

Modulation of selectivity in a fluorocarbene cyclopropanation reaction: a catalytic role for bromide ion

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Abstract—Phenylfluorocarbene is diverted to phenylfluorobromomethide carbanion (PhCFBr[−]) by adding bromide ion. The carbanion adds to acrylonitrile leading, after expulsion of bromide, to 1-fluoro-1-phenyl-2-cyanocyclopropane.

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At the heart of Hine's classic mechanism for the hydrolysis of chloroform is a carbene–carbanion equilibrium (Eq. 1).¹ Similar equilibria govern the capture of CCl₂ by other halide ions, affording trihalomethide carbanions and thence, by protonation, 'mixed' haloforms; for example, CHCl₂Y.^{1b,d} Trihalomethide carbanions are also central to various methods for the generation of dihalocarbenes, including the reaction of NaI with PhHgCCl₂Br,² and the phase transfer catalytic generation of CCl₂,³ CBr₂,⁴ CBrCl,⁴ and CBrI.⁵ In these latter cases, carbene–carbanion equilibria play important roles.^{4,5}

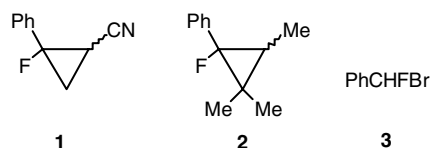


We recently showed that the deliberate manipulation of carbene–carbanion equilibria analogous to 1 permits the effective modulation of selectivity during carbene/alkene cyclopropanation reactions.⁶ Thus, the addition of chloride or bromide ions allows the concurrent cyclopropanation of electron-poor alkenes by an equilibrating mixture of phenylhalocarbenes and phenyldihalomethide carbanions, enabling a smooth variation of selectivity between electron-rich and electron-poor olefins.⁶ Here, we extend this methodology to a fluorocarbene, demonstrating that bromide ion functions as an 'umpolung catalyst' in the cyclopropanation of an electron-poor olefinic substrate.

Phenylfluorocarbene (PhCF) is known to be a moderate electrophile in addition to alkenes.⁷ Indeed, the relative

reactivity of acrylonitrile (ACN), an electron-poor olefin, versus trimethylethylene (TME), an electron-rich olefin, is 0.067^{7c} as determined by classical product-based competitive cyclopropanations⁸ of the paired substrates with PhCF generated photochemically from 3-phenyl-3-fluorodiazirine.^{7b,9}

However, the *apparent* selectivity of PhCF smoothly changes in response to the addition of bromide ion in the form of tetrabutylammonium bromide (TBABr). Thus, binary mixtures of 0.5 M TME and 0.5 M ACN in 1 M MeCN–THF solvent, containing varying quantities of added TBABr, were allowed to compete for PhCF generated by the photolysis ($\lambda > 300$ nm, $A = 2.5$ at 369 nm) of phenylfluorodiazirine. The products were cyclopropanes **1** and **2** from the additions of PhCF to (respectively) ACN and TME, as well as α -bromo- α -fluorotoluene (**3**). The latter, identified by GC–MS, arose by proton abstraction from the solvent by phenylfluorobromomethide carbanion (see below). The yield of **3** reached 13% at the highest concentration of bromide (0.49 M). Cyclopropanes **1** and **2**, each a mixture of *syn* and *anti* isomers, comprised the bulk of the product mixture, and were identified by GC and GC–MS comparisons with authentic samples. It is crucial to note that only PhCF adducts **1** and **2** were formed; adducts of PhCBr were absent. The mechanistic implications of this observation are discussed below.



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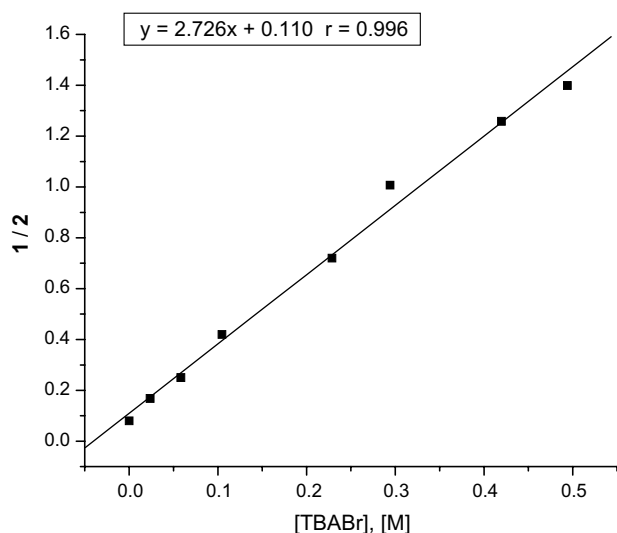


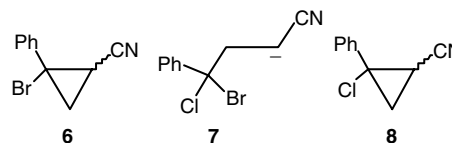
Figure 1. Product ratio (1/2) versus added TBABr (M) for the addition of PhCF to ACN/TME.

