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

Citation for published version:
Johnston, C, West, T, Dooley, R, Reid, M, Jones, AB, King, E, Leach, AG & Lloyd-jones, GC 2018, 'Anion-Initiated Trifluoromethylation by TMSCF3: Deconvolution of the Siliconate-Carbanion Dichotomy by Stopped-Flow NMR/IR', Journal of the American Chemical Society. https://doi.org/10.1021/jacs.8b06777

Digital Object Identifier (DOI):
10.1021/jacs.8b06777

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published in:
Journal of the American Chemical Society

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
Anion-Initiated Trifluoromethylation by TMSCF₃: Deconvolution of the Silicone–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 stall before 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 fluorine 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 predominant 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 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 Acidic workup affords the corresponding trifluoromethylated alcohols in good yield, Scheme 1.

Scheme 1. Trifluoromethylation of Ketones/Aldehydes¹²,¹³a

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., carboxyls,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 transfer⁷ or carbenoid CF₂ transfer¹⁸ has also been developed, as have numerous metal-mediated and -catalyzed processes involving CF₃ derived from TMSCF₃ (1a).²⁹

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 1.¹⁰ Various mechanistic dichotomies, including, inter alia, fluoride initiation versus fluoride catalysis, and silicate versus carbanion pathways, have been noted by Denmark³⁰a and by Reich,³⁰b both of whom emphasize the lack of salient kinetic data.
Herein we report the first detailed study of the mechanism of anion-initiated CF₃ transfer from TMSCF₃ (1a) to ketone and aldehyde electrophiles.¹²,¹⁷ The in situ NMR/IR investigations include analysis of reaction kinetics, selectivity, and side reactions and the contrasting behavior of homologues triethylsilylethoxide (TES) (1b) and triisopropylsilylethoxide (TIPS) (1c). Throughout the investigation, the kinetic studies have both informed and been directed by density functional theory (DFT) analysis of proposed intermediates. What emerges is a nuanced kinetic landscape in which trifluoromethylation proceeds via a carbanion pathway (CF₃⁻), with the rate dictated by the identity of the electrophile, the concentration of the initiating anion, the identity of the initiator counter-ion, and the identity of the reagent (1a−c).

### RESULTS AND DISCUSSION

#### 1. Prior Studies

In early studies, a termolecular anionic catalytic mechanism (Scheme 2) was suggested for trifluoromethylation by 1a.¹³,¹⁴ This was later expanded to a two-step process, where a pentacoordinate trialkoxy-siliconate (B) delivers CF₃ to the ketone and in doing so liberates the O-silylated product.¹⁴ Mechanism II has been extensively adopted in the design and interpretation of asymmetric trifluoromethylation.¹⁶,²⁹,³¹

In 1999, Naumann and Kolomeitsev and Röschenthaler independently reported on the reaction of a range of soluble fluoride sources (e.g., [Me₃N][CF₃]) with TMSCF₃ (1a) at low temperature. Detailed¹²,¹³,¹⁵C,¹⁹F, and Si NMR analysis identified the products as pentacoordinate complexes [Me₃Si-(F)CF₃]⁻¹M⁺ (C) and [Me₃Si(CF₃)₂]⁻¹M⁺ (D). Both complexes decompose above −20 °C.²⁵,²⁶ 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.²³,²⁵

In 2014, Prakash showed that the elusive¹⁷,²⁸ trifluoromethyl anion(oid) can be detected in situ (¹³C, ¹⁹F NMR) at low temperatures after addition of KOtBu/18-crown-6 to 1a. With the much bulkier reagent TIPS/CF₃ (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.³⁶ In 2015, Grushin demonstrated that use of crypt-222 (L, Scheme 2) facilitates generation of the free CF₃− carbocation, a tetrahydrofuran (THF) solution-phase “non-covalently bound ionic species”.³⁸ The structure of the highly air- and temperature-sensitive salt, [K(crypt-222)]/[CF₃]⁻ (E), was confirmed by single-crystal X-ray diffraction.

#### 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-fluoroacetophenone (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 (3OTMS), Scheme 3.

Reactions were assembled manually in 5 mm NMR tubes in the glovebox prior to analysis in situ by¹⁹F NMR. Three side-
products were identified: fluoroform (CF₃H), the silylenol ether (OTMS), and a homologated addition product (OTMS). Reactions conducted in d₄-THF proceeded analogously and generated CF₃H, not CF₃D.⁴⁰ The identity of OTMS, which was confirmed by independent synthesis, is consistent with difluorocyclopropanation of silylenol ether 4OTMS to generate 10, followed by a known anion-induced ring-opening elimination to give fluoroalene 11 and subsequent 1,2-selective trifluoromethylation. Addition of independently synthesized TOPTS to the reaction (Scheme 3) generated 5OTMS.

