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A Stoichiometric Haloform Coupling for Ester Synthesis

A Stoichiometric Haloform Coupling for Ester Synthesis

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Abstract

Discovered in 1822, the haloform reaction is one of the oldest known synthetic reactions. The history of this methyl ketone-to-carboxylic acid transformation, as well as methodology advances and examples of its application in modern synthetic chemistry are discussed in **Chapter 1**. The extension of the reaction to ester synthesis is also introduced.

There are two significant issues with the classical haloform reaction as a method of ester synthesis: the requirement for solvent-level alcohol, which severely limits the scope of the reaction; and the use of superstoichiometric quantities of hazardous hypohalite oxidants. An electrochemical method proceeding via halide oxidation and requiring only stoichiometric alcohol was proposed to address these issues; efforts toward the realisation of this electrochemical haloform coupling are discussed in **Chapter 2**. Although appreciable ester yields were achieved with just 2 equivalents of alcohol, fundamental issues with the electrochemistry hindered further development of this method. However, building on this work, a promising method for electrochemical synthesis of tetraethylammonium trichloride, a useful reagent for chlorination and alcohol oxidation reactions, was discovered.

The use of readily available and relatively non-hazardous elemental iodine was proposed as an alternative to electrochemical halide oxidation in the development of a haloform method with stoichiometric alcohol. The optimisation and scope of this ‘chemical’ haloform coupling with both primary and, significantly (since they have not been reported in the haloform reaction before), secondary alcohols are discussed in **Chapter 3**. Intriguing reactivity differences between primary and secondary alcohols were observed, and the mechanistic insights obtained through their investigation are also discussed.

A summary of the work is presented in **Chapter 4** and the accompanying experimental details can be found in **Chapter 5**.

Acknowledgements

First and foremost, I have to thank Ali (aka Dr Alastair Lennox) for the opportunity to work on this project and allowing me to run in quite a different direction to most others in his group. I thank him for motivating and challenging me, but most importantly, for encouraging me to approach my work with a positive, optimistic mindset. I hope to have made him at least a little bit proud somewhere along the way.

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It'd be remiss of me not to thank everyone involved in the Cardiff/Bath/Bristol Catalysis CDT, and in particular Helen Whitfield and Michal Perdjon for running the show in the

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Of my mum and dad: this isn't quite the Oscars acceptance speech they might've hoped for, but it might be the closest I ever come, so: thank you, you're the best. Their endless patience for my regular whining on the phone and the normally solid advice that came out of these conversations really did help and I don't know what I would've done without them. Looking further back, I'm also incredibly grateful for the opportunities and support they gave me growing up, that afforded me the enormous privilege to choose to do a PhD in the first place. Thanks also to my brother, Alfie; he's the best brother in the whole wide world.

Finally, of Lydia: I know that whatever I write, it won't be good enough, so suffice it to say that I think she's really great and I love her a lot. But seriously, her belief in me throughout has really made a big difference, far more than I would've acknowledged at the times it was needed, so thank you. I'm sure she's nearly as relieved as I am that this is finally all over and she can have her happy, care-free boyfriend back (even if it's only part time to begin with).

And finally finally, I'd like to thank Huel, Nairn's and Too Good To Go for ensuring I didn't starve to death over the past 4 years.

"Be excellent to each other and party on dudes."

Author’s Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

Signed: Albert Rowett Date: 30th October 2023

Table of Contents

Abbreviations

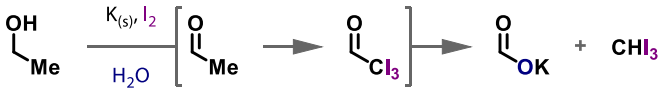
API	Active pharmaceutical ingredient
Ar	Aryl
Bn	Benzyl
Boc	tert-Butoxycarbonyl
BOM	Benzyloxymethyl ether
BTMA	Benzyltrimethylammonium
Cbz	Carbobenzyloxy
CFL	Compact fluorescent lamp
Conc	Concentration
CV	Cyclic voltammetry/voltammogram
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCDMH	1,3-Dichloro-5,5-dimethylhydantoin
DMP	Dess-Martin periodinane
Fc	Ferrocene
FCC	Flash column chromatography
IS	Internal standard
Lut	2,6-Lutidine
Lut.H	2,6-Lutidinium
MB	Mass balance
Mol frac	Mole fraction
MTBA	Methyltributylammonium
PE	Petroleum ether
Pyr	Pyridine
Pyr.H	Pyridinium
Quint	Quintet
RBF	Round-bottom flask
RLS	Rate-limiting step
Sept	Septet
rt	Room temperature
TBA	Tetrabutylammonium
TBHP	tert-Butyl hydroperoxide
TEA	Tetraethylammonium
Temp	Temperature
TLC	Thin layer chromatography
TMPA	Trimethylphenylammonium
TMS	Tetramethylsilane

Common abbreviations are used without definition.

