbinols and α,α-disubstituted ones can be converted in high yields into ketones. The pyridyl moiety remains unaffected under these oxidation conditions.

Table 1
Oxidation of trifluoromethyl carbinol with $RuCl_2(biox)_2$

Entry	Substrate	Product	Time (h)	Yield[a] (%)
	$Ar\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CHOH\text{-}CF_3$	$Ar\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CO\text{-}CF_3$		
1.	**2** Ar = C_6H_5-	**3**	32	84
2.	**4** Ar = MeO-C_6H_4-	**5**	34	85
3.	**6** Ar = Cl-C_6H_4-	**7**	36	88
	$Ar\text{-}CHOH\text{-}CF_3$	$Ar\text{-}CO\text{-}CF_3$		
4.	**8** Ar = C_6H_5-	**9**	8	76
5.	**10** Ar = MeO-C_6H_4-	**11**	8	86
6.	**12** Ar = ClC_6H_4-	**13**	7	88
7.	 **14**	 **15**	30	92
8.	 **16**	 **17**	50	72
9.	 **18** n = 8	 **19** n = 8	38	94
10.	**20** n = 15	**21** n = 15	42	96
11.	 **22**	 **23**	22	89
12.	 **24**	 **25**	10	87

[a] All yields are isolated yields

Acknowledgements

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16. Typical procedure: $NaIO_4$ (0.320 mg, 1.5 mmol, 1.5 equiv.) and $RuCl_2(biox)_2$ **1** (4.5 mg, 0.01 mmol, 0.0045 equiv.) was added to a solution of alcohol **2** (218 mg, 1 mmol) in CH_2Cl_2 (4 mL), and the mixture was refluxed until disappearance of the starting material (32 h). The reaction mixture was cooled, and then water (2 mL) was added. Organic phase was extracted (CH_2Cl_2), and then dried over anhydrous Na_2SO_4, solvent evaporated to afford the pure ketone **3** (181 mg, 84 %).[17]
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18. Trifluoromethyl alcohols **2**, **14**, **16** and **24** were prepared by the reduction of corresponding ketones[5,6] with $LiAlH_4$. Alcohols **4**, **6**, **8**, **10**, **12**, **18**, **20** and **22** were prepared by the addition of CF_3TMS to the corresponding aldehyde in the presence of TBAF.[8]
19. Mp: 77–79°C $[\alpha]_D^{23}$ +43 (*c* 1, $CHCl_3$), IR (Nujol) 2910, 1370, 1250, 1020, 978 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): 0.52–1.92 (m, 35H), 0.93 (s, 3H), 1.12 (s, 3H), 2.15 (s, 3H), 4.65 (m, 1H), 5.2 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 12.3, 13.4, 18.7, 21.1, 22.4, 25.6, 26.3, 27.4, 28.8, 30.5, 31.8, 33.2, 33.7, 34.1, 37.6, 47.3, 73.9, 76.2 (q, J=33 Hz), 112.6 (q, J=288 Hz), 170.2. ^{19}F NMR ($CDCl_3$, 188 MHz): 80.1 (d, J=4.2 Hz). Analysis for $C_{25}H_{44}O_3F_3$: calcd: C, 66.80; H, 9.86. Found: C, 66.88; H, 9.72.
20. Mp: 63–65°C $[\alpha]_D^{23}$ +55 (*c* 1, $CHCl_3$), IR (Nujol) 2915, 1745, 1372, 1260, 1014, 978 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): 0.45–1.94 (m, 33H), 0.93 (s, 3H), 1.15 (s, 3H), 2.10 (s, 3H), 4.62 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 11.8, 13.4, 18.9, 190.1, 21.6, 22.4, 25.3, 26.1, 27.4, 28.2, 30.9, 31.4, 33.0, 32.7, 34.1, 38.6, 46.3, 72.9, 114.7 (q, J=290 Hz), 170.2, 190.1 (q, J=33 Hz). ^{19}F NMR ($CDCl_3$, 188 MHz): 79.5 (s). Analysis for $C_{25}H_{42}O_3F_3$: calcd: C, 67.08; H, 9.45. Found: C, 67.15; H, 9.56.
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