FULL PAPER

The Electrophilic Fluorination of Enol Esters using SelectFluor Occurs *via* a Polar Two-Electron Process

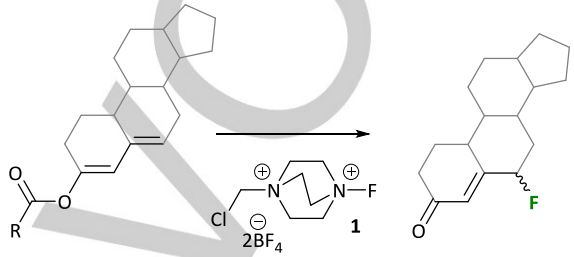
Susanna H. Wood,[a] Stephen Etridge,[b] Alan R. Kennedy,[a] Jonathan M. Percy,[a]† and David J. Nelson*[a]

Abstract: The reaction of enol esters with SelectFluor is facile and leads to the corresponding α-fluoroketones under mild conditions and, as a result, this route is commonly employed for the synthesis of medicinally important compounds such as fluorinated steroids. However, despite the use of this methodology in synthesis, the mechanism of this reaction and the influence of structure on reactivity are unclear. We present a rigorous mechanistic study of the fluorination of these substrates, informed primarily by detailed and robust kinetic experiments. The results of this study implicate a polar two-electron process via an oxygen-stabilised carbenium species, rather than a single-electron process involving radical intermediates. The structure/reactivity relationships revealed here will assist synthetic chemists in deploying this type of methodology in the syntheses of α-fluoroketones.

Introduction

SelectFluor (**1**)[1] is an easy-to-handle and stable solid that is widely used as an electrophilic fluorinating agent[2-5] and oxidant in synthetic chemistry applications.[6-8] It is relatively cost-effective compared to alternatives such as *N*-fluorobenzenesulfonimide (NFSI) and fluoropyridinium salts, is stable for extended periods of time,[9] and does not require storage at low temperatures or under a protective atmosphere. Various synthetic studies have demonstrated the ability of **1** to fluorinate 1,3-dicarbonyl compounds, enol esters, and even electron-rich arenes.[10-18] Ketones can also undergo direct α-fluorination reactions using **1** and analogous species.[19-21] Reagent **1** is one of the more reactive fluorinating reagents, as judged from recent kinetic studies.[22-23]

Steroid-like structures are often fluorinated using **1** *via* the corresponding (di)enol ester intermediates (Scheme 1); although



Scheme 1. The fluorination of steroid structures via enol ester intermediates.

1 is ultimately prepared from elemental fluorine, the use of this bench-stable solid is more convenient than the direct deployment of fluorine gas,[24] and requires no special glassware or apparatus. In addition, **1** offers advantages over expensive XeF_2 [25-26] or hazardous hypofluorites;[27-28] the latter often require cryogenic temperatures which have associated cost, safety, and environmental implications. Despite the significant utility and widespread application of **1**, there is only a limited understanding of the underlying reaction mechanisms in many of these fluorination reactions. In particular, there are many examples where reaction *via* a polar two-electron mechanism is proposed, and a corresponding set of examples where a reaction *via* radical intermediates is posited.

In support of a polar two-electron process, radical clock methods where a pendant alkene or cyclopropyl group is present on a substrate for fluorination using **1** suggest that either radical species are not formed, and or if they are, that they are not sufficiently long-lived to engage in subsequent reactions. Citronellic ester enolates react with NFSI or with a close analogue of **1**, without ring-closing reactions that might be expected to occur if a radical was formed (Scheme 2 (a));[29] in contrast, XeF_2 leads to *ca.* 10% of material undergoing such a ring-closing process. Estimated rate constants for electron transfer processes are *ca.* 10^7-times (or less) lower than measured rate constants for fluorination reactions, for some reactions between enolates or organometallic reagents and an *N*-fluorosultam reagent.[30] However, in both of these studies, the nucleophile is typically an organometallic reagent or an enolate; emerging research shows that enolates can have intriguing electron transfer behaviour, carrying out single-electron processes, despite the fact that they would traditionally be considered as two-electron nucleophiles.[31] Inner-sphere electron transfer has also been proposed as a potential mechanism for reactions of **1**, in the context of the electrophilic fluorination of alkenes.[32] Cyclopropyl-functionalised enol ethers undergo reaction with **1** to produce fluoroacetals

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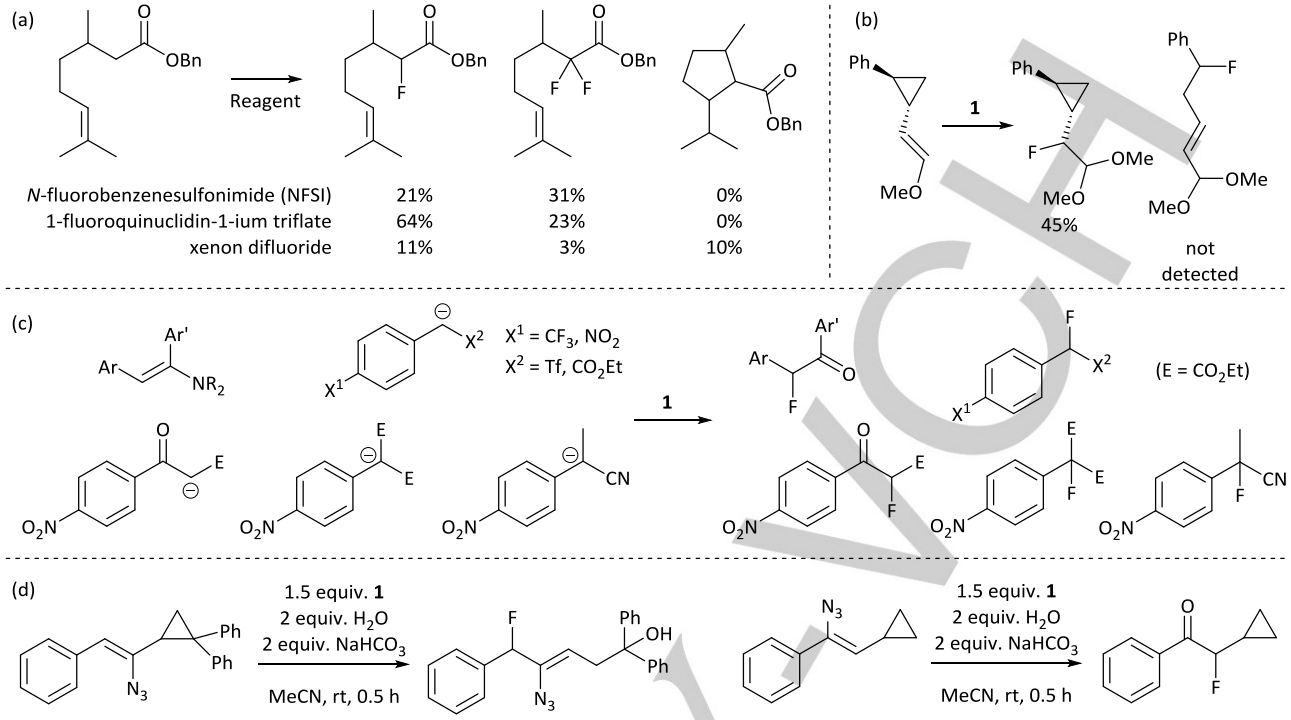


Scheme 2. Literature studies that implicate two-electron or single-electron reaction mechanisms.