Chapter 1: Introduction

1.1 History and Mechanism of the Haloform Reaction

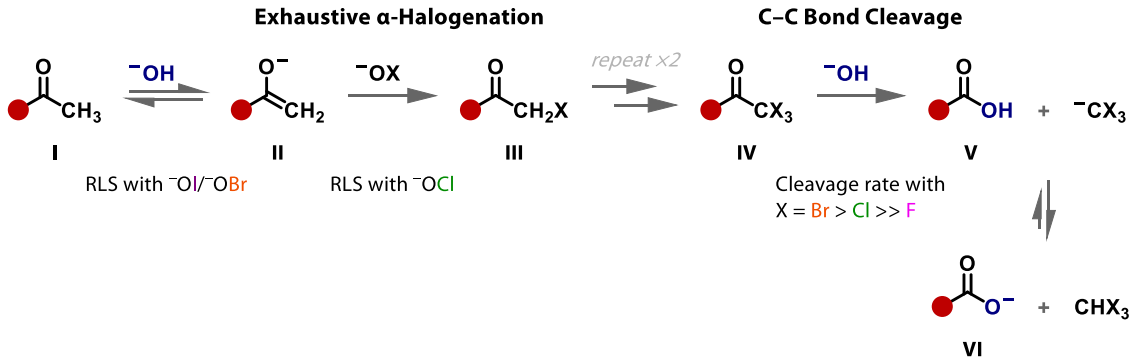
In 1822, Georges-Simon Serullas, a French chemist and pharmacist, discovered that addition of potassium to a solution of iodine in aqueous ethanol led to the formation of a yellow precipitate, which he called a *"hydroiodide of carbon"*.[1] This precipitate was actually iodoform (triiodomethane) and Serullas had, serendipitously, just discovered the haloform reaction (Scheme 1.1). Two other haloforms (so named because they produce formic acid on hydrolysis), chloroform and bromoform, were subsequently discovered by similar means in 1831 and 1834, respectively.[2–6]



Scheme 1.1. Serullas' serendipitous discovery of the haloform reaction.

According to Fuson and Bull's seminal 1934 review on the subject,[7] most of the early research on the haloform reaction was focussed on the discovery of compounds which could be subjected to the reaction, with Lieben formulating a general rule in 1870: *"a positive iodoform test [iodoform production observed on addition of hypoiodite solution] is given by compounds containing the aceto (CH_3CO–) group joined to either carbon or hydrogen, and by compounds which are oxidised under the conditions of the test to derivatives containing this structural unit"*.[8] This rule can be rationalised by considering the mechanism of the haloform reaction.

The mechanism involves two distinct phases: exhaustive α-halogenation and a nucleophilic substitution that results in C–C bond cleavage (Scheme 1.2).[7,9,10] Base-catalysed enolisation of methyl ketone **I** to enolate **II**, followed by halogenation by a hypohalite (typically formed *in situ* from a halogen and hydroxide) yields halomethyl ketone **III**. Since **III** is more acidic than **I**, these steps then repeat until the maximally halogenated trihalomethyl ketone **IV** is formed. Due to the electron-withdrawing nature of the halogen atoms, the trihalomethyl anion is well-stabilised, such that hydroxyl attack on **IV** leads to cleavage of the C–CX_3 bond. Carboxylic acid **V** is deprotonated by the trihalomethyl anion, yielding carboxylate **VI** and the haloform species, although isolation of **V** is, of course, possible after acidic work-up.