Reaction rates and extent of fluoroform 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.⁴¹ 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 (4OTMS), as confirmed by ®H-labeling (d₂-2 → CF₃D + d₂-4OTMS). The selectivity (3OTMS versus 4OTMS) 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 reestablish turnover (see SI), consistent with the known instability of pentacoordinate (trifluoromethyl) siliconates, e.g., C and D, at ambient temperatures.⁴²⁻⁴⁴ 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).⁴⁵ The rates were unaffected by visible light, by exogenous product (3OTMS), 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 trifluoroacetate (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 tetramethylyperidinoxy (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),⁴⁶⁻⁴⁸ 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 (k₂₁ = 1.93).⁵¹

### Scheme 4. Tests for Radical Intermediates

| Reaction | Product | Note |
|----------|---------|------|
| A | CF₃H | ¹⁹F NMR analysis revealed that CF₃H is liberated in two distinct phases. |
| B | CF₃D | Separate controls confirmed that the rate of trifluoromethylation is unaffected by CO₂-scrubbed air and that [Bu₄N][CF₃CO₂] is not effective as an initiator. |
| C | No cyclopropyl ring opening | 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). |

### 4. General Effects of Initiator on Rate and Selectivity.

A range of initiators (M’X’) were tested and found to strongly impact the reaction outcome. In the majority of cases, the reactions initiated “instantly” and the identity of X’ had no influence on the rate or selectivity (3OTMS/4OTMS). Specific effects were found to be dictated by the identity of the counterion (M’), Table 1.

Reactions where M’ = K⁺ and Cs⁺ proceeded rapidly to completion, with higher selectivity for 3OTMS/4OTMS compared to Bu₄N⁺. Reactions stalled when the cation was Li⁺ or Na⁺.⁴³ For the K⁺-mediated system, the rate was strongly attenuated by addition of 18-crown-6 or crypt-222, with the latter causing turnover to become slower and less selective (3OTMS/4OTMS) than reactions initiated by TBAT (counterion Bu₄N⁺). The identity of M’ was also found to affect the degree of charge development (ρ ranging from 1.8 to 3.0) in the ketone (R = Me, Scheme 5) at the product-determining transition state for CF₃ transfer. Benzaldehydes (R = H) behaved analogously.

### 5. Effect of Silyl Reagent on Rate and Selectivity.

To further probe the CF₃ transfer process, we compared TMSCF₃ (1a) with TESCF₃ (1b) and TIPSCF₃ (1c), Table 1. The effects of changing the reagent were counterintuitive and initially misleading regarding the mechanism of CF₃ transfer, vide infra. Reactions employing TESCF₃ (1b) gave lower selectivity (3OTMS/4OTMS ≈ 1.5/1) and proceeded very rapidly, even at low TBAT concentrations (150 μM, 0.0375 mol %; below this, reactions failed to initiate). In contrast, reactions employing TIPSCF₃ (1c) proceeded very slowly, requiring high initiator concentrations to proceed efficiently (>1.5 mM, 0.375 mol %) and gave even lower selectivity (3OTIPS/4OTIPS ≈ 1/1).

Further insight was afforded by reaction of a 50/50 mixture of TMSCF₃ (1a) and TESCF₃ (1b), initiated by TBAT (75 μM, 0.019 mol %), Figure 1. The first 4 min of reaction is dominated by turnover of TMSCF₃ (1a) to generate 3OTMS/4OTMS and upon near-complete consumption of 1a, turnover accelerates substantially as the TESCF₃ (1b) is engaged to generate 3OTIPS/4OTIPS. The data indicate that the less-hindered reagent (1b) monopolizes the anion, but undergoes slower turnover.

Under conditions where anion-induced reactions of TMS (1a), TES (1b) and TIPS (1c) with 2 could be conducted slowly enough to be accurately monitored in situ by ¹⁹F NMR,
the ratios of enol/addition product \((\text{3OSi}/\text{4OSi})\) 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 TMSCF\(_3\) \((1\text{a})\) the incarceration of the K\(^+\) in the crypt-222 ligand substantially attenuates the rate and selectivity. In stark contrast, for TIPSCF\(_3\) \((1\text{c})\), turnover is substantially accelerated by addition of crypt-222 to inhibit K\(^+\)/anion pairing.

\[\text{Selectivity } \frac{\text{3OSi}}{\text{4OSi} + \text{CF}_3\text{H}} \text{ measured in situ by } ^{19}\text{F NMR after manual assembly in an NMR tube; selectivity is independent of } X^- .\]

\[\text{times indicated are for } >97\% \text{ conversion of } \text{2}, \text{ at } 300 \text{ K}.\]

\[\text{Table 2. KIEs and } ^2\text{H Exchange in the Reaction of Ketone } \text{2a,c} \text{, see text for full discussion. Reaction conditions: } \text{2} (0.4 \text{ M}), \text{1a–c} (0.48 \text{ M}), \text{PhF} (0.4 \text{ M}), \text{MX} (0.00015 \text{ M; } 0.038 \text{ mol } \%), \text{Z} = \text{Ph, OMe, CF}_3, \text{Me, Br}. \text{Hammett rho values calculated from product ratios; see SI.}\]

\[\text{Reactions with labeled ketone (aryl-}^{13}\text{C}^{2}\text{)} \text{were also instructive, Table 2. Reaction of TMSCF}_3\text{ (1a) with}\]

\[\text{Scheme 5. Effect of Initiator M}^+ \text{ on Reaction Constant } (\rho)\]