(Scheme 2 (b));[33] while no ring-opened product was obtained, the fluoroacetal was recovered only in 45% yield, so much of the material is unaccounted for. The reaction of this probe with NFSI leads to 40% fluoroacetal plus 5% of ring-opened product. A recent and detailed study of the electrophilicity of common electrophilic fluorinating reagents used enamine and carbanion nucleophiles (Scheme 2 (c));[22] the data obtained ruled out mechanisms that involve single-electron transfer and are entirely consistent with a polar two-electron mechanism.

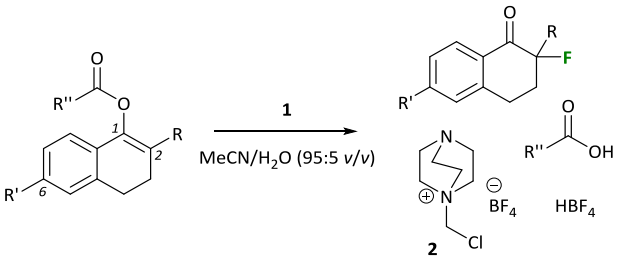
However, other studies implicate radical intermediates strongly. An ESI-MS study of the reaction of tri- and tetraphenylethene with **1** provided evidence for radical cation intermediates, while no such radical cations were observed in the absence of **1**.[34] Similar studies of the reactions of styrene, 2-phenylpropene, TEMPO, and DMPO with **1** gave rise to signals consistent with radical intermediates in fluorination reactions mediated by **1**.[35] Recent studies of vinyl azide fluorination implicate a radical cation intermediate on the basis of radical clock experiments;[36-37] however, the stability of cyclopropyl-bearing substrates depends on how close this moiety is to the azide (Scheme 2 (d)). The successful deployment of **1** in chemical processes, especially on scale in industry, depends on a detailed understanding of how the reaction proceeds, so that reaction outcomes can be understood and, ideally, predicted.

We set out to understand the reaction mechanism involved in the electrophilic fluorination of enol esters, and to identify and quantify structure/reactivity relationships. A full understanding of these issues is important to allow the rational deployment of this methodology and the judicious selection of reaction conditions. While SelectFluor is not the most expensive electrophilic fluorinating reagent, it is still likely to be the major cost for any industrial process that uses it. To the best of our knowledge, the mechanism of the fluorination of enol esters by **1** has not been unambiguously established.

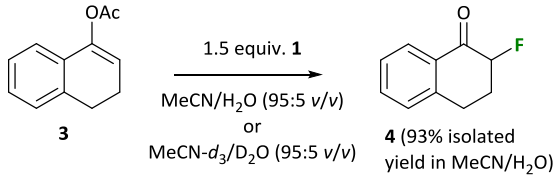
Results

Model systems based on a tetralone core provided a range of synthetically tractable compounds for this work, and have well-resolved and diagnostic ^{1}H NMR spectra. The reactions of these compounds with **1** are expected to form the corresponding α-fluoroketones, plus by-products including ammonium salt **2**, a carboxylic acid, and tetrafluoroboric acid (Scheme 3). During this work, systematic variation of the ester group at position 1 was explored, as well as substitution at the 2- and 6-positions (*vide infra*).

Parent compound **3** (R, R' = H; R'' = Me) was prepared from tetralone by reaction with isopropenyl acetate; **3** underwent smooth and complete fluorination at 298 K in a 95/5 *v*/*v* MeCN(-d_3)/water(-d_2) mixture to produce fluoroketone **4** (93% yield) plus **2**, acetic acid, and tetrafluoroboric acid (Scheme 4). Reactions in neat acetonitrile(-d_3) were often irreproducible and typically did not reach complete conversion. An authentic sample of **2** was prepared *via* an independent synthetic route to confirm the assignment.[38] High-quality, reproducible kinetic data were obtained from ^{1}H NMR kinetic experiments; the use of a small excess of **1** (1.5 equiv.) led to a pseudo-first order in **3** for three or



Scheme 3. Fluorination of tetralone derivatives using SelectFluor.



Scheme 4. Fluorination of compound **3**.

more half-lives. The reaction between **1** and **3** is first order in **1** as judged from plots of k_{obs} *versus* [**1**] (Figure 1). Kinetic experiments at different temperatures gave a good quality Eyring-Polanyi plot and values for $\Delta H^{\ddagger}$ (15.0 kcal mol^{-1}), $\Delta S^{\ddagger}$ (-24 cal K^{-1} mol^{-1}), and $\Delta G^{\ddagger}$ (22.0 kcal mol^{-1}) that are consistent with a bimolecular reaction that occurs smoothly at 298 K (Figure 2).

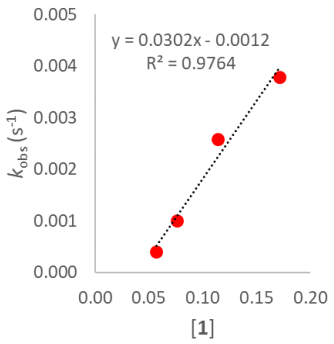


Figure 1. Plot of k_{obs} versus [**1**] for the fluorination of **3** with **1**.

Reactions with 0.8 equiv. **1** gave 78% conversion of **3** to **4**; the recovered **3** was used to measure ^{13}C kinetic isotope effects (KIEs) using Singleton's method.[39] The methyl signal (δ_C = 20.5 ppm) was used as the internal standard, assuming that this has a KIE of 1.000 due to its distance from the reacting centre. The only signal that showed a significant KIE was the arene carbon at the 6-position, which is *para* to the carbon bearing the acetoxy group (δ_C = 126.0 ppm; KIE = 1.031) (Figure 3).

Three Hammett studies were carried out to probe the electronic effects of substrate structures.[40] Initial experiments were performed with *para*-substituted enol benzoates **5a-h**

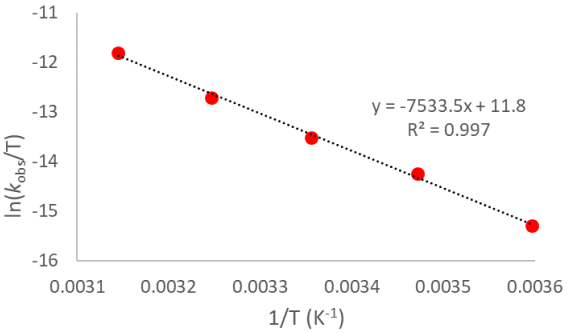


Figure 2. Eyring-Polanyi plot for the fluorination of **3** using **1**. Each point is the average of two experiments.

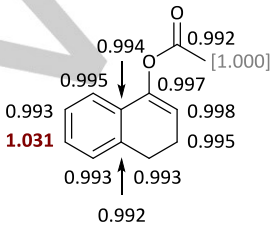
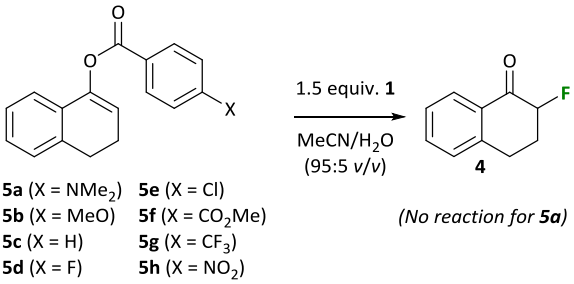


Figure 3. Kinetic isotope effects measured for substrate **3** in the fluorination reaction.

(Scheme 5), which were typically prepared by reaction of **3** with the corresponding benzoyl chloride. Substrates **5b-h** reacted smoothly with 1.5 equiv. **1**, yielding good quality kinetic data and forming **4** and the expected by-products. For **5a** (X = NMe_2) an intensely-coloured solution was formed and no fluorination occurred, and control experiments with *N*,*N*-dimethylaniline confirmed that this functional group is not tolerated by **1**; it has been reported in the literature that similar compounds react with *N*-fluoro-compounds to yield deeply coloured radical cations.[30]



Scheme 5. Reactions of benzoyl enol esters **5a-h**.

