Anion-Initiated Trifluoromethylation by TMSCF₃: Deconvolution of the Siliconate–Carbanion Dichotomy by Stopped-Flow NMR/IR

Craig P. Johnston,†,‡ Thomas H. West,†,‡ Ruth E. Dooley,† Marc Reid,† Ariana B. Jones,† Edward J. King,§ Andrew G. Leach,⊥ and Guy C. Lloyd-Jones*†

EaStChem, University of Edinburgh, Joseph Black Building, David Brewster Road, Edinburgh, EH9 3FJ, U.K.
School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, U.K.
TgK Scientific Limited, 7 Long’s Yard, St Margaret’s Street, Bradford-on-Avon, BA15 1DH, U.K.

Supporting Information

ABSTRACT: The mechanism of CF₃ transfer from R₃SiCF₃ (R = Me, Et, iPr) to ketones and aldehydes, initiated by M⁺X⁻ (<0.004 to 10 mol %), has been investigated by analysis of kinetics (variable-ratio stopped-flow NMR and IR), ¹³C/²H KIEs, LFER, addition of ligands (18-c-6, crypt-222), and density functional theory calculations. The kinetics, reaction orders, and selectivity vary substantially with reagent (R₃SiCF₃) and initiator (M⁺X⁻). Traces of exogenous inhibitors present in the R₃SiCF₃ reagents, which vary substantially in proportion and identity between batches and suppliers, also affect the kinetics. Some reactions are complete in milliseconds, others take hours, and others still fail to completion. Despite these differences, a general mechanism has been elucidated in which the product alkoxide and CF₃⁻ anion act as chain carriers in an anionic chain reaction. Silyl enol ether generation competes with 1,2-addition and involves protonation of CF₃⁻ by the α-C–H of the ketone and the OH of the enol. The overarching mechanism for trifluoromethylation by R₃SiCF₃, in which pentacoordinate siliconate intermediates are unable to directly transfer CF₃⁻ as a nucleophile or base, rationalizes why the turnover rate (per M⁺X⁻ initiator) depends on the initial concentration (but not identity) of X⁻, the identity (but not concentration) of M⁺, the identity of the R₃SiCF₃ reagent, and the carbonyl/R₃SiCF₃ ratio. It also rationalizes which R₃SiCF₃ reagent effects the most rapid trifluoromethylation, for a specific M⁺X⁻ initiator.

INTRODUCTION

The inclusion of fluoride substituents in organic molecules is of pivotal importance to developments in, inter alia, pharmaceuticals,¹ agrochemicals,² electronics,³ materials chemistry,⁴ polymers,⁵ synthesis,⁶ and catalysis.⁷ The transfer of a formally nucleophilic CF₃-moiety to an electrophile is a preeminent method for the synthesis of trifluoromethylated compounds.⁸ Conditions range from base-mediated reactions with fluoroform (CF₃H)⁹ through to finely tuned borazine-based CF₃ carbene carriers recently reported by Szymczak.¹⁰ In 1989, Ruppert reported that TMSCF₃ (1a)¹¹ undergoes addition to aldehydes and ketones in the presence of 10 mol % KF.¹² A faster process, using a soluble initiator (Bu₄NF·xH₂O; 0.6 mol %, TBAF) was reported soon after, by Prakash and Olah.¹³ Acetic workup affords the corresponding trifluoromethylated alcohols in good yield, Scheme 1.

Scheme 1. Trifluoromethylation of Ketones/Aldehydes¹²,¹³

This mild and selective process¹⁴ swiftly became adopted for the preparation of trifluoromethyl-carbinols,¹⁵ including enantioselective additions involving enantiopure ammonium salts as initiators.¹⁶ Indeed, over the past decade there has been an explosion of interest¹⁷ in CF₃ transfer from TMSCF₃ (1a) to carbon (e.g., carbonyls,¹⁴,¹⁷ imines,¹⁸ vinyl halides,¹⁹ and aromatics²⁰) and to heteroatoms such as sulfur,²¹ selenium,²² phosphorus,²³ boron,²⁴ iodine,²⁵ and bismuth.²⁶ The formal loss of fluoride from CF₃ to facilitate electrophilic TMSCF₃ transfer has also been developed, as have numerous metal-mediated and -catalyzed processes involving CF₃ derived from TMSCF₃ (1a).²⁷

Despite anion-initiated trifluoromethylation by 1a having become a mainstream synthetic method,¹⁷–²⁶ surprisingly little detail has emerged on the mechanism of CF₃ transfer, under the conditions of application, Scheme 1.¹⁷ Various mechanistic dichotomies, including, inter alia, fluoride initiation versus fluoride catalysis, and siliconate versus carbanion pathways, have been noted by Denmark³⁰a and by Reich,³⁰b both of whom emphasize the lack of salient kinetic data.

Received: June 27, 2018
Published: August 6, 2018

DOI: 10.1021/jacs.8b06777
RESULTS AND DISCUSSION

1. Prior Studies. In early studies, a termolecular anionic chain reaction (mechanism I, Scheme 2) was suggested for trifluoromethylation by 1a. This was later expanded to a two-step process (mechanism II), where a pentacoordinate alkoxysiliconate (B) delivers CF₃ to the ketone and in doing so liberates the O-silylated product. Mechanism II has been extensively adopted in the design and interpretation of asymmetric trifluoromethylation.

In 1999, Naumann and Kolomeitsev and Röschenthaler independently reported on the reaction of a range of soluble fluoride sources (e.g., [Me₄N⁺]⁻F⁻) with TMSCF₃ (1a) at low temperature. Detailed ¹H, ¹³C, ¹⁹F, and ²⁹Si NMR analysis identified the products as pentacoordinate complexes [Me₃Si(O)(CF₃)]⁻M⁺ (C) and [Me₃Si(CF₃)₂]⁻M⁺ (D). Both complexes decompose above −20 °C. The speciation (C/D) is dependent on the stoichiometry (M⁺F⁻/1a), and the structure of D was confirmed by single-crystal X-ray diffraction. Addition of cyclohexanone at −60 °C, followed by hydrolysis, afforded the corresponding trifluoromethylated alcohol, mechanism III.

In 2014, Prakash showed that the elusive trifluoromethyl anion(oid) can be detected in situ (¹⁹F NMR) at low temperatures after addition of KOtBu/18-crown-6 to 1a. With the bulky bimetal reagent TIPSCF₃ (1c), the generation of ion-paired [K(18-c-6)]⁻[CF₃⁻]⁻ (E) proceeds quantitatively at −78 °C over a period of 30 min. Subsequent addition of PhCOMe (11 equiv) or PhCHO (4 equiv) afforded CF₃-addition products (22–68%) after quenching with H₂O, mechanism IV. In 2015, Grushin demonstrated that use of crypt-222 (L, Scheme 2) facilitates generation of the free CF₃⁻ carbanion, a tetrahydrofuran (THF) solution-phase “non-covalently bound ionic species.” The structure of the highly air- and temperature-sensitive salt, [K(crypt-222)]⁻[CF₃⁻]⁻ (E), was confirmed by single-crystal X-ray diffraction.