\[\begin{align*}
\text{M}^+ & | M^- X^- |_0 \text{ mM} & \text{TMS 1a } 3/4^a (\text{time})^b & \text{TES 1b } 3/4^a (\text{time})^b & \text{TIPS 1c } 3/4^a (\text{time})^b \\
[\text{Bu}_4\text{N}]^+ & 1.5 & 12/1 (<90 s) & 1.5/1 (<90 s) & 1/1 (30 min) \\
[\text{K}^+] & 0.15 & 36/1 (<90 s) & 3.0/1' (30 min) & \text{NR} \\
[\text{K(L)}]^+ & 1.5 & 6.6/1 (6 min) & 2.4/1 (<90 s) & 1/1 (3.6 min)
\end{align*}\]

\[\text{Selectivity } \frac{\text{3OSi}}{\text{4OSi} + \text{CF}_3\text{H}} \text{ measured in situ by } ^{19}\text{F NMR after manual assembly in an NMR tube; selectivity is independent of } X^- .\]

\[\text{times indicated are for } >97\% \text{ conversion of } \text{2}, \text{ at } 300 \text{ K}.\]

\[\text{85\% conversion.}\]

\[\text{[K(L)]}^+ = \text{K(crypt-222)}^+, \text{generated in situ from KOPh + crypt-222. NR = No reaction.}\]

\[\text{Reactions with labeled ketone (aryl-}^{13}\text{C}^{2}\text{)} \text{were also instructive, Table 2. Reaction of TMSCF}_3\text{ (1a) with}\]

\[\text{Table 2. KIEs and } ^2\text{H Exchange in the Reaction of Ketone } \text{2a,c} \text{, see text for full discussion. Reaction conditions: } \text{2} (0.4 \text{ M}), \text{1a–c} (0.48 \text{ M}), \text{PhF} (0.4 \text{ M}), \text{MX} (0.00015 \text{ M; } 0.038 \text{ mol } \%), \text{Z} = \text{Ph, OMe, CF}_3, \text{Me, Br}. \text{Hammett rho values calculated from product ratios; see SI.}\]

\[\text{Reactions with labeled ketone (aryl-}^{13}\text{C}^{2}\text{)} \text{were also instructive, Table 2. Reaction of TMSCF}_3\text{ (1a) with}\]

\[\text{Table 2. KIEs and } ^2\text{H Exchange in the Reaction of Ketone } \text{2a,c} \text{, see text for full discussion. Reaction conditions: } \text{2} (0.4 \text{ M}), \text{1a–c} (0.48 \text{ M}), \text{PhF} (0.4 \text{ M}), \text{MX} (0.00015 \text{ M; } 0.038 \text{ mol } \%), \text{Z} = \text{Ph, OMe, CF}_3, \text{Me, Br}. \text{Hammett rho values calculated from product ratios; see SI.}\]

\[\text{Reactions with labeled ketone (aryl-}^{13}\text{C}^{2}\text{)} \text{were also instructive, Table 2. Reaction of TMSCF}_3\text{ (1a) with}\]

\[\text{Table 2. KIEs and } ^2\text{H Exchange in the Reaction of Ketone } \text{2a,c} \text{, see text for full discussion. Reaction conditions: } \text{2} (0.4 \text{ M}), \text{1a–c} (0.48 \text{ M}), \text{PhF} (0.4 \text{ M}), \text{MX} (0.00015 \text{ M; } 0.038 \text{ mol } \%), \text{Z} = \text{Ph, OMe, CF}_3, \text{Me, Br}. \text{Hammett rho values calculated from product ratios; see SI.}\]
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 $^{3}$H KIE, determined from [CF$_{3}$D] versus [d$_{3}$-3$_{29}$], as in Figure 2, increases the addition/enol selectivity ($k_{i}/k_{o} = 6.4$). Reactions of mixtures of 2 and d$_{3}$-2 proceeded with no detectable scrambling of D/H between 2/D$_{2}$-2 during turnover, provided that $[1_{a}]_{0} > [2]_{0}$ and again proceeded with a high KIE ($k_{i}/k_{o} = 6.1$). With TESCF$_{3}$ (1b) a moderate KIE ($k_{i}/k_{o} = 3.1$) was observed, with a trace of D/H exchange between 2 and D$_{4}$-2 on co-reaction, and thus into products d$_{1}$-3/d$_{1}$-4. With TIPSCF$_{3}$ (1c) there was no significant KIE and a statistical mixture of isotopologues of d$_{1}$-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, 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 + ii + 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. The former simply required adaptation of our recently developed thermostated ATR-FTIR stopped-flow cell, 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. 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; recalibration ensures temp$_{1}$ = temp$_{2}$. 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$_{0+}$ was collected at scan rates of 14 or 28 s$^{-1}$ with a resolution of 2 or 8 cm$^{-1}$, respectively. 19F 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$_{0+}$) 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). Control experiments in which the reactions were run in the presence of exogenous product (3$_{0+}$) confirmed that it does not act as an inhibitor.
The inhibitory effect of the TMSCF₃ reagent 1a \((K_{\text{init}}; \text{eq } 1)\) 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 \((\text{TOF} = k_{\text{obs}})\) for the majority of the reaction evolution. Conversely, when there is an excess of ketone over 1a, the rate of turnover rises as a function of conversion, becoming very rapid in the final phases of reaction where \([2]/[1a] \gg 1\).