A Hammett treatment of the kinetic data for **5b-h** using σ_p as the abscissa gave a relatively poor correlation (ρ = -0.4), indicating a build-up of positive charge in the transition state (Figure 4 (a)). A better plot was obtained using σ_p^+ (Figure 4 (b); the point for **5f** is included in both lines of best fit); this is indicative of the

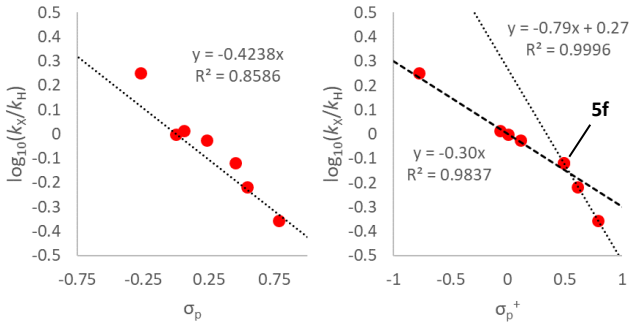


Figure 4. Hammett plots for substrates **5b-h**, constructed using (a) σ_p and (b) σ_p^+. Each point is the average of two experiments.

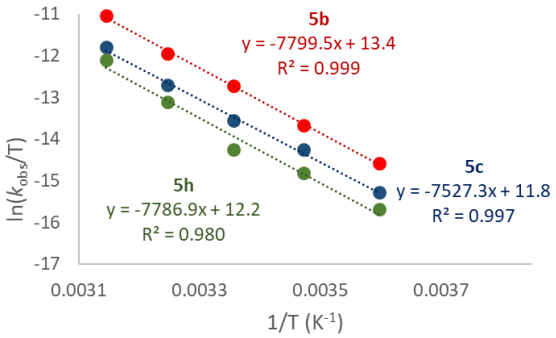


Figure 5. Eyring-Polanyi plots for the reactions of 5b, 5c, and 5h with 1. Each point is the average of two experiments.

development of a formal positive charge in conjugation with the benzoyl ester and perhaps some change in the rate-determining step as more electron-poor substrates are considered (*vide infra*).

Eyring-Polanyi plots were constructed for the reactions of **5b**, **5c**, and **5h** based on kinetic studies carried out at 5 to 45 °C (Figure 5) to further investigate this apparent break in the Hammett plot. The free energy of activation ($\Delta G^{\ddagger}$) followed the same trend as the Hammett plot (Table 1), with the fluorination of electron-rich **5b** being the most rapid. The values of $\Delta S^{\ddagger}$ obtained for **5c** and **5h** are almost identical (-23 and -24 cal K^{-1} mol^{-1} respectively), indicating a similar entropic penalty for forming the transition state. The Eyring-Polanyi plot for **5c** is almost identical to that produced for enol acetate **3**, consistent with a common mechanism between enol esters.

A set of compounds was prepared with aryl substituents at the site of fluorination (Scheme 6). While this was done to alter the electron density at this site, it must be noted that the resulting compounds are essentially stilbene derivatives. The bromination of tetralone using *N*-bromosuccinimide yielded 2-boromotetralone (**6**) which gave **7** upon treatment with NaHMDS and acetic anhydride. Compound **7** underwent palladium-catalysed cross-coupling with arylboronic acids to form **8a-e**. Compound **7** underwent smooth fluorination to form **9**, without loss of the bromine substituent (Scheme 6(a)). A molecular structure for **9** was obtained by X-ray diffraction analysis (Figure 6). Consistent with previous reports,[41] the bromide has a greater preference than fluorine for the axial position due to unfavourable interactions with the carbonyl group, placing the fluorine substituent in the equatorial position.

Table 1. Thermodynamic parameters for the reactions of **3**, **5b**, **5c**, and **5h** with 1, obtained from kinetic studies at various temperatures.

Compound	$\Delta G^{\ddagger}$/kcal mol^{-1}	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal K^{-1} mol^{-1}
3	22.0	15.0	-24
5b	21.6	15.5	-20
5c	22.0	14.9	-24
5h	22.3	15.5	-23

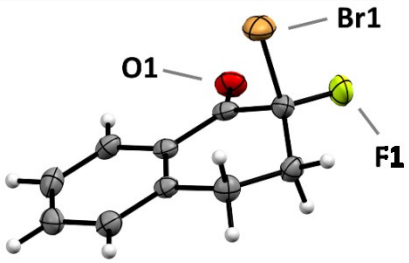
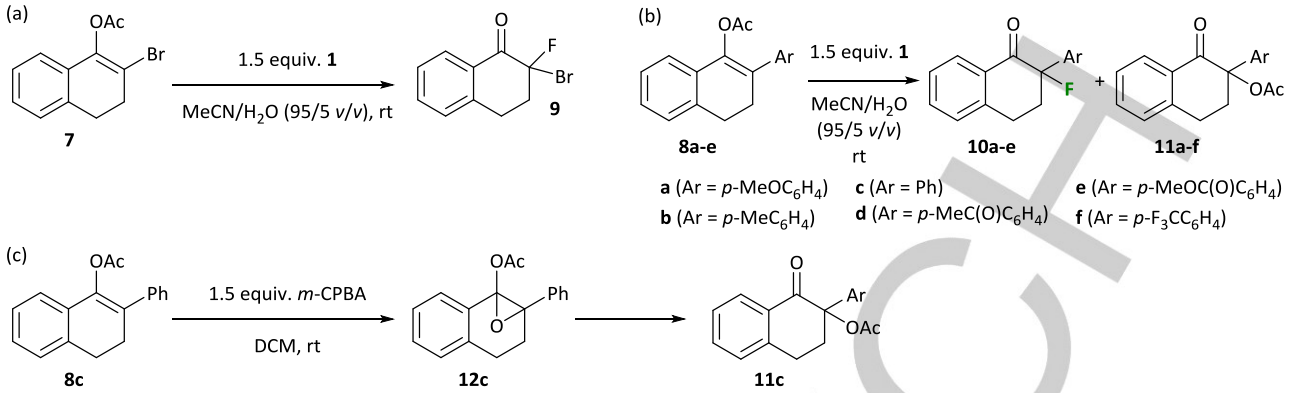


Figure 6. Molecular structure of **9**, as determined by X-ray diffraction analysis of a single crystal.



Scheme 6. (a) Reaction of compound **7**. (b) Reactions of compounds **8a-e**. (c) Independent synthesis of **11c**.

Synthetic experiments with **8c** led to the expected fluorinated product **10c**, but also to a non-fluorinated side-product (Scheme 6 (b)). The latter was determined to be **11c** on the basis of detailed 1D and 2D NMR experiments, GC-MS and IR analyses. The epoxidation of **8c** to form **12c** followed by heating to provoke rearrangement, allowed the synthesis of an authentic sample of **11c** with NMR data that matched the material produced during the fluorination reaction (see the Supporting Information). Attempts to prepare **11c** by exposing solutions of **8c** to oxygen and/or water were unsuccessful, so **1** is necessary for both pathways.

The reactions of each of **8a-e** gave various ratios of **10a-e** and **11a-e**, as determined by integration of the ^{1}H NMR spectrum using an internal standard, with more electron-rich substrates yielding more **11** (Table 2). All reactions reached ≥97% conversion. Attempts to suppress side-product formation by performing the reaction under a nitrogen atmosphere led to no change in the product ratio; similarly, the use of air-sparged solvent did not increase the proportion of **11** produced.