The pioneering studies summarized above have been highly enlightening regarding the structure and stability of pentacoordinate (trifluoromethyl)siliconates (C, D) and their ability to release the trifluoromethane anion(oid) (E) under specific conditions. However, they do not yield direct detail on the kinetics and mode of transfer of CF₃ from TMSCF₃ (1a) to a carbonyl electrophile, using a catalytic fluoride-based initiator (M⁺X⁻), at ambient temperature.

2. Preliminary Investigations. We began by studying the reaction of TMSCF₃ (1a) with aldehydes and ketones in THF, chlorobenzene, and dimethylformamide (DMF). After addition of catalytic quantities (0.1 to 1 mol %) of TBAF, ¹⁹F NMR readily facilitated analysis of the proportions of residual reagent (1a) and the [1,2]-addition products. The reaction of 4-fluorocacetophenone (2) in THF at ambient temperatures proved ideal, the additional ¹⁹F nucleus allowing simultaneous analysis of reagent (1a; 0.48 M), substrate (2; 0.40 M), and product (3ₗ₉₃), Scheme 3.

Reactions were assembled manually in 5 mm NMR tubes in the glovebox prior to analysis in situ by ¹⁹F NMR. Three side-

Scheme 2. Mechanisms I–IV for Anion-Induced Trifluoromethylation of Ketones Using Ruppert’s Reagent (1a) and Homologues

Scheme 3. Trifluoromethylation of Ketone 2

**L = 18-c-6, crypt-222. See text for full discussion.**
products were identified: fluoroform (CF₃H), the silylenol ether (OTES), and a homologated addition product (OTES). Reactions conducted in d₆-THF proceeded analogously and generated CF₃H, not CF₃D. The identity of OTMS was confirmed by independent synthesis, is consistent with difluorocyclopropanation of silylenol ether 4 to form 10, followed by a known anion-induced ring-opening elimination to give fluoroone 11 and subsequent 1,2-selective trifluoromethylation. Addition of independently synthesized 10 to the reaction (Scheme 3) generated OTMS.

Reaction rates and extent of fluoromethane generation (Scheme 3) were found to vary significantly between batches of TBAF (1 M, THF, ~5 wt % H₂O). Replacing TBAF with anhydrous [Bu₄N][Ph₃SiF₂] (TBAT) gave more reproducible data. However, the fast turnover precluded detailed kinetic analysis; this aspect was addressed using stopped-flow methods, vide infra. Nonetheless, ¹⁹F NMR analysis revealed that CF₃H is liberated in two distinct phases. The first is an initial burst of extremely rapid CF₃H generation and arises from TBAT-catalyzed reaction of TMSCF₃ (1a) with traces of adventitious water. The second phase of CF₃H generation proceeds in concert with reaction of the ketone (2) and directly correlates with the rate of generation of silylenol ether (4), as confirmed by ²H-labeling (d₂-2 → CF₃D + d₂-4OTES). The selectivity (OTES versus 4OTES) is discussed later.

3. Stability, Inhibition, and Tests for Radicals. The stability of the reaction system after complete consumption of the limiting reagent (ketone 2 or TMSCF₃, 1a) was found to depend on which one was in excess. Reactions in which 2 was in excess underwent turnover on addition of further TMSCF₃, 1a, even after a period of many hours. In contrast, for reactions where 1a was in excess, additional 2 had to be added within a few minutes to fully reinitiate turnover (see SI), consistent with the known instability of pentacoordinate trifluoromethylsilicones, e.g., C and D, at ambient temperatures.

Further tests established that the reactions were not sensitive to exogenous water per se, as they rapidly self-dehydrated via generation of CF₃H + hexamethyldisiloxane, prior to reaction of the ketone (2). The rates were unaffected by visible light, by exogenous product (OTES), and by CF₃H. Deliberate sparging of the normal reaction mixture (1a/2/TBAT 0.15 mM, 0.038 mol %, THF, Scheme 3) with air caused complete inhibition of turnover, but only when a sufficient volume of CO₂ (~400 ppm) had been added to convert the active anion(s) into trifluoracetate (i.e., [Bu₄N][CF₃CO₂], detected by ¹⁹F NMR). Separate controls confirmed that the rate of trifluoromethylation is unaffected by CO₂-scrubbed air and that [Bu₄N][CF₃CO₂] is not effective as an initiator.

However, the reactions were inhibited by addition of the persistent radical tetramethylpiperidinooxy (TEMPO). Indeed, just 0.45 mM TEMPO induced complete inhibition of the reaction of 1a with 2, initiated by 0.15 mM TBAT (Scheme 4, A). In contrast, TEMPO had a negligible impact on reactions employing TES (1b) and TIPS (1c), even when present at much higher concentrations (80 mM TEMPO); the origins of this profound difference in behavior is discussed later. Nonetheless, further tests for discrete radical intermediates were conclusively negative: 4-F-benzophenone (12) exclusively underwent 1,2-addition (Scheme 4, B), cyclopropyl ketones (6/7) reacted without any trace of competing ring-opening (Scheme 4, C), and competition between ketone 2 and 4-biphenyl methyl ketone for limiting TMSCF₃ (1a) favored 2 (k₁ = 1.93).
the ratios of enol/addition product (4OSi/3OSi) were all constant throughout the reaction evolution, Figure 2. A further distinction originated from the impact of the addition of crypt-222 to KOPh-initiated reactions. As noted above, for TMSCF3 (1a) the incarceration of the K⁺ in the crypt-222 ligand substantially attenuates the rate and selectivity. In stark contrast, for TIPSCF3 (1c), turnover is substantially accelerated by addition of crypt-222 to inhibit K+/anion pairing.

Table 1. Examples of Effect of Initiator M⁺ and Reagent (1a−c) on Selectivity (3OSi/4OSi) and Rate of Trifluoromethylation of 2

<table>
<thead>
<tr>
<th>M⁺</th>
<th>[M⁺X⁻]₀, mM</th>
<th>TMS 1a 3/4OSi (time)³</th>
<th>TES 1b 3/4OSi (time)³</th>
<th>TIPS 1c 3/4OSi (time)³</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Bu₄N]⁺</td>
<td>1.5</td>
<td>12/1 (&lt;90 s)</td>
<td>1.5/1 (&lt;90 s)</td>
<td>1/1 (30 min)</td>
</tr>
<tr>
<td>[K⁺]</td>
<td>0.15</td>
<td>36/1 (&lt;90 s)</td>
<td>3.0/1' (&lt;30 min)</td>
<td>NR</td>
</tr>
<tr>
<td>[K(L)]⁺</td>
<td>1.5</td>
<td>6.6/1 (6 min)</td>
<td>2.4/1 (&lt;90 s)</td>
<td>1/1 (3.6 min)</td>
</tr>
</tbody>
</table>

Selectivity 3OSi/(4OSi+CF₃H) measured in situ by ¹⁹F NMR after manual assembly in an NMR tube; selectivity is independent of X⁻. Times indicated are for >97% conversion of 2, at 300 K. ⁸⁵% conversion. [K(L)]⁺ = K(crypt-222)⁺; generated in situ from KOPh + crypt-222. NR = No reaction.

Scheme 5. Effect of Initiator M⁺ on Reaction Constant (ρ)

(i) 4-Z-C₆H₄COR (0.2 M), 2/13 (0.2 M), 1a (0.04 M), PhF (0.4 M), MX (0.00015 M; 0.038 mol %). Z = Ph, OMe, CF₃, Me, Br. Hammett rho values calculated from product ratios; see SI.