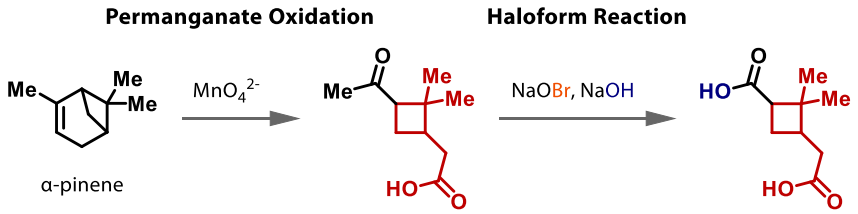


Scheme 1.2. Mechanism of the haloform reaction. RLS = Rate-limiting step.

Based on experiments carried out with acetone (the simplest methyl ketone), the initial enolisation to form enolate **II** is believed to be the rate-limiting step with hypobromite or hypoiodite.[11,12] With hypochlorite, however, the reaction is orders of magnitude slower, due to rate-limiting chlorination of enolate **II** to **III**.[11] The kinetics of the cleavage step of the reaction have also been investigated, with the relative cleavage rates of trihaloacetophenones ($PhCOCX_3$) found to follow the order: X = F (1.0) < Cl (5.3×10^{10}) < Br (2.2×10^{13}).[13] Measurement of the cleavage rate of the analogous triiodoacetophenone was not possible, since triiodomethyl ketone species have never been successfully isolated, although it may be similar to that of the tribromoacetophenone, based on the reported similarity in the acidities of bromoform and iodoform.[14,15]

Lieben's original rule for the 'iodoform test' was subsequently updated by Fuson and Tullock to account for the production of iodoform in reactions from partially-iodinated reaction intermediates, as well as to incorporate empirical evidence of the reaction's limitations: *"the test is positive for compounds which contain the grouping [sic] CH_3CO–, CH_2ICO–, or CHI_2CO– when joined to a hydrogen atom or to a carbon atom which does not carry highly activated hydrogen atoms or groups which provide an excessive amount of steric hinderance. The test will, of course, be positive also for any compound which reacts with the reagent to give a derivative containing one of the requisite groupings. Conversely, compounds which contain one of the requisite groupings will give a negative test in case this grouping is destroyed by the hydrolytic action of the reagent before iodination is complete"*.[16]

Before the introduction of modern spectroscopic techniques, the haloform reaction was a valuable tool for structural determination, owing to its high selectivity for methyl ketone oxidation. This was particularly useful in the field of terpene chemistry;[7] for example: the position of the double bond in α-pinene was established, in part, thanks to haloform degradation (Scheme 1.3).[17,18]



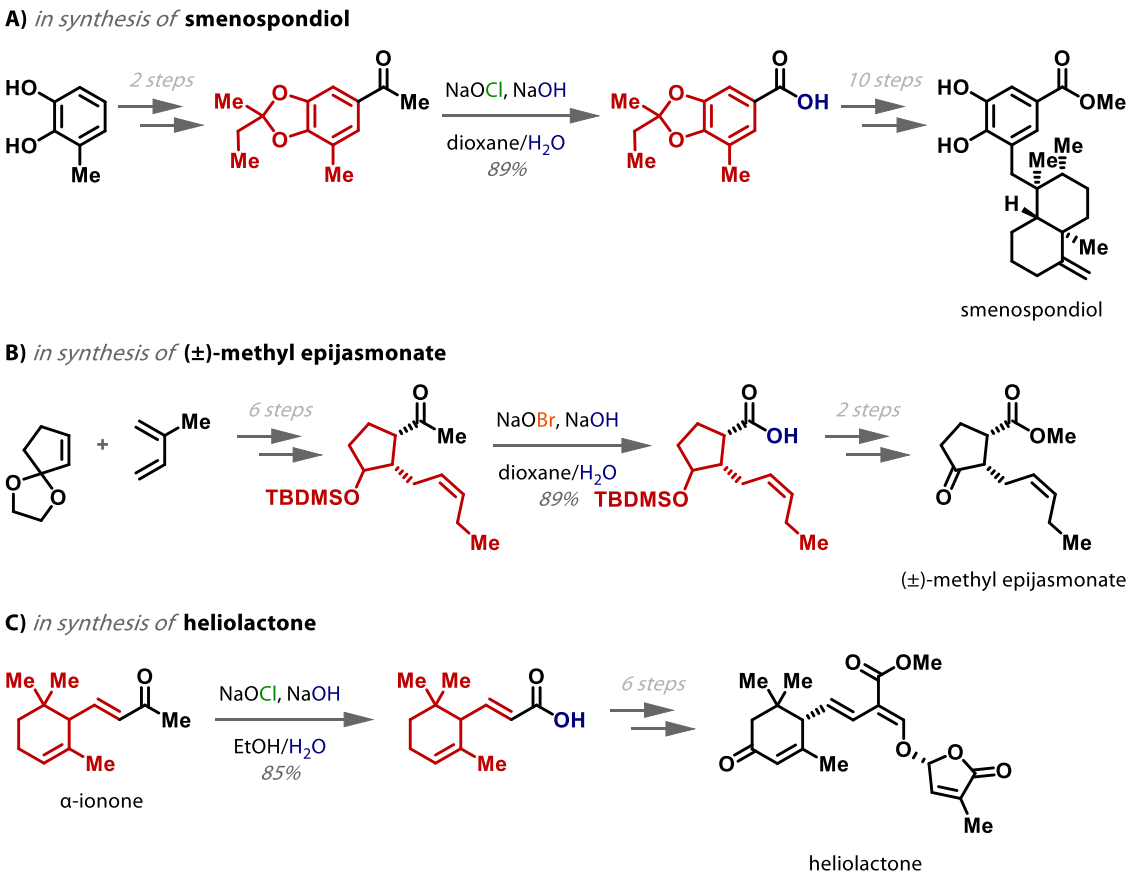
Scheme 1.3. Haloform degradation contributed to the structural determination of α-pinene, among other terpenes.

