Push–Pull Carbenes: Methoxytrifluoromethylcarbene

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Despite the possibility of 'push–pull' carbene stabilization by substituents of opposing electronic properties, absolute rate studies show methoxytrifluoromethylcarbene to be highly reactive and electronically indiscriminant in its reactions with alkenes.

A singlet carbene possesses a vacant p orbital and an unshared electron pair that resides in a σ orbital, with both features located at the carbenic carbon atom. If this centre were simultaneously substituted with a strongly electron-donating *and* a strongly electron-withdrawing substituent (a 'push–pull' carbene), one might anticipate an enhanced stabilization of the carbene that could be expressed as a mitigation of its reactivity. It was recently suggested, for example, that the isolable carbene, 1,3-di-1-adamantylimidazol-2-ylidene, might benefit from σ-electronegativity effects of the nitrogen atoms on the carbene centre.[1]

The methoxy and trifluoromethyl groups qualify as strong (resonance) donating and (inductive) withdrawing substituents,[2] respectively, so that methoxytrifluoromethylcarbene (MeO–C–CF_3) is an appropriate species to test these ideas. Dailey has found that MeO–C–CF_3, generated from 3-methoxy-3-trifluoromethyldiazirine, **1**, adds with virtually no discrimination to a variety of alkenes.[3] Here, we report on the absolute rates of addition of MeO–C–CF_3, demonstrating the extraordinary intermolecular reactivity of this carbene and its lack of response to electronic variations within the substrates. Far from stabilizing MeO–C–CF_3, the trifluoromethyl substituent elevates its reactivity and obviates the remarkable nucleophilic selectivity displayed by the related methoxymethylcarbene, MeO–C–Me.[4]

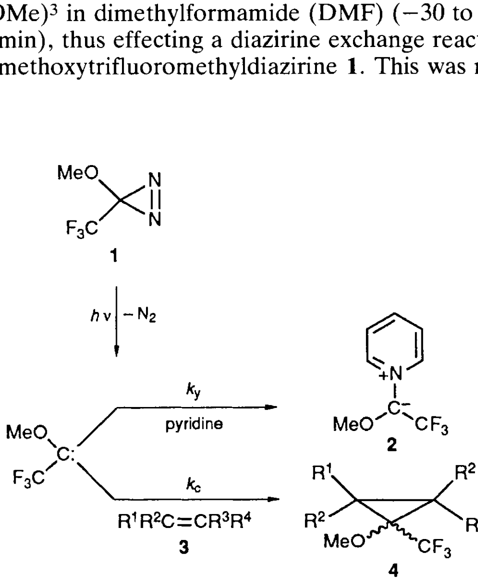
Trifluoroacetonitrile, from the P_2O_5-dehydration of trifluoroacetamide, was converted to trifluoroacetamidine,[5,6] and thence, by Graham oxidation in aqueous dimethyl sulphoxide (DMSO) solution with NaOBr,[3,7] to 3-bromo-3-trifluoromethyldiazirine. The latter was trapped under vacuum (<0.1 Torr) at −196 °C in 30–40% yield. The bromotrifluoromethyldiazirine was stirred with NaOMe[4,8] (or with Bu_4NOMe)[3] in dimethylformamide (DMF) (−30 to −40 °C, *ca.* 20 min), thus effecting a diazirine exchange reaction that led to methoxytrifluoromethyldiazirine **1**. This was removed under vacuum (<0.1 Torr) and trapped in isooctane solution at −196 °C. Diazirine **1** had λ_{max} 314, 326 and 340 nm (isooctane). It was unstable at room temperature, decomposing within 30 min. Accordingly, solutions of **1** were stored at −70 °C, and, for use in photolysis studies, diluted with isooctane or alkene until the diazirine absorbance at 314 nm was ~1.0.

Laser flash photolysis (LFP) of diazirine **1** in isooctane solution was initiated with a 14 ns, 70–80 mJ, 351 nm pulse from our XeF excimer laser.[9] No detectable transient signal was observed for MeO–C–CF_3, so that Platz's elegant ylide competition method[10] was employed to indirectly monitor the carbene. Thus, LFP of **1** in isooctane containing 0.4–1.2 × 10^{-3} mol dm^{-3} pyridine gave rise to a strong absorbtion for the ylide **2** at 340–400 nm, λ_{max} = 375 nm (see Scheme 1). The rate of ylide appearance was first-order in pyridine, so that from the dependence of k_{obs} on [pyridine] we obtained the bimolecular rate constant, $k_y = 4.3 \pm 0.1 \times 10^9\ dm^3\ mol^{-1}\ s^{-1}$ for the formation of **2**.

At constant [pyridine], the addition of alkenes **3a–e**, which are known to trap MeO–C–CF_3,[3] increased the apparent rate of ylide formation, but decreased its yield. This behaviour agrees with expectations[10] for the competitive reactions of the carbene with either pyridine or an alkene, as shown in Scheme 1. The observed rate of ylide formation at a selected constant [pyridine] was linear with [alkene], affording the bimolecular rate constants (k_c) for the carbene–alkene reactions that appear in Table 1.