Figure 1. Competition between TMSCF₃ (1a)/TESCF₃ (1b); see text for full discussion. Reaction conditions: 2 (0.4 M), 1a (0.24 M), 1b (0.24 M), PhF (internal standard, 0.4 M), TBAT (75 μM, 0.019 mol %); ¹⁹F NMR analysis, manual assembly.

Figure 2. Constant ratio of [4OSi]/[3OSi]. Conditions: 2 (0.4 M), 1a−c (0.48 M), PhF (internal standard, 0.4 M), MX (TBAT 150 μM for 1a; KOPh 0.15 mM for 1b, TBAT 1.5 mM for 1c).

Reactions with labeled ketone (aryl-d₄-2; CD₃-d₂; ¹³CO-2) were also instructive, Table 2. Reaction of TMSCF₃ (1a) with

Table 2. KIEs and ²H Exchange in the Reaction of Ketone 2

<table>
<thead>
<tr>
<th>Cl₃ (reagent)</th>
<th>1a−c</th>
<th>2,3OSi</th>
<th>k₁₃/k₁₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃ (¹³C=O)</td>
<td>1a</td>
<td>CH₃</td>
<td>1.008¹</td>
</tr>
<tr>
<td>CH₃ (C,D₁₀)</td>
<td>1a</td>
<td>CH₃</td>
<td>1.038²</td>
</tr>
<tr>
<td>CD₃</td>
<td>1a</td>
<td>CD₃</td>
<td>6.4</td>
</tr>
<tr>
<td>CD₃ + CH₃</td>
<td>1a</td>
<td>CD₃/CH₃ only</td>
<td>6.1 (rate: CF₃H/CF₃D)</td>
</tr>
<tr>
<td>CD₃</td>
<td>1b</td>
<td>CD₃</td>
<td>3.1</td>
</tr>
<tr>
<td>CD₃ + CH₃</td>
<td>1b</td>
<td>partial CD₃+H₃</td>
<td>3 (3/4OTES = 2.3/1)</td>
</tr>
<tr>
<td>CD₃</td>
<td>1c</td>
<td>CD₃</td>
<td>1.1</td>
</tr>
<tr>
<td>CD₃ + CH₃</td>
<td>1c</td>
<td>full CD₃+H₃</td>
<td>1.0 (rate: CF₃H/CF₃D)</td>
</tr>
</tbody>
</table>

¹Ketone (2/¹³H₂; 0.40 M), 1a−c (0.48 M), THF, 300 K. TBAT (0.04 mol %, 0.15 mM). ²Selectivity 3OSi/(4OSi + CF₃H/D) and exchange measured in situ by ¹⁹F NMR analysis. ³KIE determined by competition with aryl-d₄-2. ⁴²H KIE induced by aryl-deuteration, determined by competition with unleveled 2.
2 initiated by TBAT (0.15 mM) proceeds with a very low $^{13}$C kinetic isotope effect (KIE), determined by competition with aryl-d$_2$-2, after normalizing for the effect of aryl deuteriation.

In contrast, a substantial primary $^2$H KIE, determined from [CF$_3$D] versus [d$_3$-3OTMS], as in Figure 2, increases the addition/enol selectivity ($k_8/k_9 = 6.4$). Reactions of mixtures of 2 and d$_3$-2 proceeded with no detectable scrambling of D/H between 2/D$_3$-2 during turnover, provided that $[1a]_0 > [2]_0$ and again proceeded with a high KIE ($k_8/k_9 = 6.1$). With TESCF$_3$ (1b) a moderate KIE ($k_8/k_9 = 3.1$) was observed, with a trace of D/H exchange between 2 and D$_3$-2 on co-reaction, and thus into products d$_3$-3/d$_3$-4. With TIPSCF$_3$ (1c) there was no significant KIE and a statistical mixture of isotopologues of d$_3$-2/3 ($n = 0$–3) was evident immediately after initiation of the reaction.$^{14}$

6. Variable-Ratio Stopped-Flow NMR and IR. Detailed exploration of the kinetics of the trifluoromethylation by 1a required techniques for rapid acquisition of kinetic data (some systems had formal turnover frequencies well in excess of 5000 s$^{-1}$, vide infra) in a time- and material-efficient manner. Stopped-flow techniques are ideal for rapid and reproducible initiation and analysis of these reactions. However, the classic fixed-ratio dual input mode of operation ($A + B$; Figure 3a)

requires separate solutions to be prepared for every variation in conditions. For a three-component process such as R$_3$SiCF$_3$ (1) + ketone 2 + initiator (M′$^{−}$X$^{−}$), a very large number of stock solutions are required to study reactions with different concentrations of reactants and initiator.

To address this issue, we constructed a stopped-flow system, in which the delivered volumes of three solutions ($A$, $B$, $C$) are independently variable,$^{15}$ using a computer-controlled triple stepper-motor system, Figure 3b. This setup allowed systematic analysis of the kinetics across a wide range of initial conditions, using just four stock solutions, mixing {i + iii + iv} varies $[1]_0$; mixing {ii + iii + iv} varies $[1]_0$; and mixing {ii + iv + THF} varies $[M′X′]_0$ while keeping the other species constant; see SI for full details. The new system was implemented in two modes: IR and NMR.$^{56}$ The former simply required adaptation of our recently developed thermostated ATR-FTIR stopped-flow cell,$^{57}$ replacing the dual mixing stage with a triple mixer and a gated reaction volume. The analogous setup for variable-ratio stopped-flow NMR required bespoke construction. The principles for continuous-flow NMR recently reported by Foley et al.$^{58}$ were employed for the basic design, such that the reaction vessel and associated components can be installed simply by insertion of the device into the sample transit of a standard unmodified NMR spectrometer. Nuclei premagnetization is facilitated in three independent reservoirs ($A$, $B$, $C$) located as close as possible to the magnetic field center, Figure 3c. The reservoirs connect at a tripodal-geometry mixer that discharges via a 0.5 mm i.d. glass capillary into a 3 mm external diameter 300 µL glass NMR flow-cell. The tube terminates at the base of the cell, with the waste outlet at the top. A fourth input to the mixer allows the system to be flushed with solvent between runs. Thermostating is achieved by passage of a heat-transfer medium (aqueous ethylene glycol), using an externally controlled recirculator, through an umbilical containing all stages of the stopped-flow circuit, except for the glass flow-cell, which is located within the spectrometer-thermostated probe head; precalibration ensures temp1 = temp2. During a typical stopped-flow (SF) “shot”, a total of 600 µL is delivered through the flow-cell at a rate of 1–2 mL s$^{-1}$, fully displacing the previous contents and replacing it with 300 µL of freshly assembled reaction mixture; charging requires 70–130 ms (measured independently by UV–vis), with high-quality NMR spectra (N$_2$-cryoprobe) achievable immediately thereafter. Control of the timing of the NMR pulse sequence is achieved by a trigger signal, sent to the spectrometer console from the computer-controlled triple stepper-motor system, immediately after the 300 µL flow-cell has been freshly charged.