The iodoform reaction was also used for quantitation of susceptible compounds, since iodoform is a relatively easily-isolable, yellow solid.[19] Such was the power of this gravimetric method, that, as early as 1870, alcohol could be detected in aqueous solutions at concentrations as low as 500 ppm.[8] Volumetric methods based on titrations of iodine with thiosulfate were also developed around this time.[20]

1.2 The Haloform Reaction in Modern Synthetic Chemistry

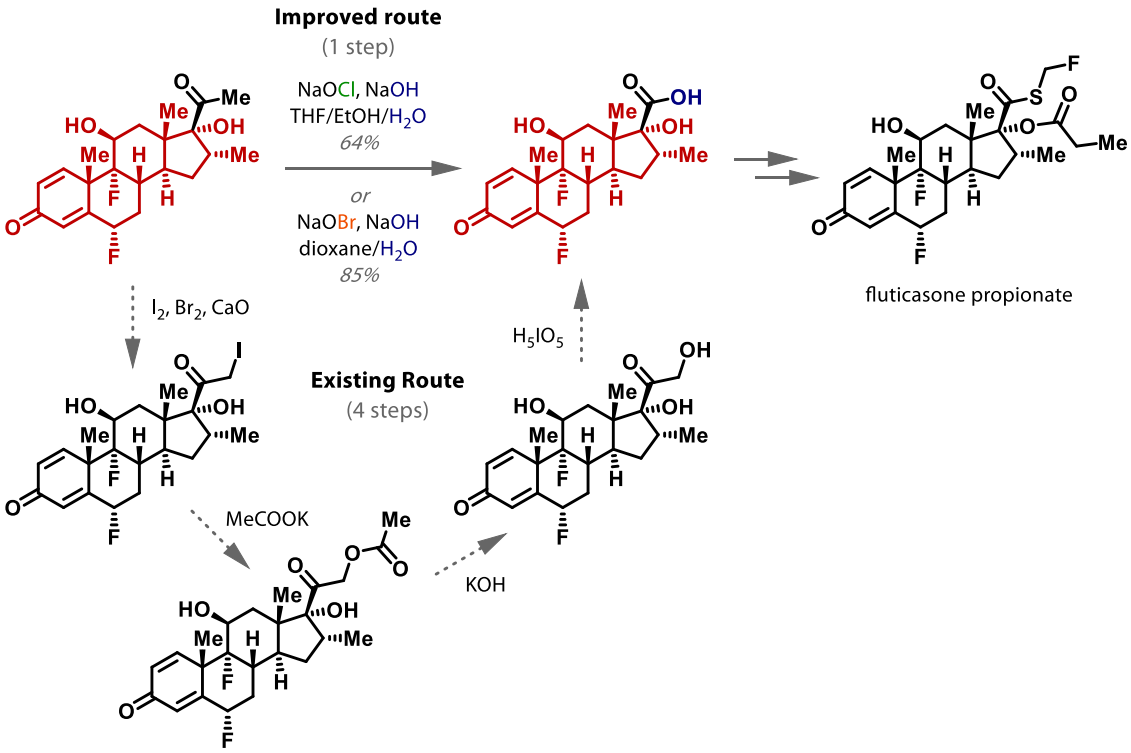
While the haloform reaction was used for the production of haloforms themselves in the decades following their discovery, this is no longer prevalent, whereas its application to the synthesis of carboxylic acids, which did not start in earnest until the turn of the 20th Century,[7] has continued up to the present day. This is particularly true in the field of total synthesis, where the haloform reaction is regularly called upon as a reliable method for the installation of carboxylic acids.[21–32]