Table 2. Results of the fluorination of **8a-e** in 95/5 *v*/*v* MeCN-d_3/D_2O, as determined from kinetic experiments. Conversions are determined by integration *versus* an internal standard (cyclohexane capillary).

Entry	Substrate	Ar *p*-subs.	Conv. to 10	Conv. to 11
1	**8a**	MeO	57	40
2	**8b**	Me	70	27
3	**8c**	H	84	16
4	**8d**	Ac	85	15
5	**8e**	MeO_2C	90	10
6	**8f**	F_3C	87	13

An Eyring analysis of the reaction of **8c** with **1** revealed very similar parameters to those for **3**, **5b**, **5c**, and **5h**, even though two products result ($\Delta H^‡$ = 15.5 kcal mol^{-1}, $\Delta S^‡$ = -21 cal K^{-1} mol^{-1}, $\Delta G^‡$ = 21.9 kcal mol^{-1}; Figure 7). This is consistent with a common rate-determining step involving both **8c** and **1**, followed by a subsequent step (or steps) in which **9c** and **10c** are formed.

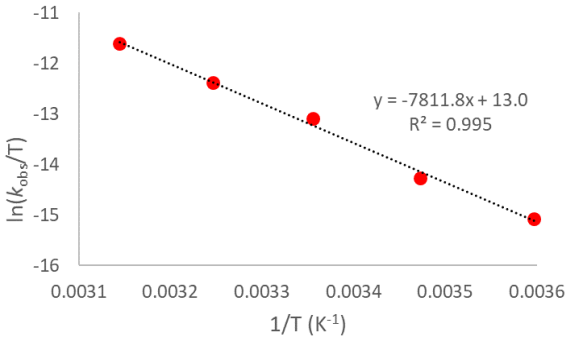


Figure 7. Eyring-Polanyi plot for the reaction of 8c with 1. Each point is the average of two experiments.

Kinetic experiments with **8a-e** allowed rate constants to be measured for their reaction with SelectFluor in acetonitrile/water (95/5 *v*/*v*). The correlation with σ_p was again rather poor (Figure 8 (a)), but a much better correlation was obtained with σ_p^+ (Figure 8 (b)); unfortunately, a value for σ_p^+ is not available for acetyl so **8d** could not be included in the correlation. These results are also indicative of the build-up of a formal positive charge. The slope is steeper than observed in Figure 4 (b) (above), with ρ = -0.87 *versus* -0.30 to -0.79. Each experiment produced some by-product **11** but the decrease in concentration of **8c** was well-behaved pseudo-first order when 1.5 equiv. of **1** were used. This well-behaved kinetic behaviour and the results of an Eyring-Polanyi analysis for **8c** are indicative of a common rate-determining step followed by different pathways for the formation of **10** and **11**.

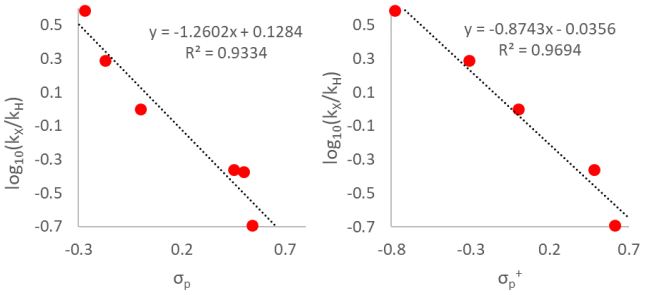
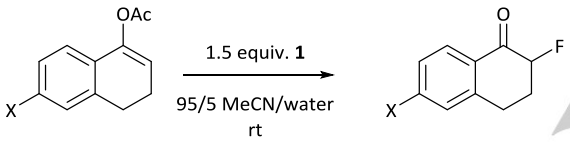


Figure 8. Hammett plot for the fluorination of **8a-e** in acetonitrile/water (95/5 *v*/*v*) versus (a) the σ_p parameter and (b) the σ_p^+ parameter.

A set of substrates was prepared in which the 6-position of the tetralone core was systematically varied (Scheme 7), as KIE experiments (*vide supra*) suggest that this position is important in the fluorination reaction. A set of compounds was prepared, using 6-methoxytetralone (**13a**), 6-aminotetralone (**13b**), and 6-carboxytetralone (**13c**) as the starting materials (see the Supporting Information).



15a (X = OMe; 45% yield)
15b (X = OAc; 65% yield)
15c (X = Cl; 79% yield)
15d (X = CO_2Me; 74% yield)

Scheme 7. Reactions of enol esters **14a** – **14d**.

The fluorination reactions of **14a-d** proceeded smoothly with pseudo-first order kinetics. Hammett plots using σ_p and σ_p^+ showed a better fit with σ_p^+ (R^2 = 0.75 for σ_p *versus* 0.94 for σ_p^+) (Figure 9). The value of ρ obtained for this series (-1.36) was greater in magnitude than those observed for studies with compounds **5** and **8** (*vide supra*).

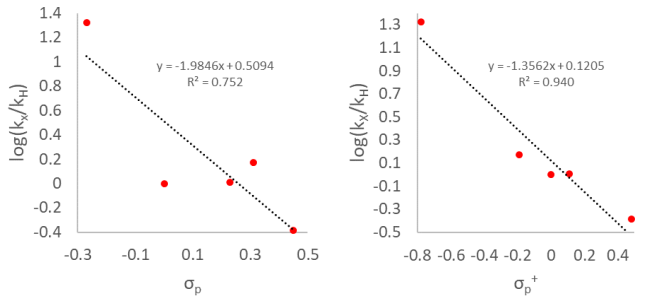
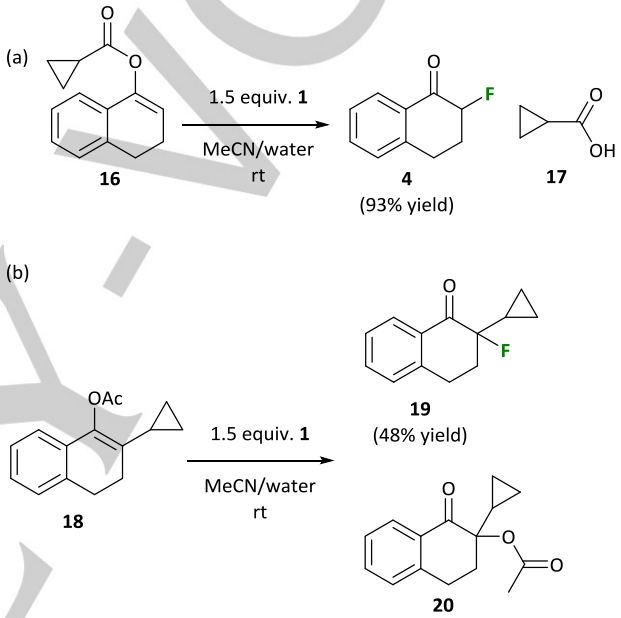


Figure 9. Hammett plots for the reactions of **14a-e** with **1**, plotted using (i) σ_p and (ii) σ_p^+.

Cyclopropyl-substituted substrates were prepared to probe whether radical species were involved; the formation of a radical close to the cyclopropyl group would be expected to lead to ring-opening. Compound **16** was prepared from tetralone and subjected to the standard reaction conditions (Scheme 8 (a)); the products of this reaction were α-fluoroketone **4** and cyclopropyl carboxylic acid **17**. Compound **18** was prepared *via* a palladium-catalysed Suzuki-Miyaura cross-coupling of **7** and cyclopropylboronic acid. As observed with the α-aryl substituted series **8**, reaction with **1** produced the corresponding α-fluoroketone **19**, ester side product **20** and acetic acid (Scheme 8 (b)). There was no evidence of cyclopropyl ring-opening.