7. Kinetics of Trifluoromethylation by TMSCF$_3$ (1a) and TIPSCF$_3$ (1c). The kinetics of reactions initiated by M′$^{−}$X$^{−}$, where M′ = Bu$_4$N$^+$, K$^+$, and Cs$^+$, were studied in detail by SF-IR and SF-NMR across a wide range of concentrations of 1a, 2, and [M′X′]$_0$. For FTIR, the decay in the IR C–F stretching mode (1056 cm$^{-1}$) of the TMSCF$_3$ (1a) and the growth in C–F stretching mode (1165 cm$^{-1}$) of 3$_{OTMS}$ were collected at scan rates of 14 or 28 s$^{-1}$, with a resolution of 2 or 8 cm$^{-1}$, respectively.$^{19}$F NMR analysis allowed detailed analysis of the reaction components, but was naturally more limited in terms of temporal resolution. For faster reactions, a technique involving the interleaving of a series of spectra from a sequence of stopped-flow NMR “shots” was employed, affording a higher virtual temporal resolution.

A key component in analysis of the kinetics was the dependence of the temporal-concentration evolution of the product (3$_{OTMS}$) on the concentration ratio of ketone 2 and TMSCF$_3$ (1a). Systematic studies of initial rates using TBAT led to an empirical rate equation for turnover frequency (TOF) in which the initiator (Bu$_4$N$^+$X$^-$) and ketone 2 are first order and the TMSCF$_3$ (1a) reagent approximately inverse first order (eq 1).$^{59}$ Control experiments in which the reactions were run in the presence of exogenous product (3$_{OTMS}$) confirmed that it does not act as an inhibitor.
The inhibitory effect of the TMSCF₃ reagent 1a (Kᵢ, eq 1) results in very distinctive temporal concentration profiles for the reaction, simulations of which are presented later. For example, when the initial ratio of reactants is equal ([2]₀ = [1a]₀), their ratio remains constant ([2]/[1a] = 1) throughout the reaction. What arises is an apparent pseudo-zero-order consumption of the reactants (TOF = k₁(obs)) for the majority of the reaction evolution. Conversely, when there is an excess of ketone 2 over 1a, the rate of turnover rises as a function of conversion, becoming very rapid in the later phases of reaction where [2]/[1a] ≫ 1.

\[
\text{TOF} \approx \frac{k₁\text{obs}[\text{M}^+\text{X}^-][2]₀(1 - x_{\text{fl}})}{1 + K_1[1]₁} ≈ k₁\text{obs}[2]₁
\]

(1)

\[
\text{TOF} \approx \frac{k₁\text{obs}[\text{M}^+\text{X}^-][1a]₀(1 - x_{\text{fl}})}{1 + K_{12}[2]₂} ≈ k₁\text{obs}[2]₂
\]

(2)

Systematic studies using M⁺X⁻ (M⁺ = Li⁺, Na⁺, K⁺, Cs⁺), which induce very rapid turnover, proved more challenging. Reactions where M⁺ = Li⁺ and Na⁺ stalled before completion and were not reproducible. KOPh and CsOPh initiated at very low concentrations, without an evident induction period, proceeded to completion, and provided reproducible kinetics. Study of the initial rates suggested higher-order dependencies on TMSCF₃ ([1a]₀ again inverse) and on [M⁺X⁻]₀ with the ketone 2 remaining first-order. However, the reactions evolve with near-identical behavior to those initiated by TBAT (eq 1). The dichotomy is indicative of the presence of exogenous inhibitor(s) in low concentration in the TMSCF₃ (1a) reagent that are not consumed during reaction. Increasing the initial concentration of the reagent ([1a]₀) or decreasing the initiator concentration ([M⁺X⁻]₀) causes a greater mole fraction of exogeneous inhibition (x_{fl}), eq 1. Addition of [K⁺][[(C₆F₅)₄B]⁺]⁺, to provide an additional soluble K⁺ source with a non-nucleophilic counteranion, had no impact on the kinetics of reactions initiated by KOPh, indicative that the rate is dependent on the initiating anion concentration and the countercation identity (but not its concentration). Addition of potassium-binding ligands attenuated the rates substantially, and with crypt-222, the system underwent turnover slower than with Bu₄N⁺ (a 3 orders of magnitude rate reduction compared to free K⁺).

The kinetics of trifluoromethylation of 4-fluorobenzaldehyde (13) by 1a were also explored using TBAT as initiator. The aldehyde undergoes significantly faster trifluoromethylation than ketone 2 (k_{fl}/k₁ = 80, at 21 °C), requiring lower initial TBAT concentrations and causing the traces of exogeneous inhibitor(s) in 1a to complicate the kinetics. Competing ketone 2 with aldehyde 13 (9/1 ratio) using stopped-flow ¹⁹F NMR to analyze the transient substrate ratio (2/13) during the first 5–30 s of reaction indicated that the relative rate of trifluoromethylation is independent of [TBAT]₀ (96–384 μM) and 1a (0.08 to 0.48 M). Overall, the data are indicative that aldehyde 13 follows the same general kinetics as ketone 2, i.e., eq 1. The rate of trifluoromethylation of ketone 2 using TIPSCF₃ (1c) was much slower than with 1a. Again, the kinetics were impacted by exogenous inhibitor(s) in the reagent ([1c]₀), the effect of which (x_{fl}) varied from batch to batch of 1c; see SI. Using TBAT as initiator, the reactions evolve with a first-order dependency on the inhibitor and on the reagent ([1c]₀), with inhibition by the ketone (K_1, eq 2).

In other words, the kinetic dependencies are the opposite to that found for 1a (compare eqs 1 and 2), with reactions accelerating when there is an excess of 1c over 2. Reactions of 2 with 1c initiated by KOPh were slower than those initiated by TBAT and were accelerated on addition of crypt-222, the opposite phenomena to those observed with 1a.

8. Stopped-Flow ¹⁹F NMR Analysis of Silicate and Alkoxide Intermediates, Exchange Dynamics with TMSCF₃ and Initiator Regeneration. By use of 4-F-benzophenone (12; δ₂ = −107.0 ppm), which reacts slower than 2, and reducing the reaction temperature to 275 K, the temporal speciation of the initiator-derived species (10 mol % TBAT) was monitored using stopped-flow ¹⁹F NMR, Figure 4.
The known but unstable hypervalent bis-CF₃-siliconate (D; δF −63.3 ppm)³²−³⁴ is generated instantly. Integration against fluorobenzene (internal standard, δF −113.2 ppm) shows D to be present at 10 mol % and thus the predominant anion speciation. A key feature in the time series is the dynamic line-broadening in D that is constant throughout the reaction, but develops in the TMSCF₃ (1a) reagent (δF −66.6 ppm) as its concentration is depleted by the overall reaction with super-stoichiometric ketone 12. In parallel with this is a marked acceleration in product generation (14OTMS, δF −72.4 and −113.7 ppm), consistent with eq 1. After 6 s, the TMSCF₃ (1a) is fully consumed and TBAT (δF −97.4 ppm) is regenerated from Ph₃SiF/Me₃SiF. The dynamic line-broadening in D/1a can be satisfactorily simulated using a three-spin exchange process in which D is in rapid dissociative equilibrium (k_{exch} ≈ 180 s⁻¹; ΔG°^‡ ≈ 13 kcal mol⁻¹) with 1a and a low concentration of (unobserved) [Bu₄N][CF₃] (E)⁶². At 300 K, the line-broadening is very extensive and D short-lived.