The syntheses shown below exemplify the range of aromatic (Scheme 1.4A),[23] aliphatic (B)[29] and α,β-unsaturated methyl ketones (C)[24] that can be subjected to the reaction. Furthermore, the haloform reaction can been employed at both early (A and C) and late (B) stages in a synthesis, demonstrating its utility. All the natural product syntheses used either hypochlorite or hypobromite oxidants, with the use of hypoiodite less common in synthetic haloform reactions generally. As a point of interest: the first step in the synthesis of heliolactone (Scheme 1.4C) was a haloform reaction on the terpene α-ionone, whose structure was elucidated using the haloform reaction over 100 years earlier.[33]



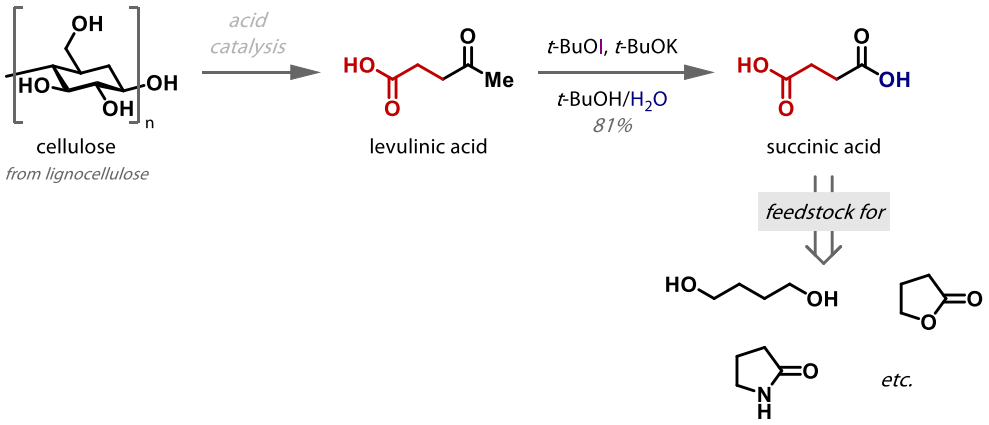
Scheme 1.4. Examples of the haloform reaction in total synthesis.

The haloform reaction has been proposed as a means of improving the synthesis of the anti-inflammatory drug, fluticasone propionate. Su and co-workers envisaged that the existing 4-step conversion of a methyl ketone intermediate to a carboxylic acid in the route to the active pharmaceutical ingredient (API) could be accomplished in a single step (Scheme 1.5).[34] They showed that the transformation could be achieved with sodium hypochlorite or hypobromite, giving yields of 64% and 85% on 50 g- and 100 g-scales, respectively. This shorter route should enable significant cost savings and an improvement in the total yield of API. Since the reaction was demonstrated on a hectogram (100 g) scale and requires only cheap, readily-available reagents, further scale-up and therefore commercialisation may be viable.



Scheme 1.5. Proposed improvement to the synthetic route to fluticasone propionate.