\[
\text{TOF} \approx \frac{k_{\text{cat}}M^+X^-[2]_0(1 - x_{\text{fi}})}{1 + K_{i1}[1]_0} \approx k_{\text{obs}}\frac{2}{1} \quad (1)
\]

\[
\text{TOF} \approx \frac{k_{\text{cat}}M^+X^-[1]_0(1 - x_{\text{fi}})}{1 + K_{i2}[2]_0} \approx k_{\text{obs}}\frac{1}{2} \quad (2)
\]

Systematic studies using \(M^+X^-\) \((M^+ = \text{Li}^+, \text{Na}^+, \text{K}^+, \text{Cs}^+)\), which induce very rapid turnover, proved more challenging. Reactions where \(M^+ = \text{Li}^+\) and \(\text{Na}^+\) 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 \((\text{eq } 1)\).\(^{59}\) 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 reactant \(([1a]_0\) or decreasing the initiator concentration \([M^+X^-]_0\) causes a greater mole fraction of exogenous inhibition \((x_{\text{fi}})\), eq 1.\(^{59,60}\) Addition of \([K^+[\text{C}_6\text{F}_5\text{B}]]^-\), to provide an additional soluble \(K^+\) source with a non-nucleophilic counterion, 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).\(^{61}\) Addition of potassium-binding ligands attenuated the rates substantially, and with crypt-222, the system underwent turnover slower than with \(\text{Bu}_4\text{N}^+\) (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 \((k_{\text{cat}}/k_{\text{init}} \approx 80, \text{at } 21 \, ^\circ\text{C})\), requiring lower initial TBAT concentrations and causing the traces of exogeneous inhibitor(s) in 1a to complicate the kinetics.\(^{59}\) Competing ketone 2 with aldehyde 13 \((9/1 \text{ ratio})\) using stopped-flow \(\text{¹九F NMR}\) 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 \([\text{TBAT}]_0\), \((96–384 \mu\text{M})\) and 1a \((0.08 \text{ to } 0.48 \mu\text{M})\). Overall, the data are indicative that aldehyde 13 follows the same general kinetics as ketone 2, i.e., \(\text{eq } 1\).\(^{59,60}\) 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 \((x_{\text{fi}})\) varied from batch to batch of 1c; see SI. Using TBAT as initiator, the reactions evolve with a first-order dependency on the initiator and on the reagent \(([1c]_0)\), with inhibition by the ketone \((K_{i2}; \text{eq } 2)\). 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 \(\text{¹九F NMR Analysis of Silicate and Alkoxide Intermediates, Exchange Dynamics with TMSCF₃, and Initiator Regeneration.}\) By use of 4-F-benzophenone \((12; \delta_F = -107.0 \text{ ppm})\), which reacts slower than 2, and reducing the reaction temperature to 275 K, the temporal speciation of the initiator-derived species \((10 \text{ mol } \% \text{ TBAT})\) was monitored using stopped-flow \(\text{¹九F NMR}, \text{Figure } 4.\)
The known but unstable hypervalent bis-CF₃-siliconate (D; δF −63.3 ppm) 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 superstoichiometric ketone 12. In parallel with this is a marked acceleration in product generation (14 OTMS, 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 (kexch ≈ 180 s⁻¹; ΔG⧧ ≈ 13 kcal mol⁻¹) with 1a and a low concentration of (unobserved) [Bu₄N][CF₃] (E). 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 (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 TMSDCF₃ (1a) involves an electrophile–nucleophile reaction, in which the CF₃ transfer is accompanied by M’.
Enolsilane $\text{4}_{\text{TMS}}$ is also generated ($\leq 2\%$ when $M^* = K^+$ and $7\%$ when $M^* = \text{Bu}_4\text{N}^+$) with coproduct $\text{CF}_3\text{H}$ ($k_{\text{T}}$/ $k_D = 6.1$). Using TIPSCF$_3$ (1c), approximately $50\%$ of the product is $\text{4}_{\text{TIPS}}$ and $k_{\text{H}}$/ $k_D = 1.0$. 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., siliconate 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 ($3_{\text{OSi}}$/ $4_{\text{OSi}}$), 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 considered$^{63}$ (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.$^{68}$ 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--CF$_3$ 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 CF$_3$ from the silicon center to an electrophile requires concomitant inversion of the CF$_3$, with a prohibitively large barrier ($>100$ kcal mol$^{-1}$; in line with the barrier for inversion of the free CF$_3$ anion).$^{67}$ The pentacoordinate silicate anions thus act as reservoirs, not active nucleophiles, liberating free (non-silicon-coordinated) CF$_3$ via dissociation. The transition state for addition of the CF$_3$ 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 ($k_{\text{CH}}$) in the gas phase$^{67}$ and for addition ($k_{\text{CO}}$) once solvation is introduced, as observed experimentally for TMSCF$_3$ (1a). The loose addition transition state leads to a negligible $^{13}\text{C}$ KIE (carbonyl) for addition, while a large primary $^1\text{H}$ KIE is computed for $\text{C} = \text{H}$ deprotonation. Relative rates computed from activation free energies suggest $\rho = 2.0$ for addition to acetoephones and a lower barrier for addition to 4-F-benzaldehyde (13) versus 2 ($\Delta\Delta G^\ddagger = 2.6$ kcal mol$^{-1}$; $k_{\text{H}}$ = 81). All of these computed values are in excellent agreement with experiment.