A correlation of the molar product ratio (1/2)¹⁰ versus the concentration of added TBABr for the addition of PhCF to ACN/TME appears in Figure 1. We observe that (1/2) smoothly increases from 0.080 in the absence of TBABr¹¹ to 1.40 in the presence of 0.494 M TBABr, a 17.5-fold increase. The change in product ratio seems to imply a change in the selectivity of PhCF from electrophilic to nucleophilic caused by the addition of bromide.

Mechanistically, these results can be understood in terms of Scheme 1. Here, PhCF generated by the photolysis of the diazirine is reversibly captured by bromide ion (k_1/k_{-1}), affording the phenylfluorobromomethide carbanion (4). Michael addition of 4 to ACN (which is probably reversible)¹² generates new carbanion 5, whence rapid ring closure with loss of bromide (*not* fluoride) gives cyclopropane 1 (overall rate constant k_4). Product 1 also forms directly by the addition of PhCF to ACN (k_3). However, carbanion 4 does not readily add to the electron-rich TME; cyclopropane 2 comes only from the addition of PhCF to TME (k_2).

As we increase the concentration of bromide, the equilibrium between PhCF and PhCFBr⁻ shifts to the right, augmenting the formation of cyclopropane 1 via carbanion 4, relative to the formation of cyclopropane 2 via PhCF. Therefore, the apparent selectivity for ACN increases, relative to TME, as illustrated in Figure 1. Bromide ion therefore functions as an ‘umpolung catalyst’

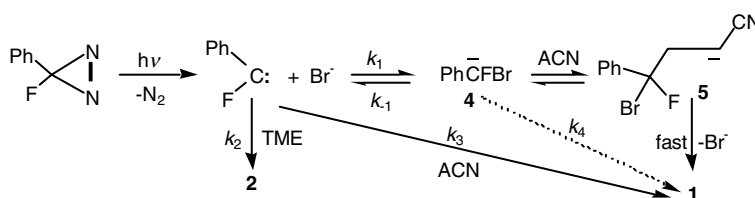
mediating the cyclopropanation of the electron-poor substrate. The key to this phenomenon is the exclusive expulsion of Br⁻ rather than F⁻ in the ring closure of carbanion 5 (as evidenced by the formation of cyclopropane 1 and the absence of cyclopropane 6). Of course, bromide is the superior leaving group; fluoride is not generally subject to nucleophilic displacement. Note that in the related closure of carbanion 7, formed by the addition of PhCClBr⁻ to ACN, Cl⁻ and Br⁻ are competitively expelled in a ratio of 1:1.5, leading to a mixture of cyclopropanes 6 and 8.⁶



Laser flash photolysis (LFP) enables us to visualize PhCF and PhCFBr⁻ (cf., Scheme 1). LFP of phenylfluorodiazirine in MeCN–THF gives an absorption for PhCF at 290 nm.¹³ In the presence of 0.2 M added TBABr, we also observe PhCFBr⁻ at 500 nm; see Figure 2.¹⁴

Carbanion 4, monitored at 500 nm, is quenched by added ACN with $k_q = 4.25 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, which we take as equivalent to k_4 in Scheme 1. Similarly, we measure $k_1 = 2.46 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for the quenching of PhCF by TBABr (monitored at 300 nm); $k_2 = 4.20 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for the quenching of PhCF by TME; and $k_3 = 2.23 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for the direct addition of PhCF to ACN. With these absolute rate constants, and the slope (2.73) of the correlation in Figure 1, it is possible to estimate $k_{-1} = 9.12 \times 10^5 \text{ s}^{-1}$, so that $k_1/k_{-1} = K_{\text{eq}} \sim 27 \text{ M}^{-1}$ for the equilibrium between (PhCF + Br⁻) and PhCFBr⁻ (see Scheme 1). However, this value is specific to the 1 M MeCN–THF solvent, and is likely to be solvent dependent. Moreover, the estimate ignores the probable solvent dependent aggregation of TBABr, as well as the reversibility of the addition of carbanion 4 to ACN. Therefore our estimates of k_{-1} and K_{eq} must be viewed with caution.