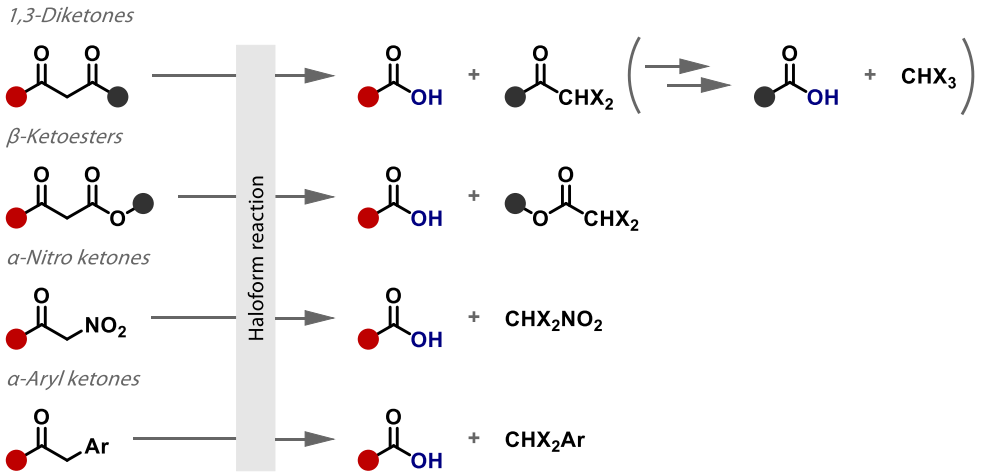
The haloform reaction has also shown promise in the production of commodity chemicals via biomass valorisation. Uchiyama and co-workers recently demonstrated that succinic acid, a major four-carbon chemical feedstock, can be obtained via a haloform reaction with levulinic acid, which can be produced in a single step from lignocellulose (Scheme 1.6).[35] Other methods for the conversion of levulinic acid to succinic acid have considerable drawbacks and, indeed, Uchiyama found that a 'classical' iodoform reaction (i.e. with hypoiodite) suffered from significant side-reactions, resulting in poor yields. Their solution was a novel haloform method in which *tert*-butyl hypoiodite (*t*-BuOI), formed *in situ* from iodine and potassium *tert*-butoxide, was the oxidant, enabling selective synthesis of succinic acid in high yield at room temperature. Chromatography-free, gram-scale synthesis was demonstrated, as was a one-pot synthesis from cellulose, suggesting there may be potential for the development of a sustainable, low-cost process for the valorisation of non-edible lignocellulosic biomass.



Scheme 1.6. Production of the commodity chemical succinic acid from lignocellulosic biomass.

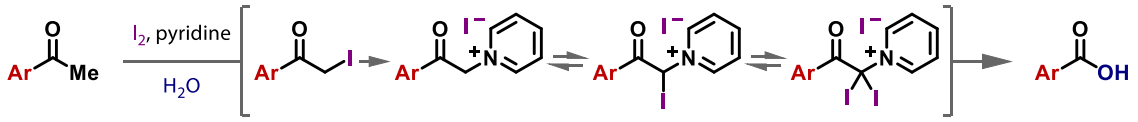
1.3 Methodology Developments in Haloform Chemistry

It has been known for well over a century that alkyl, aryl and alkenyl methyl ketones are viable substrates in the haloform reaction and the reaction conditions typically employed (i.e. an alkaline aqueous mixture of hypohalite) have changed remarkably little since the earliest reports, as demonstrated by more recent examples from total synthesis (Scheme 1.4). Early research also identified several other substrate classes which appeared to react in the same way, most notably 1,3-diketones[36–39] and β-ketoesters,[40] but also α-nitro[41] and α-aryl methyl ketones[42] (Scheme 1.7). These reactions, however, violated the original definition that *"the haloform reaction comprises those processes whereby the haloforms are derived from organic compounds by the action of hypohalites"*,[7] since haloforms are not produced (except in the case of 1,3-diketones, where further reaction of the dihalomethyl ketone produced does eventually yield a haloform). Clearly though, these examples are fundamentally the same transformation. In each case, one of the halogen atoms that would be installed by the hypohalite has instead been replaced by an alternative, pre-installed electron-withdrawing group, resulting in the formation of $–CX_2Y$ leaving groups (where X is a halogen atom and Y is the alternative electron-withdrawing group). A potentially improved definition of the haloform reaction, that encapsulates these examples, as well as those that followed, would therefore be: a reaction in which initial mono- or polyhalogenation of a methyl, methylene or methine unit leads to formation of a leaving group, which is then cleaved to generate new functionality.



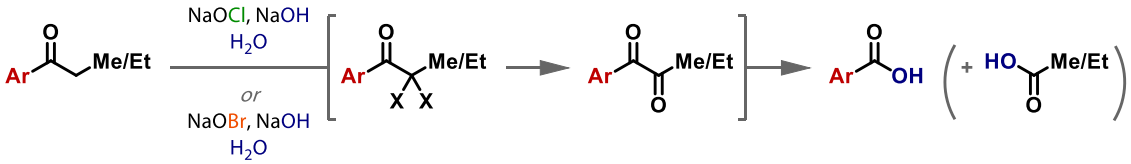
Scheme 1.7. Non-methyl ketone substrate classes susceptible to the haloform reaction. Ar = Aryl.