A general mechanism for the trifluoromethylation of ketones and aldehydes by R$_3$SiCF$_3$ reagents (1) in the presence of a catalytic quantity of initiator (M”X”) can thus be assembled, Figure 7. The one overarching mechanism, discussed 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 TMSCF$_3$ (1a), the dominant anion speciation is the bis(trifluoromethyl) silicate (D),$^{13–34}$ generated in rapid equilibrium (K$_3$) with CF$_3$ (E)$^{35,36}$ and 1a, as observed by NMR, Figure 4. The product-determining step ($k_I$) involves reaction of CF$_3$ (E) with the ketone (2) ($k_{\text{CO}} + k_{\text{CH}}$), and the reagent (1a) thus acts as a reversible inhibitor. The stronger the association of M” with CF$_3$ (see Section 13) and with the carbonyl oxygen, the faster the turnover rate: Bu$_4$N$^+ < [K(\text{crypt-222})]^+ < [K(18-c-6)]^+ < K^+$. The initial concentration ratios of the reagent versus the reagent dictate the temporal evolution of the reaction. When $[2]_0/([1a]_0 = 1$, pseudo-zero-order kinetics are obtained, whereas when $[2]_0/([1a]_0 \geq 1$, the rate rises throughout the reaction, becoming very fast (asymptoting to $k_{\text{H}}$D) in the final stages. The kinetics of trifluoromethylation of ketone 2 by TMSCF$_3$ (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 \([2b]/[1a]\) evolves.

\[
\begin{align*}
&k_{1}\left[K_{1}^{-}\right] = 7.1 \pm 1.2 \text{s}^{-1} \\
&k_{2} \approx k_{1} \approx 2000 \text{M}^{-1}\text{s}^{-1}
\end{align*}
\]

\[
\text{Bu}_4\text{N}^+\xrightarrow{[\text{TMS}(\text{CF}_3)]^2} \text{CF}_2 \xrightarrow{k_{1}} 1a \xrightarrow{k_{2}} 3
\]

Figure 8. Simulation of experimental data (open circles, SF-IR; \([3_{\text{OTMS}} + \text{4}_{\text{OTMS}}]\), based on simplified mechanism Vi, for reaction of ketone \(2\) with \(\text{TMS}(\text{CF}_3)\) (1a), initiated by 3.6 mM TBAT (Bu4N+)X. For \([2]\)/[1a]1 > 1, [2]0 = 0.40 M and [1a]0 = 144, 192, 248, 288, 336, 384 mM (i to vi). For \([2]/[1a]0 < 1, [1a]0 = 0.48 M and [2]0 = 400, 320, 240, 200, 160, 120, 80 mM (vii to xiii). Induction and turnover by 1a are set to arbitrary high values. Fitted parameters \([k_{1}, k_{2}, k_{i}, k_{f}]\) are as indicated; \(x_{11} = 0.69\).

11. Mechanism Vii. In this regime, which describes reactions involving TIPSCF3 (1c), the dominant anion speciation is a combination of the product alkoxide \((3_{\text{OH}}^{-})\), the enolate anion \((4_{\text{OH}}^{-})\), and MX. Ketone \(2\) can reversibly H-bond (see F in Figure 7) with oxy-anions \([3]/[4_{\text{OH}}^{-}]\), as observed by NMR, Figure 5, leading to inhibition \((K_{\text{i}})\). 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 \([3]/[4_{\text{OH}}^{-}]\), the slower the reaction with 1c, leading to rates increasing in the series \(K’ < [K(18-c-6)]^{-} < \text{Bu}_4\text{N}^+ < [K(\text{crypt}-222)]^{-}\), i.e., the opposite order to Vi. 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 \(K_{\text{i}} = 0\), and eq 2, where \(K_{\text{i}} = 0\)).

12. Competing Enolization. Also shown in Figure 7 is the generation of the enol ether \((4_{\text{OSi}})\) and CF3H from ketone 2, for which the selectivity \((4_{\text{OSi}}/[3_{\text{OSi}}])\) is dependent on \(M’\) and the reagent (1a–c), Table 1. The major pathway for generation of \(4_{\text{OSi}}\) in mechanism Vii is via C–H deprotonation \((k_{\text{CH}})\) with an attendant large primary \(^2\text{H-KIE}\). In contrast, for mechanism Vii, the significant concentration of \([3]/[4_{\text{OH}}^{-}]\) allows keto–enol equilibrium \((pK_{\text{eq}} \approx 8)\) in 2 to be approached, with attendant intermolecular scrambling of \(^2\text{H}\) between ketone methyl groups. Deprotonation \((k_{\text{OH}})\) of the enol \((2_{\text{OH}})\) is predicted (DFT) to be of very low barrier and thus proceed with a negligible \(^2\text{H-KIE}\). Despite their different origins \((k_{\text{CH}}\) versus \(k_{\text{OH}})\) mechanisms Vi and Vii 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 \(\text{Me}_4\text{N}^+\) (as a model for \(\text{Bu}_4\text{N}^+)\) were explored computationally, with multidentate 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 \(\text{Me}_4\text{N}^+\) (Figure 9i) show how an ammonium cation might simultaneously interact with a CF3 anion and control a developing alkoxide anion, Figure 9ii. Mechanism Vi contrasts most, but not all, prior interpretations, where mechanisms II/III (Scheme 2) involving CF3-silicates bearing the initiating (C) or propagating (B) anion, are proposed to play key roles in the enantioselective trifluoromethylation step.