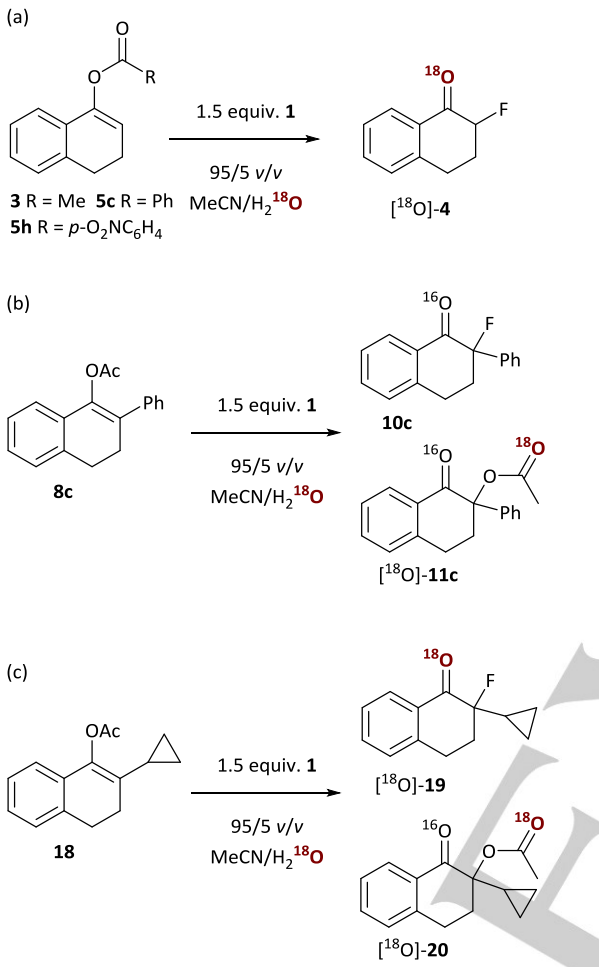


Scheme 8. Reactions of cyclopropyl-substituted substrates.

The storage of **19** in $CDCl_3$ for three weeks resulted in discolouration of the solution. ^{1}H and ^{19}F NMR analyses indicated complete decomposition of the compound to several fluorinated products, including some with large coupling constants (*J* = *ca*. 45 Hz) that are indicative of $^2J_{HF}$ coupling. It is likely that these compounds have arisen as a result of the loss of fluoride from **19**, producing a carbenium adjacent to the cyclopropane followed by ring opening/rearrangement and reintroduction of fluoride to the molecule. Analogous compound **11c** is stable under these conditions.

Reactions in acetonitrile/$H_2{}^{18}O$ solvent were used to identify the source of the oxygen in **4**; these reactions were analysed by mass spectrometry.[42] The reactions of **3**, **5c**, and **5h** led to complete incorporation of ^{18}O into **4** (Scheme 9(a)). For **8c**, there was no incorporation of ^{18}O into the product (Scheme 9 (b)). The molecular ion of the side-product **11c** was not detected by GC-MS with EI ionisation, but **21c** was and this did not contain ^{18}O (Figure 10); IR analysis of a mixture of **10c** and **11c** from this experiment showed the characteristic shift in the wavenumber of the ester C=O signals that would be expected if ^{16}O was replaced

with ^{18}O. When **18** underwent reaction with **1** in the presence of $H_2{}^{18}O$, there was ^{18}O incorporation into the product, but not into the side-product (Scheme 9 (c)).



Scheme 9. Fluorination of compounds **3**, **5c**, **5h**, and **17** in acetonitrile/ [^{18}O]water. Reaction yields were not determined.

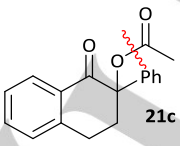
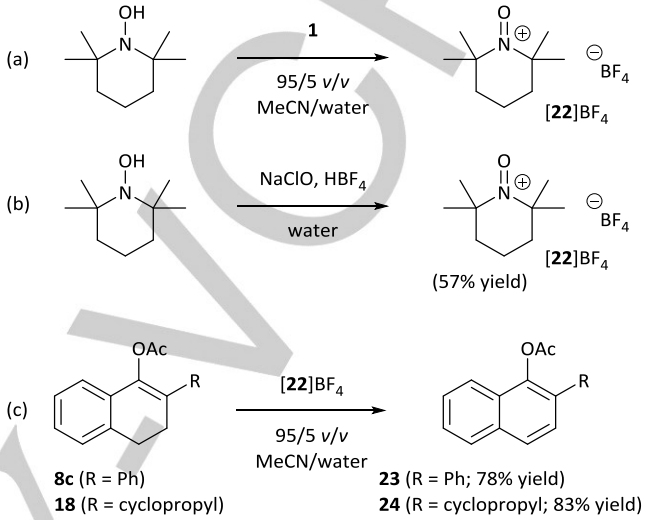


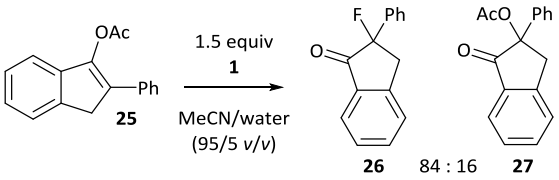
Figure 10. Des-acetate compound **21c** identified by GC-MS (EI) analysis.

Attempts to probe the involvement of radicals by adding TEMPO to kinetic reactions were unsuccessful. While the reaction did indeed cease completely upon the addition of TEMPO, this was due to the immediate and complete destruction of **1**.[33] The reaction between **1** and TEMPO leads to complete conversion of **1**, as judged by ^{19}F NMR spectroscopy, and the formation of oxoammonium salt [**22**]BF_4 (Scheme 10 (a)) as judged by the comparison of IR and UV spectra with those of an authentic sample prepared by the reaction of TEMPO with bleach and tetrafluoroboric acid (Scheme 10 (b)).[43] The use of TEMPO as a radical trap in reactions mediated by **1** is therefore unreliable. However, while [**22**]ClO_4 reacts with vinyl azides to form various functionalised products,[44] [**22**]BF_4 reacts with **8c** and **18** to form the corresponding naphthalenes **23** and **24** (Scheme 10 (c)).



Scheme 10. (a) Formation of [**22**]BF_4 from the reaction of TEMPO with SelectFluor. (b) Formation of [**22**]BF_4 by oxidation of TEMPO using bleach. (c) Reactions of **8c** and **18** with [**22**]BF_4.

Indanone derivative **25** was prepared *via* a sequence of bromination acetylation, and palladium-catalysed cross-coupling and underwent reaction with **1** to form product **26** and side-product **27** in a ratio of 84:16 (Scheme 11). This ratio is identical to that obtained for the reaction of tetralone derivative **8c** with **1**.



Scheme 11. Reaction of indanone derivative **25**.