Such an expanded definition of the haloform reaction would include King and Pearson's (separate) reports that a methyl ketone to carboxylic acid transformation can be achieved with iodine and pyridine (or other, similar nitrogen bases[43]) through formation of pyridinium-containing intermediates (Scheme 1.8).[44–46] The *N*,*N'*-methylenedipyridinium iodide by-product formed (not shown) bears little resemblance to a haloform, but this reaction is mechanistically very similar to the classical haloform reaction.



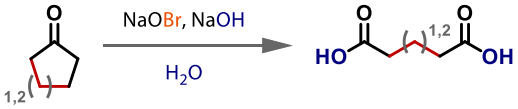
Scheme 1.8. Non-classical haloform reaction with iodine and pyridine.

In 1949, the first definitive synthesis and isolation of carboxylic acids from a haloform reaction with higher alkyl (i.e. non-methyl) ketones was reported by Farrar and Levine,[47] although earlier reports of similar reactions appear to have overlooked the significance.[48,49] A handful of arylalkyl and heteroarylalkyl ketones were converted to their corresponding carboxylic acids (e.g. propiophenone to benzoic acid) in good yields by treatment with alkaline hypochlorite[47] or, subsequently, hypobromite[50] (Scheme 1.9). The reaction mechanism proposed involves halogenation to an α,α-dihalo species, which is converted to a 1,2-diketone, followed by cleavage to two carboxylic acids.[50] Since cleavage consumes another equivalent of hypohalite and cannot be achieved with hydroxide alone, formation of an acyl halide intermediate may be involved.



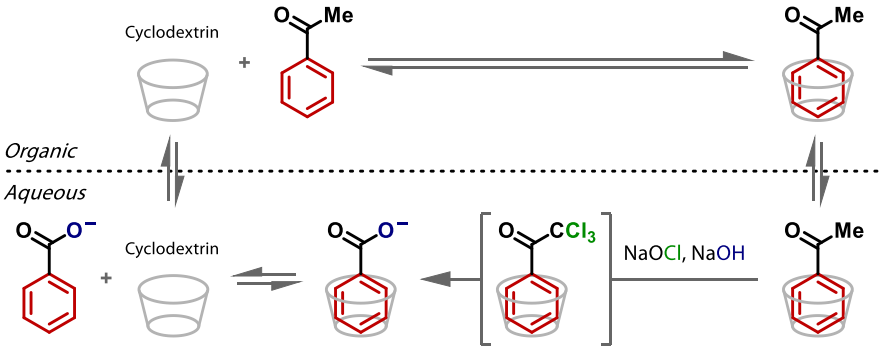
Scheme 1.9. Haloform reaction of higher alkyl (i.e. non-methyl) ketones.

An extension of this method to cycloalkanones followed in 1957, when Farrar reported the synthesis of diacids from cyclohexanone and cyclopentanone with alkaline sodium hypobromite (Scheme 1.10).[51] The analogous reaction with hypochlorite has subsequently also been reported, in which tetraalkylammonium halide species were employed as phase-transfer catalysts.[52]



Scheme 1.10. Haloform reaction of cycloalkanones.

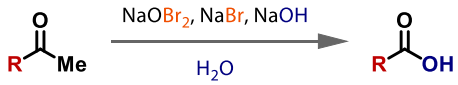
The classical haloform reaction involves aqueous solvent, but methyl ketones are often poorly soluble in water and the halogenated intermediates produced during the reaction are even more hydrophobic. In 2000, Trotta and co-workers reported on their attempts to address this issue using cyclodextrins as inverse phase-transfer catalysts.[53] The apolar cyclodextrin cavity helps to solubilise the lipophilic reaction species in the aqueous phase containing the hypohalite, where the haloform reaction therefore occurs (Scheme 1.11). This enabled modest increases (up to threefold) in the reaction rate of acetophenone with sodium hypochlorite, although a more pronounced catalytic effect was observed with 2-acetonaphthone, due to its lower water solubility (in the absence of cyclodextrin).



Scheme 1.11. Haloform reaction under inverse phase-transfer catalysis conditions with cyclodextrins.