14. Broader Mechanistic Aspects. The mechanistic features elucidated in the current study extend beyond carbonyl trifluoromethylation. A number of corollaries follow for generic anion-initiated trifluoromethylation of an electrophile \((E)\) by 1a, or deprotonation \((R-H)\), via pathways analogous to mechanism Vi, and where \([E, R-H]_0 \gg \]
Thus, the initiator \((\text{M}^+ \text{X}^-)\) affects the rate of reaction in a number of ways. \([\text{X}^-]_0\) sets the initial concentration of the silicate \((\text{[D]}_0 = (1 - x_{\text{R}})[\text{X}^-]_0)\), which, in the absence of endogenous inhibitors, is essentially constant throughout the reaction. The insurmountable barrier for CF₃ inversion\(^{65}\) means that, independent of the identity of the electrophile, \(E\), or proton donor, \(R\)-\(H\), 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 \(M^+\) plays a key role: the stronger \(\text{OH}\) (deprotonation), but without significant regeneration of the siliconate \((\text{[D]}_0)\), \(x_{\text{R}} \approx 1\). In contrast, efficient regeneration of the siliconate (\(x_k\), Figure 7) is favored by weaker interactions between \(M^+\) and the anionic acpophot from trifluoromethyl transfer \((\text{CF}₃ E ; R^* ; \text{or products thereof})\). When the anion is unable to react with \(1\), stoichiometric initiation by \([\text{M}^+ \text{X}^-]\) is required.\(^{14-26}\)

15. Exogenous Inhibition. Trifluoromethylations initiated by low concentrations of \((\text{M}^+ \text{X}^-)\) are highly sensitive to traces of exogenous inhibitor(s) or substrates that generate an unreactive anion, \(\text{LG}^-\). In our experience, a diverse range of inhibitors and competitors (e.g., \(\text{CCl}_4\) and \(\text{CHCl}_3\)) are present, in low concentrations and variable proportions, in commercial samples of \(\text{TMSCF}₃\) (1a). This leads to substantial differences in reaction outcome, depending on the supplier. For example, comparison of the reaction of 2 (0.40 M) with five samples of distilled 1a (0.48 M) revealed that the concentration of initiator (\(\text{TBAT}, \text{KOPh}\)) required to effect >99% conversion of 2 ranged from 30 \(\mu\text{M}\) to 2.0 \(\text{mM}\) (0.0075 to 0.5 mol %); see SI.

A major difference found between reactions involving reagent 1a versus 1b,c is the impact of the persistent radical, TEMPO, which powerfully inhibits reactions involving 1a, Scheme 4A. The difference in behavior toward TEMPO cannot arise from oxidation of the CF₃ anion (\(E\)), as this is a common intermediate to all three reagents (1a–c), and the partitioning of \(E\) between reaction with the ketone (2) versus TEMPO will be constant across the series, i.e., independent of the provenance of the carbanion \(E\). Since the major difference between reagents 1a and 1c under the conditions of the reaction is the dominant anion speciation (\(\text{D}\), mechanism \(\text{V}_{\text{i}}\), 1a, versus alkoxides \(3\text{O}^-/4\text{O}^-\), mechanism \(\text{V}_{\text{ii}}, 1\text{c}\)), this suggests that reaction of silicate \(D\) with TEMPO is responsible for the inhibition. We were unable to identify any products \textit{in situ} or by quenching, arising from TEMPO under the standard reaction conditions; see SI. While silicates of type \(D\) are also generated from 1b and 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 \(\text{TMSCF}_3\) (1a), initiated by catalytic fluoroide ion, has been employed in synthesis for three decades.\(^{17}\) Previous mechanistic work has focused on stoichiometric reactions of \(\text{RSiCF}_3\) (1a,c) with anions at low temperatures, generating unstable trifluoromethyl silicates (\(C, D\))\(^{32-34}\) and carbanion(oids) (\(E\))\(^{36-38}\) 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 (Figure 3) has been developed to facilitate time- and material-efficient analysis of a wide range of initiator \((\text{M}^+ \text{X}^-)\) and reactant concentrations. Change of reagent from \(\text{TMSCF}_3\) (1a) to \(\text{TIPS} \text{CF}_3\) (1c) has a profound impact on the reaction. For example, the conversion of 4-F-acetophenone (2, 0.4 M) to 3\text{OTMS} by equimolar 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{OTMS}. Whereas with TIPS\text{CF}_3 (1c) and 3.75 mol % KOPh, the reaction proceeds to just 60% conversion in 16 h and generates 50% 4\text{OTMS}. The rates of reaction are strongly affected by traces of inhibitors present in the reagents (1), especially at the low concentrations of initiator \((\text{M}^+ \text{X}^-)\) employed for the fastest reacting systems; see eqs 1 and 2.\(^{59,60}\) 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 (\(\text{V}\)) for the reaction of \(\text{RSiCF}_3\) reagents (1a–c) with ketones and aldehydes under conditions of catalytic anionic initiator \((\text{M}^+ \text{X}^-)\) is presented in Figure 7. The work confirms that the carbanion \((\text{M}^+ \text{X}^-)\) mechanism prevails...
under conditions of application (Scheme 1). Mechanism V allows a number of initially confusing observations to be rationalized. The main difference between use of TMSCF₃ (1a) versus TIPSCF₃ (1c) reagents is an inversion in the major anion speciation in the overall anionic chain reaction. This inversion leads to opposing in the major anion speciation in the overall anionic chain reaction. This inversion leads to opposing in the major anion speciation in the overall anionic chain reaction. This inversion leads to opposing in the major anion speciation in the overall anionic chain reaction. This inversion leads to opposing in the major anion speciation in the overall anionic chain reaction.