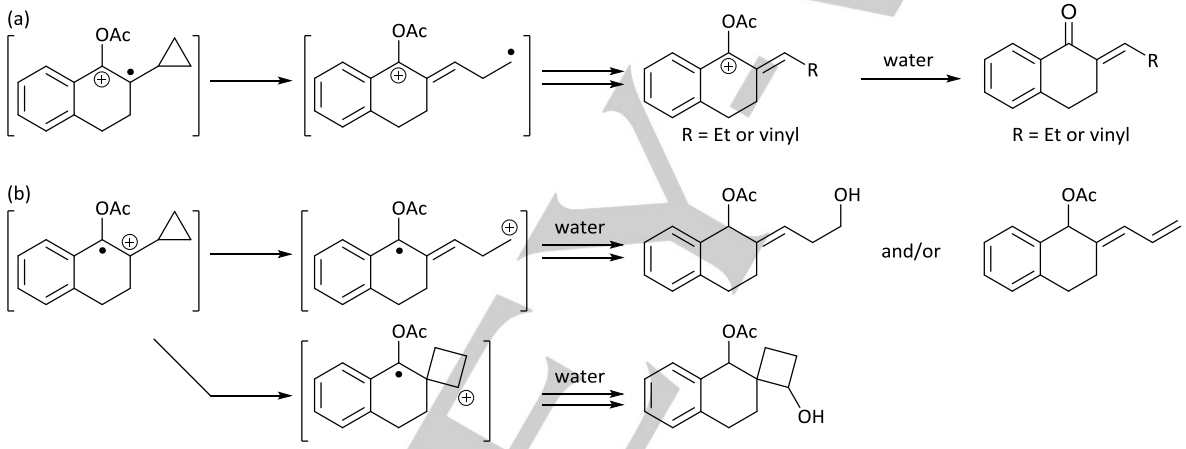
Discussion

The data gathered for the fluorination of **3**, **5b**, **5c**, and **5h** show that the rate-determining step is bimolecular ($\Delta S^{\ddagger}$ = -20 to -24 cal K^{-1} mol^{-1}), and has a free energy of activation that is consistent with a facile reaction that takes a few hours at room temperature to reach completion ($\Delta G^{\ddagger}$ = 20.9 to 22.3 kcal mol^{-1}). The consistency between each series indicates that each enol ester fluorination reaction is occurring *via* a common mechanism. The

reaction is pseudo-first order under the reaction conditions when a small excess of **1** is used, first order in **1**, and no longer pseudo-first order in enol ester if less than 1.5 equivalents of **1** are used. This bimolecular reaction therefore involves **1** and the enol ester.

It is not likely that ester hydrolysis is rate-determining. Experiments with **5c** in 95/5 *v*/*v* acetonitrile/water and acetonitrile/methanol proceed with similar rates (k_{obs} (MeCN/water) = 4.97 x 10^{-4} s^{-1}; k_{obs} (MeCN/MeOH) = 6.21 x 10^{-4} s^{-1}; at 298 K). Water and methanol have very different nucleophilicities, as determined by Mayr:[45] a 90/10 acetonitrile/water mixture has N = 4.56 (s_N = 0.94), while 90/10 acetonitrile/methanol has N = 5.55 (s_N = 0.97); note that N is a logarithmic scale and so a one unit difference in N translates to a *ten-fold* difference in reaction rate.[46] Other ratios of acetonitrile/solvent (80/20, 67/33, 33/67, 20/80, and 9/91) show the same trend, so we assume that this holds for 95/5 mixtures also. If ester hydrolysis was rate-determining, then reactions in methanol should be much faster. In addition, the rates of fluorination of **5b-h** *increase* when electron-donating groups are present; such a structural change would render the ester carbonyl group *less* electrophilic. The enol ester must therefore be the nucleophile in the rate-determining step, not the electrophile. The outcomes of the $H_2{}^{18}O$ experiments show that the nucleophilic attack must occur from the enol ester not the enolate; if the enolate was the nucleophile, as a result of ester hydrolysis, then ^{18}O would be incorporated into the carboxylic acid side-product and not into the ketone.

Evidence from other experiments is entirely consistent with a polar two-electron mechanism that proceeds *via* a carbenium intermediate. Substrates with cyclopropyl groups (**16** and **18**), which are known to undergo rapid ring-opening when radicals are nearby (*ca.* 10^8 s^{-1}),[47] do not lead to the types of alkene side-products that might be expected if a single-electron process was in operation (e.g. Scheme 12 (a)). Furthermore, if a carbenium ion was to be formed adjacent to the cyclopropyl group, ring-opening or ring-expansion products would also be expected (e.g. Scheme 12 (b)). It is unlikely that, if a radical intermediate was generated in this reaction, it could undergo a bimolecular reaction before



Scheme 12. Expected, but unobserved, reaction pathways if (a) a radical species was generated or (b) a carbenium ion was generated adjacent to the cyclopropyl group via single-electron transfer from **18**.

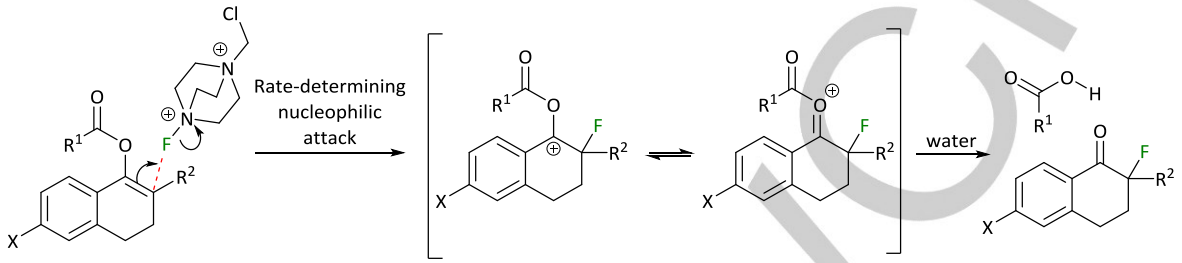
side-reactions occurred because at the concentrations studied such a reaction would have to occur faster than diffusion through solution (*ca*. 10^{10} L mol^{-1} s^{-1}).

A third possibility – the formation of carbenium adjacent to the ester after nucleophilic attack of **1** by the enol ester – is supported by all of our experimental data (Scheme 13). Such an intermediate would gain resonance stabilisation from the adjacent oxygen atom, and the absence of a radical species precludes cyclopropyl ring-opening. The results of the Hammett study in Figure 9 are the strongest evidence for such a mechanism, with the substituent at the tetralone 6-position clearly supporting a developing positive charge. The correlation with σ_p is very poor, yet the correlation with σ_p^+ is excellent; the σ_p^+ scale takes into account the ability of +R substituents to stabilise cations, and so the excellent correlation in Figure 9 is indicative of carbenium ion stabilisation. Figures 4 and 8 are also consistent with this proposal, showing again that electron-donating groups accelerate the reaction, with – in both cases – better correlations to σ_p^+ than to σ_p. If electron transfer to **1** from the substrate and fluorine atom transfer from a putative radical anion of **1** to the radical thus formed occur as discrete steps, they must occur in such rapid succession that they are best considered as a single step; species such as [**22**]BF_4 that act only as oxidants lead to formation of the corresponding naphthalene. The ^{13}C KIE experiments with **3** rather surprisingly showed the greatest KIE (1.03) at the 6-position of the tetralone core. This is consistent with a concomitant change in the electronic structure of the aryl ring which would be expected if a carbenium ion was formed in a position in which it was in conjugation with this aryl ring.