Analogous experiments using TIPSCF₃ (1c) gave a very different outcome. Reactions conducted with 1c at 275 K were slow enough to be followed using ketone 2 (δF = −106.7 ppm), Figure 5. The ¹⁹F NMR signal for 1c remains sharp until 2 has been fully consumed. In contrast to reactions with 1a (Figure 4) the alkoxide (3_{O⁻}; δF = −118.4) is present in significant concentration and exhibits dynamic line-broadening (see inset in Figure 5). The signal for ketone 2 also exhibits dynamic line-broadening, immediately after addition of TBAT. On complete consumption of 2 (∼120 s), the signals for remaining 1c and CF₃H are broadened, presumably due to indirect exchange involving CF₃⁻. After a further 300 s, 1c is fully consumed and the CF₃H doublet becomes sharp again.

9. General Mechanism for Anion-Initiated CF₃ Transfer from R₃SiCF₃ to Ketones and Aldehydes. The data outlined in Sections 2 to 8 above (see SI for full details) indicate that the M’X⁻–initiated trifluoromethylation of ketone 2 by TMSCF₃ (1a) involves an electrophile–nucleophile reaction, in which the CF₃ transfer is accompanied by M’.

Figure 5. Selected spectra from in situ ¹⁹F NMR analysis (manual assembly) of the reaction of 4-F-acetophenone 2 (0.20 M) with 1c (0.24 M) in THF at 275 K after initiation by 10 mol % TBAT (t = 0, no TBAT). Inset: Line-broadening in ketone 2 and alkoxide 3_{O⁻} (++) C₆H₅F is internal standard. (x) = 3_{O⁻}. Free 4_{O⁻} not located, possibly due to degenerate exchange with 2. Ph₃SiF is not observed.

Figure 6. Selected structures and energies (M06L/6-31+G*; PCM (THF); standard state, 1 M; 298 K) of naked anions in the reaction of ketone 2 with R₃SiCF₃ 1a–c. Energies have been normalized to [CF₃⁺ + 1 + 2] = 0.00 kcal mol⁻¹. See text, Figure 9, and the SI for discussion of the binding modes and effects of cations. The structures and energies of other potential intermediates examined, including hexacoordinate dianions and fluoride adducts, are provided in the SI.
Enolsilane 4_TMS is also generated (≤2% when M’ = K’ and 7% when M’ = Bu4N+) with coproduct CF3-H (k6/k7 = 6.1). Using TIPSCF3 (1c), approximately 50% of the product is 4_TIPS and k6/k7 = 1.0. Contrasting kinetic behavior is observed for 1a (eq 1) versus 1c (eq 2), with the roles of reactant for turnover and inhibitor reversed between the two systems. These disparate sets of observations can easily be misinterpreted as turnover for 1a versus 1c arising from different pathways, e.g., silicate versus carbanion. However, analysis of the kinetics, KIEs, and DFT calculations of a wide range of potential intermediates (see SI) eventually leads to the conclusion that the two reagents elicit contrasting kinetics, selectivity (3 OSS/4 OSS), and KIEs, by biasing one of two extremes in a single overarching mechanism.

Calculations employed the M06L/6-31+G* level of theory, which was selected from a range of other functionals and larger basis sets that were considered35 (see SI), as it provided the best quantitative agreement with experiment. All calculations were performed in Gaussian09,64 with THF solvation incorporated via a polarizable continuum model (PCM) single point at the same level of theory and with T = 298 K and pressure at 24.45 atm to achieve a 1 M standard state.65—66 Kinetic isotope effects were computed using the Kinisot program.65 Some of the TES- and TIPS-bearing structures required the “loose” settings during the geometry optimization, presumably because of the flat potential energy surface associated with the long Si–CF3 bonds.

The calculations permitted several possible structure types (such as hexacoordinate silicon dianions) to be excluded from consideration and also revealed pronounced differences between intermediates based on TMS, TES, and TIPS, where the increasing steric bulk substantially destabilizes the pentacoordinate anions, Figure 6. Extensive calculations were conducted to test for direct nucleophilic reactivity of the pentacoordinate anions B and D. All calculations revealed that direct transfer of CF3 from the silicon center to an electrophile requires concomitant inversion of the CF3 with a prohibitively large barrier (>100 kcal mol–1; in line with the barrier for inversion of the free CF3 anion).67 The pentacoordinate silicate anions thus act as reservoirs, not active nucleophiles, liberating free (non-silicon-coordinated) CF3 via dissociation. The transition state for addition of the CF3 anion(oid) to the ketone formally involves movement between a nonclassical hydrogen-bonded complex and the addition product, a process that occurs with low calculated barrier (7.5 kcal mol–1) and well represents the process that occurs once the two species are in contact. The calculations support the known preference for deprotonation (kCH) in the gas phase68 and for addition (kCO) once solvation is introduced, as observed experimentally for TMSCF3 (1a). The loose addition transition state leads to a negligible 19C KIE (carbonyl) for addition, while a large primary 1H KIE is computed for C–H deprotonation. Relative rates computed from activation free energies suggest ρ = 2.0 for addition to acetoephones and a lower barrier for addition to 4-F-benzaldehyde (13) versus 2 (∆∆G‡ = 2.6 kcal/mol; krel = 81). All of these computed values are in excellent agreement with experiment.

A general mechanism for the trifluoromethylation of ketones and aldehydes by R2SiCF3 reagents (1) in the presence of a catalytic quantity of initiator (M’X–) thus can be assembled, Figure 7. The one overarching mechanism, described below in the context of two extremes (Vi and Vii), rationalizes why the turnover rate (per M’X– initiator) for a given electrophile depends on the initial concentration (but not identity) of X–, the identity (but not concentration) of M’, the identity of the reagent (1a–c), and the electrophile/reagent ratio (2/1).

10. Mechanism Vi. In this regime, which describes reactions involving TMSCF3 (1a), the dominant anion speciation is the bis(trifluoromethyl) silicate anion (D), generated in rapid equilibrium with CF3– (E), and 1a, as observed by NMR, Figure 4. The product-determining step (k2) involves reaction of CF3– (E) with the ketone (2) (kCO + kCH), and the reagent (1a) thus acts as a reversible inhibitor. The stronger the association of M’ with CF3– (see Section 13) and with the carbonyl oxygen, the faster the turnover rate: Bu4N+ < K(crypt-222) < K(18-c-6) < K+. The initial concentration ratios of the reactant versus the reagent dictate the temporal evolution of the reaction. When [2]/[1a] ≥ 1, pseudo-zero-order kinetics are obtained, whereas when [2]/[1a] ≤ 1, the rate rises throughout the reaction, becoming very fast (asymptotically to krel[D]) in the final stages. The kinetics of trifluoromethylation of ketone 2 by TMSCF3 (1a) can be satisfactorily simulated, Figure 8, using a truncated form of mechanism Vi that retains relationships
required for TOF modulation as the temporal concentration ratio \([2]_0/[1a]_0\) evolves.

\[
\begin{align*}
&k_1k_F \approx 7.1 \pm 1.2 \text{ s}^{-1} \\
&k_2k_i \geq 2k_1 \geq 2000 \text{ M}^{-1} \text{s}^{-1}
\end{align*}
\]

Figure 8. Simulation of experimental data (open circles, SF-IR; \([3_{\text{OTMS}} + 4_{\text{OTMS}}]\)) based on simplified mechanism \(V_i\), for reaction of ketone 2 with TMSCF₃ (1a), initiated by 3.6 mM TBAT (Bu₄N⁺X⁻). For \([2]_0/[1a]_0 > 1, [2]_0 = 0.40 \text{ M and } [1a]_0 = 144, 192, 248, 288, 336, 384 \text{ mM (i to vi)}. For \([2]_0/[1a]_0 < 1, [1a]_0 = 0.48 \text{ M and } [2]_0 = 400, 320, 240, 200, 160, 120, 80 \text{ mM (vii to xiii)}. Induction and turnover by 1a are set to arbitrary high values. Fitted parameters (\(k_i, k_0, k_{−}i\)) are as indicated; \(k_{−i} = 0\).