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)
(24) Liu, X.; Xu, C.; Wang, M.; Liu, Q. Chem. Rev. 2015, 115, 683−730. (b) Takeshi Komiyama, T.; Minami, Y.; Hiyama, T. ACS Catal. 2017, 7, 631−651.

(30) Danish, S. E.; Buettner, G. L. Angew. Chem., Int. Ed. 2008, 47, 1560−1638. (b) Reich, H. J. Mechanism of C−Si Bond Cleavage Using Lewis Bases (n−σ∗). In Lewis Base Catalysis in Organic Synthesis; 1st ed.; Vedejs, E.; Denmark, S. E.; Eds.; Wiley VCH: Weinheim, Germany, 2016; Vol. I, pp 251−253.

(31) For leading references see: (a) Yang, X.; Wu, T.; Phips, R. J.; Toste, F. D. Chem. Rev. 2015, 115, 826−870. (b) Shibata, N.; Mizuta, S.; Kawai, H. Tetrahedron: Asymmetry 2008, 19, 2633−2644.

(32) Maggioros, N.; Tyrra, W.; Naumann, D.; Kirij, N. V.; Yagupolskii, Y. L. Angew. Chem., Int. Ed. 1999, 38, 2252−2253.

(33) Kolometsev, A.; Biskyy, G.; Lork, E.; Movchun, V.; Rumasov, E.; Kirsch, P.; Röschenthaler, G. V. Chem. Commun. 1999, 1017−1018.

(34) Tyrra, W.; Kremlev, M. M.; Naumann, D.; Scherer, H.; Schmidt, H.; Hoge, B.; Pantenburg, I.; Yagupolskii, Y. L. Chem. − Eur. J. 2005, 11, 6514−6518.

(35) Kottun, S. P.; Anderson, J. D. O.; DesMarateau, D. D. J. Org. Chem. 1992, 57, 1124−1131.

(36) Prakash, G. K. S.; Wang, F.; Zhang, Z.; Haiges, R.; Rahm, M.; Christe, K. O.; Mathew, T.; Olah, G. A. Angew. Chem. Int. Ed. 2014, 53, 11575−11578.

(37) Santschi, T.; Gilmour, R. Angew. Chem. Int. Ed. 2014, 53, 11414−11415.

(38) (a) Lishchynskyi, A.; Miloserdov, F. M.; Martin, E.; Benet-Buchholz, J.; Escudero-Adán, E. C.; Konovolov, A. I.; Grushin, V. S. Angew. Chem., Int. Ed. 2015, 54, 15289−15293. (b) Miloserdov, F. M.; Konovolov, A. I.; Martin, E.; Benet-Buchholz, J.; Escudero-Adán, E. C.; Lishchynskyi, A.; Grushin, V. S. Helv. Chim. Acta 2017, 100, e1700302. (c) Harlow, R. L.; Benet-Buchholz, J.; Miloserdov, F. M.; Konovolov, A. I.; Marshall, W. J.; Martin, E.; Benet-Buchholz, J.; Escudero-Adán, E. C.; Martin, E.; Lishchynskyi, A.; Grushin, V. S. Helv. Chim. Acta 2018, 101, e1800015.

(39) The X-ray structural analysis of E (ref 38a) was challenged: Becker, S.; Müller, P. Chem. − Eur. J. 2017, 23, 7081−7086. The original interpretation was comprehensively defended; see ref 38c.

(40) The CF3H contained traces of CF3D (0.1% 19F NMR) likely from adventitious DOH/D2O in the d9-THF.

(41) Song, X.; Chang, J.; Zhu, D.; Li, J.; Xu, C.; Liu, Q.; Wang, M. Angew. Chem., Int. Ed. 2015, 17, 1712−1715.

(42) Song, X.; Xu, C.; Du, D.; Zhao, Z.; Zhu, D.; Wang, M. Org. Lett. 2017, 19, 6542−6545.

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

(44) Turnover rates were affected only by the impact on TMSCF3/ ketone ratio resulting from the rapid prior consumption of TMSCF3 by the H2O.

(45) For a review of CF3 transfer involving CF3 radicals, see: Studer, A. Angew. Chem., Int. Ed. 2012, 51, 8950−8958.