Thermal (25 °C) or photochemical decompositions of diazirine **1** in alkenes **3b**, **3c** and **3e** gave very similar results, and established independently that the corresponding cyclopropanes (**4b**, **4c** and **4e**) indeed formed as major products in our experiments. Cyclopropanes **4a**, **4b**, **4d** and **4e** have already been prepared and characterized by Dailey;[3] we substantiated the structure of **4c** by NMR and GC–mass spectrometry. NMR data for **4c** included: ^1H NMR (δ, $CDCl_3$, mixture of isomers) 0.75–0.88 (m, 2H, cyclopropyl H), 0.96 (t, *J* 7 Hz, 3H, CH_2CH_3), 1.18 and 1.16 (s, 3H, C–CH_3 of each isomer), 1.40–1.60 (m, 2H, CH_2CH_3), 3.43 and 3.41 (s, 3H, OCH_3 of each isomer); ^{19}F NMR ($CDCl_3$, upfield from $CFCl_3$, mixture of isomers) 68.7 and 69.9 (singlets).

The rate constants in Table 1 demonstrate that singlet† MeO–C–CF_3 is extremely reactive and quite indiscriminate.



a; $R^1 = R^2 = R^3 = R^4 = Me$
b; $R^1 = R^2 = R^3 = Me, R^4 = H$
c; $R^1 = Me, R^2 = Et, R^3 = R^4 = H$
d; $R^1 = CN, R^2 = R^3 = R^4 = H$
e; $R^1 = CO_2Me, R^2 = R^3 = R^4 = H$

Scheme 1

Table 1 Rate constants (k_c) for additions of MeO-C-CF_3 to alkenes

Alkene	10^3[alkene] /mol dm^{-3} [a]	10^3[pyridine] /mol dm^{-3}	$10^{-8}k_c$ /$dm^3\ mol^{-1}\ s^{-1}$ [b]
$Me_2C{=}CMe_2$	10.0–250	1.21	0.045 ± 0.002
$Me_2C{=}CHMe$	2.3–12	0.61	1.24 ± 0.04
$MeEtC{=}CH_2$	2.3–12	0.61	0.90 ± 0.04
$CH_2{=}CHCN$	3.0–15	0.60	1.40 ± 0.1
$CH_2{=}CHCO_2Et$	2.7–14	0.60	2.10 ± 0.1

[a] Range of alkene concentrations used in LFP kinetics runs at the cited [pyridine]. All experiments were in isooctane solvent. [b] The errors are standard deviations.

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† Dailey has calculated that the singlet state of MeO-C-CF_3 is ~21 kcal mol^{-1} (1 cal = 4.184 J) more stable than its triplet state.[3]

Alkenes **3b–e** each react with the carbene with k_c ~10^8 dm^3 mol^{-1} s^{-1}, irrespective of their degree of substitution or whether their substituents are electron donating or withdrawing. This lack of selectivity by MeO–C–CF_3 is clearly a function of the CF_3 moiety. From absolute and relative reactivity data, one can estimate that k_c for the cyclopropanation of **3b** by MeO–C–Me is ~5×10^3 dm^3 mol^{-1} s^{-1}.[4] The corresponding rate constant for MeO–C–CF_3 (Table 1) is ~1×10^8 dm^3 mol^{-1} s^{-1}, representing an enhancement of 20000, attributable to the CF_3-for-Me carbene substituent exchange. A parallel, but less dramatic effect is seen with the acrylonitrile substrate **3d**, where the k_c values are 1.5×10^6 dm^3 mol^{-1} s^{-1} for MeO–C–Me[4] and 1.4×10^8 dm^3 mol^{-1} s^{-1} for MeO–C–CF_3, a reactivity increase of ~90.

Rather than the pronounced nucleophilic selectivity pattern exhibited by MeO–C–Me,[4] MeO–C–CF_3, shows little electronically-based discrimination between alkenes. The CF_3 group does not stabilize MeO–C–CF_3 in a kinetic sense, rather it 'activates' the carbene. This is reminiscent of Cl–C–CF_3, where, relative to CCl_2, the replacement of Cl by CF_3 also leads to a significant loss of substrate selectivity by the carbene.[5] Indeed, calculational studies indicate that a CF_3-for-Me 'exchange' in Cl–C–Me, or a CF_3-for-Cl exchange in CCl_2, afford Cl–C–CF_3 with 28 or 25 kcal mol^{-1} less carbene 'stabilization energy', respectively.[5,11] No doubt the CF_3-for-Me exchange that formally converts MeO–C–Me to MeO–C–CF_3 is also accompanied by significant carbene destabilization.

The only selectivity manifested by MeO–C–CF_3 is toward tetramethylethylene **3a**, which is 20–30 times less reactive than alkenes **3b–d**; Dailey observed very similar behaviour in relative reactivity experiments.[3] The reactivity diminution with **3a** is very likely to be steric in origin. A related, though milder, trend is apparent with Cl–C–CF_3.[5] Alkene **3a** is also very unreactive towards MeO–C–Ph.[12]

In conclusion, MeO–C–CF_3 is voraciously reactive and electronically unselective in its reaction with alkenes. Despite the intuitively attractive possibility of push–pull stabilization by carbenic substituents of opposing properties, it is the 'pull' by CF_3 that appears to dominate the 'push' by MeO in the substituents' electronic tug of war. Relative to MeO–C–Me, this leads to enhanced reactivity for MeO–C–CF_3, rather than increased stability.

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