11. Mechanism \(V_i\). In this regime, which describes reactions involving TIPSCF₃ (1c), the dominant anion speciation is a combination of the product alkoxide \((3_{\text{O}})\), the enolate anion \((4_{\text{O}})\), and MX. Ketone 2 can reversibly H-bond (see F in Figure 7) with oxy-anions \(3/4_{\text{O}}\), as observed by NMR, Figure 5, leading to inhibition \((K_k)\). When \([1c]_0/ [2]_0 = 1\) pseudo-zero-order kinetics are observed; reactions in which \([1c]_0/ [2]_0 > 1\) exhibit accelerating rate in the last stages of reaction. The more strongly bound \(M’\) to \(3/4_{\text{O}}\), the slower the reaction with \(1c\), leading to rates increasing in the series \(K’ < [K(18-c-6)]^1 < Bu_4N’ < [K(crypt-222)]\), i.e., the opposite order to \(V_i\). When the nonenolizable ketone 4-F-benzophenone 12 is employed, the kinetics show clean pseudo-first-order decay in 1c (see SI), with no inhibition by 12 (i.e., mechanism \(Vii\), where \(K_{−i} = 0\), and eq 2, where \(K_{−i} = 0\)).

12. Competing Enolization. Also shown in Figure 7 is the generation of the enol ether \((4_{\text{O}})\) and CF₃H from ketone 2, for which the selectivity \((4_{\text{O}})/3_{\text{O}}\) is dependent on \(M’\) and the reagent (1a–c), Table 1. The major pathway for generation of \(4_{\text{OTMS}}\) in mechanism \(V_i\) is via C–H deprotonation \((f_{\text{CH}})\) with an attendant large primary \(^2\)H-KIE.\(^{70,71}\) In contrast, for mechanism \(V_{ii}\), the significant concentration of \([3/4_{\text{O}}]\) allows keto–enol equilibrium \((PK_{\text{enol}} \approx 8)\) in 2 to be approached, with attendant intermolecular scrambling of \(^2\)H between ketone methyl groups. Deprotonation \((k_{\text{enol}})\) of the enol \((2_{\text{enol}})\) is predicted (DFT) to be of very low barrier and thus proceed with a negligible \(^2\)H-KIE.\(^{70}\) Despite their different origins \((f_{\text{CH}}\) versus \(k_{\text{enol}})\) mechanisms \(V_i\) and \(V_{ii}\) both lead to \(4_{\text{OSi}}/3_{\text{OSi}}\) ratios that are independent of the concentration of reactants \((1, 2)\) and constant throughout the reaction, Figure 2.

13. Cation–CF₃ Interactions. The interactions between the CF₃⁻ anion (free and Si-bound) and the counter-cations K’ and Me₄N’ (as a model for Bu₄N’) were explored computationally, with multideterminate CF₃ interactions found to be favored, e.g. Figure 9; see SI for details.

The indirect transfer of CF₃ from reagent 1a to the ketone/aldehyde, i.e., via a silicon-free carbanion E, has implications for the mode by which enantioselective catalysis can be achieved using chiral ammonium initiators, e.g., cinchonidinium salts. The CF₃⁻ anion binding modes found computationally for Me₄N’ (Figure 9i) show how an ammonium cation might simultaneously interact with a CF₃⁻ anion and control a developing alkoxide anion, Figure 9ii. Mechanism \(V_i\) contrasts most,\(^ {16d,e,31}\) but not all,\(^ {16f}\) prior interpretations, where mechanisms II/III (Scheme 2) involving CF₃-siliconates for the mode by which enantioselective catalysis can be achieved using chiral ammonium initiators, e.g., cinchonidinium initiators. Inset: Structure of TS for addition of enantioselective addition beneath the quinuclidinium core of a cinchonidinium initiator. Figure 9. Cation binding to free CF₃ anion: (i) various modes of binding of K’ and Me₄N’ cations; (ii) concept (schematic) for enantioselective addition beneath the quinuclidinium core of a cinchonidinium initiator. Inset: Structure of TS for addition of enantioselective addition beneath the quinuclidinium core of a cinchonidinium initiator.
Thus, the initiator \( \text{M}^X \) affects the rate of reaction in a number of ways. \( \text{X}^− \) sets the initial concentration of the silicate \( [\text{D}]_0 = (1 - x_{\text{FF}})[\text{X}^−]_0 \), which, in the absence of endogenous inhibitors, is essentially constant throughout the reaction. The insurmountable barrier for CF3 inversion means that, independent of the identity of the electrophile, \( \text{E} \), or proton donor, \( \text{H} \), the silicate is unable to effect direct anionic trifluoromethyl transfer, Figure 10i. In all cases, the reaction must proceed via a dissociative pathway, Figure 10ii, in which \( \text{M} \) plays a key role: the stronger the association of \( \text{M}^+ \) with \( \text{CF3} \), the more favorable \( k_{\text{FF}} \). In contrast, efficient regeneration of the silicate \( k_{\text{FF}} \), Figure 7) is favored by weaker interactions between \( \text{M}^+ \) and the anionic coproduct from trifluoromethyl transfer \( \text{CF3}^−; \text{E} \); \( \text{R}^+ \); or products thereof). When the anion is unable to react with \( \text{1a} \), stoichiometric initiation by \( [\text{M}^X]^+ \) is required.\(^{14−26} \)

**15. Exogenous Inhibition.** Trifluoromethylations initiated by low concentrations of \( [\text{M}^X]^+ \) are highly sensitive to traces of exogenous inhibitor(s). Species that generate an anion \( [\text{LG}^−] \) of insufficient reactivity toward \( \text{1a} \) to propagate will terminate the anionic chain reaction, Figure 10iii. In a series of control experiments, additives of the form \( \text{Z-LG} \), \( \text{Z} = \text{H}, \text{R}_3\text{Si}, \text{LG} = \text{Cl}, \text{Br} \) were found to function as powerful inhibitors for the anion-initiated reaction of \( \text{2} \) with \( \text{1a} \). For example, the trifluoromethylation of \( \text{2} \) \((0.4 \text{ M})\) initiated by \( 150 \mu\text{M} \) \( \text{TBAT} \) ceases immediately on addition of \( 150 \mu\text{M} \) \( \text{TMSCl} \); see SI. Slower-onset irreversible inhibition is effected by the more hindered TIPSCI, which also inhibits the reaction of TIPSCF\(_3\) \((1c)\). Competing consumption of \( \text{1a} \) is effected by other species in low concentrations, including \( \text{CCl}\_3 \) (Cl transfer).\(^{27} \) \( \text{Cl}_2\text{CH} \) (deprotonation/Cl transfer),\(^{38} \) and \( \text{TMS-OH} \) (deprotonation), but without significant chain termination. There was no detectable inhibition by dichloroethane \( \text{(DCE)} \), \( \text{CH}_2\text{Cl}_2 \), TMS-O-TMS, \( \text{Ph}_3\text{SiF}, \text{Me}_3\text{SiCF}_2\text{H} \), or \( \text{MeCN} \).\(^{73c} \)