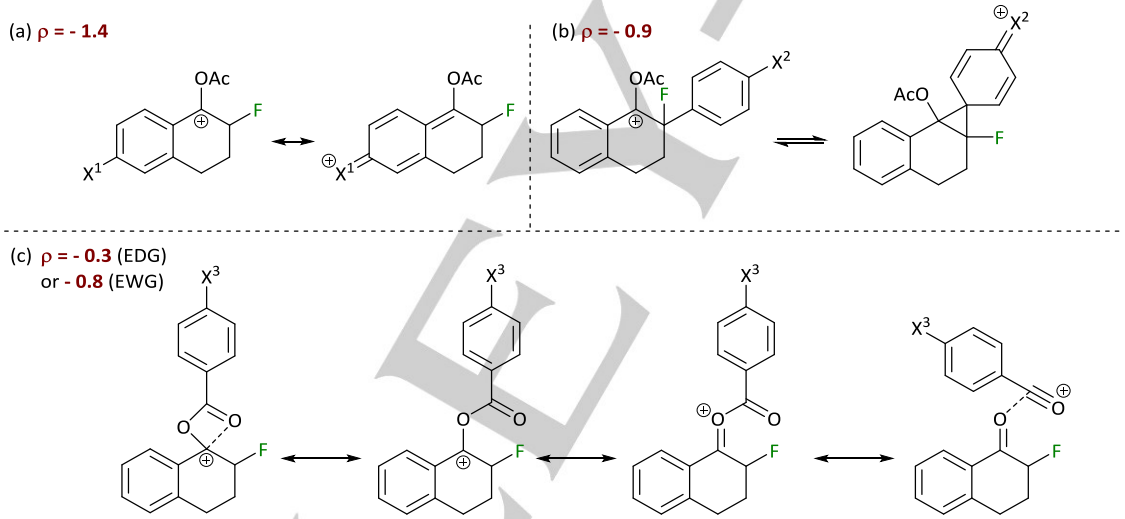
The value of ρ decreases for substitution at X^1 > X^2 > X^3 (Scheme 14), which can be rationalised by considering the behaviour of an intermediate formed after nucleophilic attack of **1**. Substitution at the 6-position of the tetralone core (X^1, ρ = -1.4) has the strongest effect, because a resonance form can be envisaged in which a lone pair of electrons directly stabilises the carbenium ion, while retaining essentially the same geometry within the compound. For substitution at the other end of the molecule (X^2, ρ = -0.9), even though the arene is not directly in

conjugation with the carbenium, neighbouring group participation can stabilise the carbenium ion. Finally, X^3 is sufficiently remote from the carbenium ion centre that again some form of neighbouring group participation would be the manner in which it could stabilise a carbenium ion. The comparable rates of benzoate and acetate fluorination (Table 1; the benzoate reacts only slightly faster), rule out neighbouring group effects involving Wheland-type intermediates for enol benzoate substrates.

This leads to a rationale for the change of slope in the Hammett plot for enol benzoate fluorination (see Figure 4). When considering the resonance (*R*) and field (*F*) parameters for the substituents,[40] it is found that MeO, Cl, and F are +*R* and CO_2Me, CF_3, and NO_2 are –*R* (*R* = -0.56, -0.19, -0.39, 0.11, 0.16, and 0.13, respectively); the former three substituents are therefore capable



Scheme 13. Proposed mechanism for fluorination of enol esters by **1**.



Scheme 14. Values of ρ for the three different Hammett studies conducted during this work.

of participating in the process outlined in Scheme 14 (c), while the latter three are not, leading to a precipitous decline in the reaction rate as the benzoate group becomes less electron-rich. The interception of carbenium intermediates intra- and intermolecularly (with carboxylic acids and esters, and with acetonitrile, respectively) has been reported in previous studies of fluorination using **1**.[48]

Once fluorination has occurred, and a carbenium ion is formed, the final step is hydrolysis using water. This could occur either *via* attack of water at the ester carbonyl group, or directly at the carbenium. When $H_2{}^{18}O$ was used in place of $H_2{}^{16}O$, complete incorporation of ^{18}O at the ketone was identified by GC-MS analysis of the reactions of **3**, consistent with the presence of a highly-reactive carbenium species which undergoes reaction with water (Scheme 15 (a)). Experiments with **8c** in acetonitrile/ [^{18}O]water suggest a rather different hydrolysis mechanism for this reaction, as no ^{18}O is incorporated at the ketone; the hydrolysis mechanism must therefore be different, perhaps as a result of the increased steric bulk adjacent to the ketone, rendering this similar to neopentyl systems which are infamously bad electrophiles (Scheme 15 (b)).

The origins of the side products **11** (from the reactions of **8**) and **20** (from **18**) are currently unclear. Compound **19** is rather unstable in solution, and so it is possible that **20** is a side-product arising from decomposition. The formation of **11c** is likely to occur subsequent to the rate determining step between **1** and **8c**, but not from ketone **10c**, for a number of reasons: (i) **10c** is stable in solution, even in the presence of added acid; (ii) the formation of

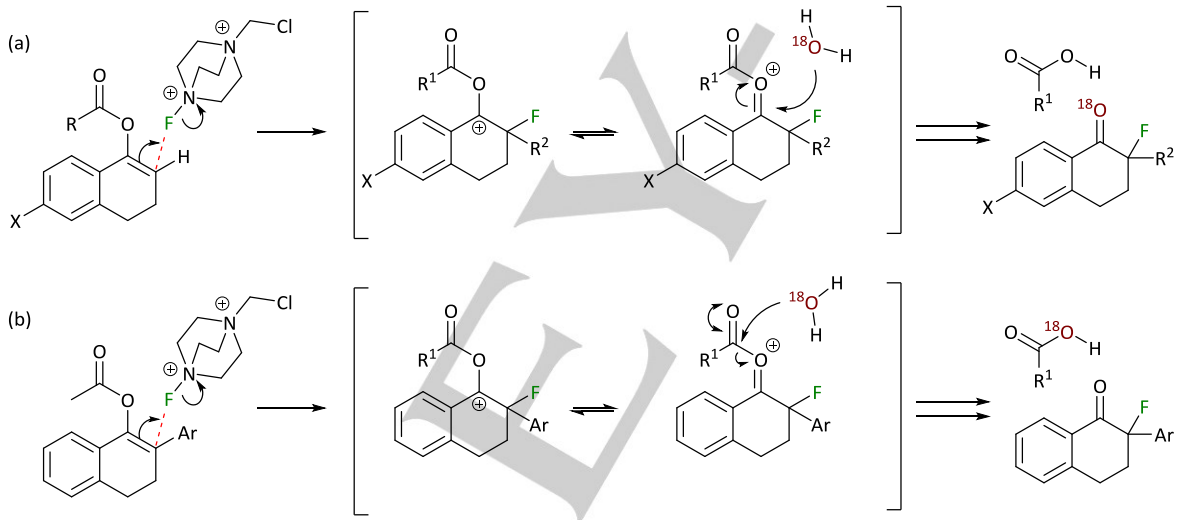
a carbenium adjacent to the carbonyl in **10c**, such as from the loss of fluoride, in MeCN/$H_2{}^{18}O$ solvent might lead to some products from the reaction of the carbenium with water or acetic acid, incorporating an ^{18}O label;[49] and (iii) the ^{18}O label is incorporated exclusively into the carbonyl oxygen of the ester, while intramolecular reactions involving $[^{18}O]_1$-AcOH would be expected to result in a *ca.* 1:1 ratio of $R^{18}OC(O)Me$ and $ROC(^{18}O)Me$. The similar ratio of product to side product obtained from the indanone-derived analogue **25** shows that this pathway is not limited to our tetralone system. Several mechanistic hypotheses are currently under investigation using further experimental studies and computational modelling.

Conclusions

This work represents the most detailed study to date of mechanism and structure/reactivity relationships in the fluorination of enol esters using **1**. The collection of high quality kinetic data, and the use of isotopic labelling, have allowed us to gather a significant body of evidence that points towards a polar two-electron process for the fluorination reaction (Scheme 12, above). All of the Hammett studies indicate that a carbenium ion is formed as a crucial intermediate, with +*R* substituents leading to significant increases in the reaction rate. Attempts to provoke any radical species present into undergoing reactions such as cyclopropyl group ring-opening were unsuccessful; cyclopropyl-substituted compounds undergo smooth and facile fluorination without the formation of side-products.