(46) 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.

(47) Competing 1,4- and 1,6-addition to the ary1 ring are characteristic of SET-type mechanisms for nucleophile addition to benzonitriles; see: Holm, T.; Crossland, I. Acta Chem. Scand. 1971, 25, 59−69 and references therein.

(48) A near-continuum sequential SET pathway is possible; see e.g.: Eisch, J. J. Res. Chem. Intermed. 1996, 22, 145−187.

(49) (a) Newcombe, M. J.; Johnson, C. C.; Manek, M. B.; Varick, T. R. J. Am. Chem. Soc. 1992, 114, 10915−10921. (b) Miyazo, H.; Yamago, S.; Yoshida, J. Angew. Chem., Int. Ed. 2000, 39, 3669−3671.

(50) Biphenyl is significantly more stabilizing for radical pathways than 4-fluorophenyl (ζC*, +0.46 and −0.06 respectively), see: Creary, X. Acc. Chem. Res. 2006, 39, 761−771.
(52) For example, BuN’X’ where X’ = Ph2SiF2−, F−, HO−, PhO−, AcO− and 30°, behaved identically within experimental error. However when X’ was less nucleophilic, e.g., BzO−, or 3,5-(CF3)2C6H3O−, significant induction periods were evident. Induction periods were extreme with KOCF3).

(53) Luo, G.; Luo, Y.; Qiu, J. New J. Chem. 2013, 37, 3274–3280.

(54) Control experiments confirmed that TBAT induces negligible H/D exchange between 2 and D2O over the reaction period, whereas 30° induces complete scrambling in under 95 s.

(55) For examples of mechanical variable ratio mixing for stopped-flow kinetics see: Goetz, M. J. Phys. E: Sci. Instrum. 1988, 21, 440–442 and references therein.

(56) For recent developments see: (a) Dunn, A. L.; Landis, C. R. Magn. Reson. Chem. 2017, 55, 329–336. (b) Thomas, A. A.; Denmark, S. E.; Ernest, L. Eliel, a Physical Organic Chemist with the Right Tool for the Job: Rapid Injection Nuclear Magnetic Resonance. In Stereochemistry and Global Connectivity: The Legacy of Ernest L. Eliel, Cheng, H. N., Ed.; American Chemical Society: Washington DC, 2017; Vol. 2, pp 105–134.

(57) Cox, P. A.; Reid, M.; Leach, A. G.; Campbell, A. D.; King, E. J.; Lloyd-Jones, G. C. J. Am. Chem. Soc. 2017, 139, 13156–13165.

(58) Foley, D. A.; Bez, E.; Codina, A.; Colson, K. L.; Fey, M.; Krull, R.; Piroli, D.; Zell, M. T.; Marquez, B. L. Anal. Chem. 2014, 86, 12008–12013.

(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 − xfi) represents the mole fraction of active anion relative to total anion [M+X−]. Based on a 1:1 inhibition mode, xfi = (Kfi/[1 + Kfi]) with [M+X−] = xM+fi where xi = mole fraction inhibitor in reagent i. Experimental data (see SI) suggest Kfi is substantially greater with 1c.

(61) This contrasts with the borazine systems recently developed by Szmyczak (see ref 10), where addition of KBARF profoundly accelerates CF3-transfer rates.

(62) Simulations were conducted using the three-spin parametric representation in WNDNMR, with the rates and frequencies as indicated in eqs 4 (κex = 2κex, where κex is the apparent 19F nuclei exchange rate through reassociation). The fraction of CF3 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 CF3[M] is reported as δCF3 = 18.7 ppm (see ref 38, and −17.2 ppm, see ref 36), depending on the identity of [M].

(63) Hariharan, P. C.; Pople, J. A. Theor. Chem. Acta 1973, 28, 213–222.

(64) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; J.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Gaussian, Inc.: Wallingford, CT, 2009.

(65) (a) Zhao, Y.; Truhlar, D. G. Theor. Chem. Acc. 2008, 120, 215–241. (b) Zhao, Y.; Truhlar, D. G. Acc. Chem. Res. 2008, 41, 157–167. (c) Tomasi, J.; Mennucci, B.; Cammi, R. Chem. Rev. 2005, 105, 2999–3049.

(66) (a) Brown, S. B.; Dewar, M. J. S.; Ford, G. P.; Nelson, D. J.; Rzepa, H. S. J. Am. Chem. Soc. 1978, 100, 7832–7836. (b) Dewar, M. J.; Olivella, S.; Rzepa, H. S. J. Am. Chem. Soc. 1978, 100, 5650–5659. (c) Rzepa, H. S. KINISOT. A basic program to calculate kinetic isotope effects using normal coordinate analysis of transition state and reactants; http://doi.org/10.5281/zenodo.19272, 2015. (d) Patent, R. S. Kinisot v 1.0 public API for Kinisot.py; http://doi.org/10.5281/zenodo.60082, 2016.

(67) Han, H.; Alday, B.; Shuman, N. S.; Wiens, J. P.; Troe, J.; Viggs, A. A.; Guo, H. Phys. Chem. Chem. Phys. 2016, 18, 31064–31071.