In our experience, a diverse range of inhibitors and competitors \((\text{e.g., CCl}_4 \text{ and CHCl}_3)\) are present, in low concentrations and variable proportions, in commercial samples of TMSCF\(_3\) \((1a)\). This leads to substantial differences in reaction outcome, depending on the supplier. For example, comparison of the reaction of \( \text{2} \) \((0.40 \text{ M})\) with five samples of distilled \( \text{1a} \) \((0.48 \text{ M})\) revealed that the concentration of inhibitor \( \text{TBAT} \) \((\text{KOPh}) \) required to effect >99% conversion of \( \text{2} \) ranged from \( 30 \mu\text{M} \) to \( 2.0 \text{ mM} \) \((0.0075 \text{ to } 0.5 \text{ mol %})\); see SI.

A major difference found between reactions involving reagent \( \text{1a} \) versus \( \text{1b,c} \) is the impact of the persistent radical, TEMPO, which powerfully inhibits reactions involving \( \text{1a} \), Scheme 4A. The difference in behavior toward TEMPO cannot arise from oxidation of the CF3 anion \( \text{(E)} \), as this is a common intermediate to all three reagents \((1a-c)\), and the partitioning of \( \text{E} \) between reaction with the ketone \( \text{(2)} \) versus TEMPO will be constant across the series, i.e., independent of the provenance of the carbanion \( \text{E} \). Since the major difference between reagents \( \text{1a} \) and \( \text{1c} \) under the conditions of the reaction is the dominant anion speciation \( \text{(D)} \), mechanism Vi, \( \text{1a} \), versus alkoxides \( \text{3}_{\text{OSi}^+}/4_{\text{OSi}^+} \), mechanism Vii, \( \text{1c} \), this suggests that reaction of silicate \( \text{D} \) with TEMPO is responsible for the inhibition. We were unable to identify any products in situ or by quenching, arising from TEMPO under the standard reaction conditions; see SI. While silicates of type \( \text{D} \) are also generated from \( \text{1b} \) and \( \text{1c} \), they (a) are only present at low concentration or as transient species, thus reducing their net rate of reaction with TEMPO, and (b) may be more resistant to reaction with TEMPO due to their greater steric bulk.

**CONCLUSIONS**

The trifluoromethylation of ketones and aldehydes by TMSCF\(_3\) \((1a)\), initiated by catalytic fluorde ion, has been employed in synthesis for three decades.\(^{17} \) Previous mechanistic work has focused on stoichiometric reactions of \( \text{R}_3\text{SiCF}_3 \) \((1a,c)\) with anions at low temperatures, generating unstable trifluoromethyl silicates \( \text{(C, D)} \)\(^{32−34} \) and carbanion(oids) \((\text{E}) \)\(^{36−38} \) depending on conditions. Which of these two pathways is followed in catalytic reactions at ambient temperature has been a long-standing mechanistic dichotomy.\(^{30} \) A variable-ratio stopped-flow NMR/IR approach \((\text{Figure 3})\) has been developed to facilitate time- and material-efficient analysis of a wide range of initiator \( \text{M}^X^+ \) and reactant concentrations. Change of reagent from TMSCF\(_3\) \((1a)\) to TIPSCF\(_3\) \((1c)\) has a profound impact on the reaction. For example, the conversion of 4-F-acetophenone \((2, \text{0.4 M})\) to 3-TMPS by equimolar \( \text{1a} \) in THF at ambient temperature takes <125 ms to complete using 0.1 mol % KOPh initiator and generates <2% of silylenol ether \( 4_{\text{TMPS}} \); whereas with TIPSCF\(_3\) \((1c)\) and 3.75 mol % KOPh, the reaction proceeds to just 60% conversion in 16 h and generates 50% \( 4_{\text{TIPPS}} \). The rates of reaction are strongly affected by traces of inhibitors present in the reagents \((\text{1})\), especially at the low concentrations of initiator \( \text{M}^X^+ \) employed for the fastest reacting systems; see eqs 1 and 2.\(^{26,39,60} \) Nonetheless, while these render misleading initial rate data, study of the full reaction time-course, e.g., Figure 8, provides a coherent kinetics analysis.

A unified mechanism \( (V) \) for the reaction of \( \text{R}_3\text{SiCF}_3 \) reagents \((1a-c)\) with ketones and aldehydes under conditions of catalytic anionic initiator \( \text{M}^X^+ \) is presented in Figure 7. The work confirms that the carbanion \( \text{36−38} \) mechanism prevails.
under conditions of application (Scheme 1). Mechanism V allows a number of initially confusing observations to be
raionalized. The main difference between use of TMSCF$_3$ (1a) versus TIPSCF$_3$ (1c) reagents is an inversion in the major
anion speciation in the overall anionic chain reaction. This inversion leads to opposing influences of electrophile and
silicon reagent (mechanisms Vi and Vii) and to keto-enol equilibration (2/2$_{\text{eq}}$) with 1c (Vii). When TBAT is used as
initiator, TESCF$_3$ (1b) effects the most rapid trifluoromethylation in the series 1a–c. The increased steric bulk in 1b
reduces reagent inhibition ($K_i$) relative to 1a, without the substantial kinetic penalty in $k_3$ experienced by 1c. These
factors shift the reaction with 1b closer to an “ideal” catalytic cycle in which the intermediates are all connected by low TS
barriers, with reduced off-cycle speciation. A consequence of adding TMSCF$_3$ (1a) to TESCF$_3$ (1b) is therefore to strongly
inhibit turnover of 1b until all of 1a has been consumed, Figure 1.

The overarching mechanism (V, Figure 7) for anion-initiated reactions of $R_3$SiCF$_3$ (1) with ketones and aldehydes
should prove of utility in their application in synthesis. For example, in the context of the design and analysis of
enantioselective trifluoromethylation processes, 15,16,25,30,31 mechanism V shows that control must be achieved by the
CF$_3^+$/[M]$^+$ ion pair, Figure 9ii, and not by a siliconate intermediate. Moreover, the key mechanistic features of the
anion-initiated reactions of 1 with carbonyl compounds (Figure 7) translate to reactions of 1 with other electrophiles
(E)$^{3-31}$ and proton donors (R–H to generate R$^+$), Figure 10. Thus, all processes in which siliconate D or analogous
species formally acts as a nucleophilic or basic source of CF$_3$, must proceed via a dissociative pathway (Figure 10ii)
Siliconate D is inherently unstable and decomposes at ambient temperature to generate, \textit{inter alia}, complex perfluorocarba-
nions.34,38 The rate of anionic chain transfer, as dictated by the reactivity of the electrophile (E) 29–31 or carbon acid (R–
H) 77 toward CF$_3^-$, as well as the presence of species able to attenuate decomposition (e.g., via CF$_2$ capture, 4$_{\text{Si}}$ $\rightarrow$ 10,
Scheme 3), controls the formal lifetime of D and in turn the minimum loading of initiator (M”X”) that will be required to
achieve complete conversion of substrate. Moreover, traces of exogenous inhibitor(s) (e.g., Z$\rightarrow$–LG, Figure 10iii) ubiquitous in
$R_3$SiCF$_3$ reagents (1) act to reduce the net active anion in the chain reaction, again increasing the requisite loading of
initiator (M”X”). Compounds employed in synthetic routes to reagents 1a–c, e.g., TMSCl and TIPSCI,11 function as
powerful inhibitors. However, the identity and effect of the inhibitors in reagents 1a–c vary substantially from batch to
batch and between commercial suppliers (see S1). Electrophiles or carbon acids (R–H) that react with CF$_3^-$ to
ultimately generate an anion of inherently low reactivity toward 1 require a stoichiometric initiator to proceed to completion.14,26

**ASSOCIATED CONTENT**

*Supporting Information*

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b06777.