In conclusion, added bromide diverts PhCF to the phenylfluorobromomethide carbanion (4) which undergoes Michael addition to ACN leading, after closure of carbanion 5 with the release of bromide, to cyclopropane 1, the PhCF adduct of ACN. The action of bromide ion is functionally equivalent to catalytic umpolung of the normally electrophilic carbene, thus mediating the nucleophilic cyclopropanation of an electron-poor olefin. We are extending these studies to other fluorocarbenes and other substrates.



Scheme 1.

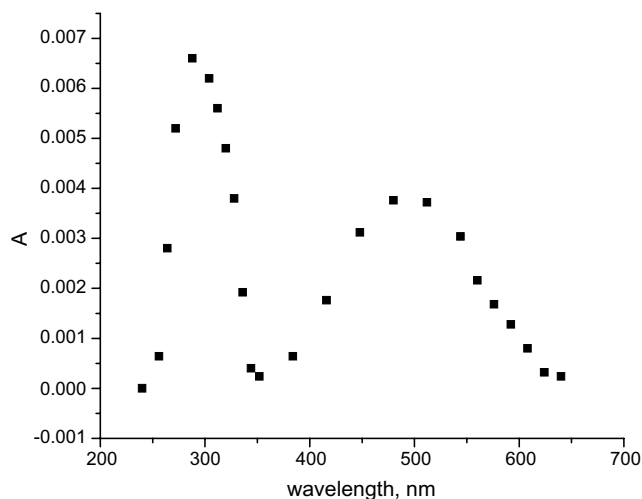


Figure 2. LFP-UV spectra of PhCF (290 nm) and PhCFBr⁻ (500 nm) in 1 M MeCN-THF.

Acknowledgements

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References and notes

- (a) Hine, J. *J. Am. Chem. Soc.* **1950**, *72*, 2438; (b) Hine, J.; Dowell, A. M., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 2688; (c) Hine, J.; Ehrenson, S. J. *J. Am. Chem. Soc.* **1958**, *80*, 824;

- (d) Hine, J. *Divalent Carbon*; Ronald Press: New York, 1964; pp 36f.
- Seyferth, D.; Gordon, M. E.; Mui, J. Y.-P.; Burlitch, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 959.
- (a) Dehmlow, E. V. *Annalen* **1972**, 148; (b) Dehmlow, E. V.; Slopianka, M. *Annalen* **1979**, 1465.
- Dehmlow, E. V.; Lissel, M.; Heider, J. *Tetrahedron* **1977**, *33*, 363.
- Dehmlow, E. V.; Broda, W. *Chem. Ber.* **1982**, *115*, 3894.
- Moss, R. A.; Tian, J. *J. Am. Chem. Soc.* **2005**, *127*, 8960.
- (a) Moss, R. A. *Acc. Chem. Res.* **1989**, *22*, 15; (b) Moss, R. A.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3828; (c) Moss, R. A.; Lawrynowicz, W.; Hadel, L. M.; Hacker, N. P.; Turro, N. J.; Gould, I. R.; Cha, Y. *Tetrahedron Lett.* **1986**, *27*, 4125.
- Moss, R. A.. In *Carbenes*; Jones, M., Jr., Moss, R. A., Eds.; Wiley, 1973; Vol. 1, pp 153f.
- Cox, D. P.; Moss, R. A.; Terpinksi, J. *J. Am. Chem. Soc.* **1983**, *105*, 6513.
- Product ratios were determined by capillary GC; the flame ionization detector was calibrated for differential response with known blends of **1** and **2**.
- With equimolar TME and ACN, this value (0.080) is equal to the relative reactivity of ACN/TME. We attribute the slight increase, relative to the literature value (0.067^{7c}), to the polar MeCN-THF solvent used in the present case.
- Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017.
- In a 3-methylpentane matrix at 77 K, PhCF is reported to absorb at 270 nm: Gould, I. R.; Turro, N. J.; Butcher, J., Jr.; Doubleday, C., Jr.; Hacker, N. P.; Lehr, G. F.; Moss, R. A.; Cox, D. P.; Guo, W.; Munjal, R. C.; Perez, L. A.; Fedorynski, M. *Tetrahedron* **1985**, *41*, 1587.
- Absorption maxima of PhCCl₂⁻ and PhCBr₂⁻ are observed at 410 and 430 nm, respectively, in MeCN-THF.⁶