It is important to consider these results in the context of recent studies that imply that similar polar two-electron mechanisms are in operation for the fluorination of enamines,[22] stabilised carbanions,[22] and 1,3-dicarbonyl species.[23] The carbanions in particular are more electron-rich than the enol ester substrates considered here, and the enamines would also be expected to be more electron rich. The enol forms of the 1,3-dicarbonyl compounds considered by Sandford and Hodgson possibly have similar nucleophilicities to the enol esters considered here, but unfortunately the nucleophilicities of these species have not yet been measured. However, (silyl) enol ethers have nucleophilicities (*N* = *ca.* 4 – 7)[50] that are ≥ 10^4-times lower than enamines (*N* = *ca.* 10 – 16)[51] and ≥ 10^{10}-times lower than the carbanions studied by Mayr.[52-54] The nucleophilicities of vinyl azides, which under some circumstances undergo fluorination with **1** *via* a radical mechanism,[36-37] have not yet been measured. The fact that nucleophiles with such a wide range of reactivity all undergo reaction *via* a two-electron mechanism leads us to propose that radical reactions between organic nucleophiles and reagent **1** are the exception, rather than the rule.

Further mechanistic studies of electrophilic fluorination reactions with **1** are currently underway in our laboratories using a variety of substrates, as we continue to work towards a quantitative understanding of this class of reaction.



Scheme 15. Proposed mechanisms for the hydrolysis of (a) **3** and (b) **8c** after fluorination.

Experimental Section

General. General experimental details are provided here. Full characterisation for all compounds can be found in the Supporting Information. Unless stated otherwise, all compounds were obtained from commercial sources and used as supplied. Each batch of SelectFluor (**1**) was analysed by iodometric titration and confirmed to be >95% pure. Compounds **2** and [**22**]BF_4 were prepared according to literature methods.[38, 43]

Analysis. NMR characterisation was carried out using Bruker AV3-400 equipped with a liquid nitrogen Prodigy cryoprobe, or a Bruker AV400 equipped with a BBFO-*z*-ATMA probe; kinetic data were obtained using a Bruker AVII-600 NMR spectrometer equipped with a BBO-*z*-ATMA probe.

All NMR chemical shifts are quoted in units of parts per million (ppm). ^{1}H NMR spectra were referenced to residual solvent signals,[55] $^{13}C\{^{1}H\}$ spectra were referenced to the solvent signal,[55] and ^{19}F and $^{19}F\{^{1}H\}$ spectra were externally referenced to $CFCl_3$. Assignments of the spectra were achieved by the use of [^{1}H, ^{1}H] COSY, [^{1}H, ^{13}C] HSQC, and [^{1}H, ^{13}C] HMBC experiments, as required. Mass spectrometry data was obtained using an Agilent 7890A GC system coupled to an Agilent 5975C mass spectrometer in electron impact mode. High resolution mass spectrometry was carried out on a ThermoFinnigan Exactive mass spectrometer. Infrared spectra were obtained using a Shimadzu IRAffinity-1 IR spectrometer with an ATR accessory. Thin layer chromatography was performed on pre-coated aluminium-backed silica gel plates (silica gel 60 F254, 0.2 mm thick). Column chromatography was performed on silica gel (40 – 63 μm).

Procedure for SelectFluor titration. A nominally 0.01 mol L^{-1} aqueous solution of SelectFluor (10 mL) was added to a 0.02 mol L^{-1} aqueous solution of potassium iodide (20 mL), followed by 1.9 mol L^{-1} aqueous sulfuric acid (5 mL). The liberated iodine was titrated against a 0.05 mol L^{-1} aqueous solution of sodium thiosulfate.

General procedure A for fluorination reactions with 1 (synthetic experiments). Substrate (1 equiv.) and SelectFluor (1 equiv.) were suspended in 95/5 *v*/*v* MeCN/H_2O (0.38 mol L^{-1}) and the mixture was stirred at room temperature for 4-19 hours.

General procedure B for fluorination reactions with 1 (kinetic experiments). The substrate was weighed into an NMR tube, dissolved in 0.7 mL of the pre-made solvent mixture and a sealed capillary containing 5 μL cyclohexane and $CDCl_3$ was added to the tube. This sample was used to tune, match, lock and shim the spectrometer, and to set the receiver gain. SelectFluor was then added and ^{1}H NMR spectra (2 scans per spectrum) were acquired at 120 s intervals until more than 4 half-lives had elapsed.

General procedure C for the synthesis of enol esters. Tetralone (1 equiv.), isopropenyl acetate (2 equiv.) and acid chloride (1.25 equiv.) were combined and heated to 100 °C for 1-2 h in a flask equipped with still head, condenser and a collection flask. The temperature was then increased to 170 °C for 4 – 16 h. The resulting brown residue was cooled to room temperature, suspended in DCM and concentrated onto silica. The silica was then washed (10% ethyl acetate/hexane) and the filtrate was concentrated and chilled, resulting in precipitation of the desired product.

General procedure D for the synthesis of enol esters. Compound **3** (1 equiv.) was suspended in toluene and *p*-toluenesulfonic acid monohydrate (0.1 equiv.) and acid chloride (1.5 equiv.) were added. The reaction was heated to 160 °C for 7 h with a Dean-Stark trap fitted. Upon cooling to room temperature the residue solidified. This was suspended in toluene and filtered. The filtrate was concentrated and the residue was dissolved in DCM. This solution was washed with saturated aqueous sodium bicarbonate solution (to pH 8). The organic phase was collected, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* onto silica. The silica was then washed (10% ethyl acetate/hexane) to yield a filtrate from which the compound precipitated on cooling.

General procedure E for the synthesis of alpha-substituted enol esters. Vinyl bromide (1 equiv.), boronic acid (1.1 equiv.), 1,1-[bis(diphenylphosphino)ferrocene]dichloropalladium(II) (5 mol%), K_3PO_4 (3 equiv.) and water (10 equiv.) were suspended in toluene (0.25 mol L^{-1} in bromide) under a nitrogen atmosphere and heated to 85 °C for 2.5 - 19 h. The mixture was then allowed to cool to room temperature, filtered through silica and the silica was washed with 10% ethyl acetate in hexane. The filtrate was concentrated *in vacuo* and the residue re-suspended in hexane resulting in the precipitation of the desired compound.

General procedure F for the synthesis of alpha-ester ketones. Enol ester (1 equiv.) and *m*-CPBA were dissolved in DCM and heated to reflux for 24 h. The mixture was extracted with 1 mol L^{-1} NaOH solution. The organic phase was collected, concentrated and passed through silica in 10% ethyl acetate/hexane solution. The filtrate was concentrated to yield the desired compound.

Compounds 10 and 11. Note that the fluorination of compounds **8** leads to the formation of mixtures of **10** and **11.** Fluorinated compounds **9a, 9b**, **9d** and **9f** were characterised by their ^{1}H NMR spectra. Side products **11** were characterised by NMR spectroscopy and HRMS. See the Supporting Information for full details.

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Keywords: fluorine • reaction mechanisms • structure-activity relationships • kinetics • hydrolysis

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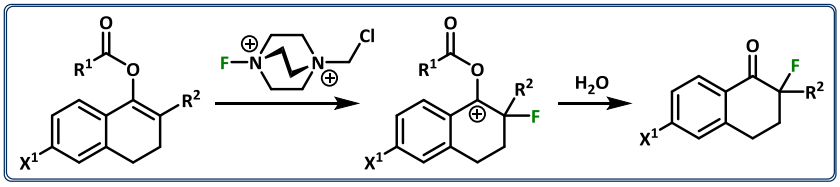

Kinetic studies of the reactions of enol esters with SelectFluor show that these occur *via* a polar two-electron mechanism.

*S. H. Wood, S. Etridge, A. R. Kennedy, J. M. Percy, and D. J. Nelson**

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The Electrophilic Fluorination of Enol Esters using SelectFluor Occurs via a Polar Two-Electron Process