Additional discussion, experimental procedures, further kinetic data and analysis, characterization data, and
NMR spectra (PDF)

---

**AUTHOR INFORMATION**

*Corresponding Author*

**ORCID**

Andrew G. Leach: 0000-0003-1325-8273

Guy C. Lloyd-Jones: 0000-0003-2128-6864

**Author Contributions**

* C. P. Johnston and T. H. West contributed equally to this work.

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

The research leading to these results has received funding from the European Research Council under the European Union’s
Seventh Framework Programme (FP7/2007–2013)/ERC grant agreement no. 340163. The Carnegie Trust provided a
collaborative research grant. C.P.J. thanks the EC for an International Outgoing Fellowship (PIOF-GA-2013-627695).
We thank Veronica Forcina (Edinburgh, UK) and Prof. Dusan S. V. (Imperial, UK) for valuable mechanistic discussions in the
early phases of this work.

**REFERENCES**

Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, D. J.; Meen, N. J. Med. Chem. 2015, 58, 8315–8359. (c) Zhou, Y.; Wang, J.;

10–27.


(9) For see for example: (a) Zhang, Y.; Fujiu, M.; Serizawa, H.; Mikami, K. J. Fluorine Chem. 2013, 156, 367–371. (b) Musio, B.; Gla, E.;


(12) (a) Kruse, A.; Siegemund, G.; Schumann, A.; Ruppert, I. A process for the production of perfluoralkyl compounds, and the

For example, a substructure search on 14/06/2018 for the addition of TMSCF3 (1a, exact reagent) to C=O (any carbonyl) using Reaxys/SciFinder gave 434/450 primary research papers and 631/811 patents.


(18) Water may be liberated from the NMR tube surface, the reagents (1a, 2 freshly distilled), the TRAB (anhydrous solid; THF solutions prepared and stored in a glovebox), or the THF (∼ 8 ppm H2O, Karl Fischer titration).

(19) Turnover rates were affected only by the impact on TMSCF3/keto reaction resulting from the rapid prior consumption of TMSCF3 by the H2O.


(21) For an example of CF3 radical character transfer from TMSCF3 via AgCF3 intermediates, see: Ye, Y.; Lee, S. H.; Sanford, M. S. Org. Lett. 2011, 13, 5464–5467 and references therein.

(22) Competing 1,4- and 1,6-addition to the aryl ring are characteristic of SET-type mechanisms for nucleophile addition to benzenophenes; see: Holm, T.; Crossland, I. Acta Chem. Scand. 1971, 25, 59–69 and references therein.

(23) A near-continuum sequential SET pathway is possible; see e.g.: Eisch, J. J. J. Org. Chem. 2012, 77, 10915–10921.

(24) A biphenyl is significantly more stabilizing for radical pathways than 4-fluorophenyl (σC, +0.46 and −0.06 respectively), see: Creary, K. O.; Mathew, T.; Olah, G. A. J. Org. Chem. 2006, 2006, 79, 761–771.
(52) For example, Bu$_3$N$^+$ where $X$ = Ph$_3$SiF$^-$, F$^-$, HO$^-$, PhO$^-$, AcO$^-$, and 3$_0^-$, behaved identically within experimental error. However when $X$ = less nucleophilic, e.g., B$_2$O$_4^-$, or 3.5-(CF$_3$)$_2$C$_2$H$_4$O$_2^-$, significant induction periods were evident. Induction periods were extreme with KOC(CF$_3$)$_3$.


(54) Control experiments confirmed that TBAT induces negligible H/D exchange between 2 and D$_2$ over the reaction period, whereas 3$_0$$_{KI}$ induces complete scrambling in under 95 s.


(59) Plots of initial rate versus [TBAT] for reaction of 2 and 13 with 1a both have a nonzero x-axis intercept (0.03 mM) with curvature evident at low [TBAT] concentrations, suggesting the inhibitor(s) are present at <0.02% 1a, in the specific batches of commercial reagents that were employed; see SI.

(60) In eqs 1 and 2 and elsewhere, (1 – $x_{K_{EI}}$) represents the mole fraction of active anion relative to total anion [M$^+X^-_0$]. Based on a 1:1 inhibition mode, $x_{K_{EI}} = (K_{EI}/1 + K_{EI})]$, where $x_i$ = mole fraction inhibitor in reagent $i$. Experimental data (see SI) suggest $K_{EI}$ is substantially greater with 1c.

(61) This contrasts with the borazaine systems recently developed by Szmyczek (see ref 10), where addition of KBARF profoundly accelerates CF$_3$-transfer rates.

(62) Simulations were conducted using the three-spin parametrization in WNDNMR, with the frequencies and rates as indicated in Figure 4 ($K_{e_{II}} = 2K_{e_{II}}$, where $K_{e_{II}}$ is the apparent $^{13}$C nuclear exchange rate through reassociation). The fraction of CF$_3$ present as $E$ was arbitrarily set to 0.1%, with the remaining 99.9% partitioned between D and 1a as required to fit. The chemical shift of CF$_3$[M] is reported as $\delta_F = -18.7$ ppm (see ref 38, and 17.2 ppm, see ref 36), depending on the identity of [M].


(69) For a range of anion–ketone interactions, including H-bonded adducts and aldolate products, see: Kolonko, K. J.; Reich, H. J. J. Am. Chem. Soc. 2008, 130, 9668–9669. The lowest energy of these was an enolate-ketone H-bonded adduct (F).


(71) The $^2$H-KIE for $\alpha$-$C$–$H$ deprotonation of $d_2$ by LDA/LiOR is $k_{\alpha}^D/k_0 = 6.3$; with (LDA), it is 1.7; Kolonko, K. J.; Wherrit, D. J.; Reich, H. J. J. Am. Chem. Soc. 2011, 133, 16774–16777.


(75) The kinetics for reactions of 2 (0.4 M) with 1b (0.48 M) are again complicated by inhibitors. When initiated by 0.3 mM KOPh, the reaction is pseudo-zero-order throughout; this result is consistent with a number of mechanisms, including for example turnover and inhibition by 1b or rate-limiting dissociation of CF$_3$ from dominant anion B. The faster rates of reaction with Bu$_3$N$^+$ versus K$^+$ counterion suggest mechanism Vii dominates.