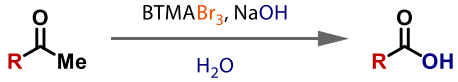
Alternatives to the classical hypohalite preparations have also been reported. In 1985, Kajigaeshi and co-workers demonstrated that a mixture of sodium bromite ($NaOBr_2$) and sodium bromide in aqueous sodium hydroxide could effect haloform reactions with a range of aryl, alkyl and alkenyl methyl ketones, generally achieving good yields

(Scheme 1.12).[54] Although *in situ*-formed hypobromite was believed to be the active species, as a stable, crystalline solid, sodium bromite was proposed to be a practical alternative to molecular halogens for preparing such solutions. With elevated temperatures and extended reaction times, secondary alcohols which could be oxidised to methyl ketones could also be converted to carboxylic acids.



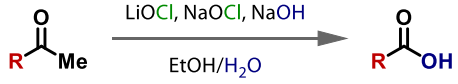
Scheme 1.12. Haloform reaction with sodium bromite (*in situ* hypobromite formation suspected).

Kajigaeshi and co-workers reported similar reactivity with benzyltrimethylammonium tribromide ($BTMABr_3$) as a drop-in replacement for bromine in bromoform reactions in aqueous sodium hydroxide (Scheme 1.13).[55,56] $BTMABr_3$ is a relatively non-hazardous, commercially-available solid and is therefore an attractive alternative to using elemental bromine.



Scheme 1.13. Haloform reaction with $BTMABr_3$ as a substitute for bromine.

Similarly, Berlin and co-workers demonstrated that a combination of lithium hypochlorite (cheaply available as a pool oxidant/cleaner) and sodium hypochlorite bleach could be used to effect haloform reactions (Scheme 1.14).[57] The lithium cation was hypothesised to coordinate better (than the sodium cation) to the oxygen atom of the carbonyl group, leading to more acidic α-protons and thus increased reactivity compared to using a sodium hypochlorite solution alone. Carboxylic acid synthesis was reported with a range of aryl, alkyl and alkenyl methyl ketones, as well as secondary alcohols (via oxidation to methyl ketones) and propiophenone.

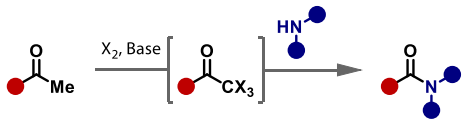


Scheme 1.14. Haloform reaction with a combination of lithium hypochlorite and sodium hypochlorite.

1.4 Alternative Nucleophiles in the Haloform Reaction

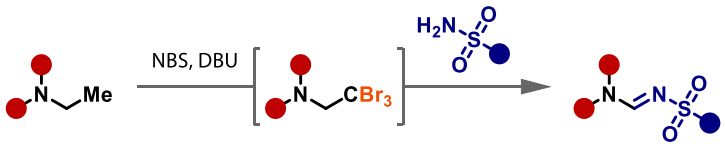
In addition to carboxylic acids, several other product classes can be accessed using variants of the haloform reaction. Building on early reports on the cleavage of trihalomethyl ketones by ammonia[58–60] and benzamide formation by treatment of acetophenone with nitrogen triiodide,[61] amide synthesis is the most developed of these.[62–73] These methods proceed via the classical haloform mechanism: generation of a trihalomethyl ketone intermediate, followed by C–C bond cleavage, induced by attack

of a nitrogen nucleophile (Scheme 1.15). Ammonia has most commonly been employed, yielding primary amides,[62,63,66–69] although several methods for the synthesis of secondary or tertiary amides from the corresponding amines have also been reported.[70–73]



Scheme 1.15. Synthesis of amides via haloform methodology.

A haloform reaction with non-ketone substrates has also been reported: tertiary amines can be oxidised via β-tribromination to amidines (Scheme 1.16).



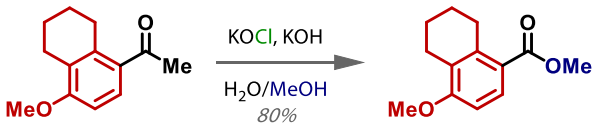
Scheme 1.16. Synthesis of amidines via a bromoform reaction with tertiary amines.

Haloform-like mechanisms have also been invoked in the synthesis of acyl chlorides and for aminations of an isoxazole bearing vinylogous nitro and methyl groups.[74,75]

1.4.1 Ester Synthesis via the Haloform Reaction

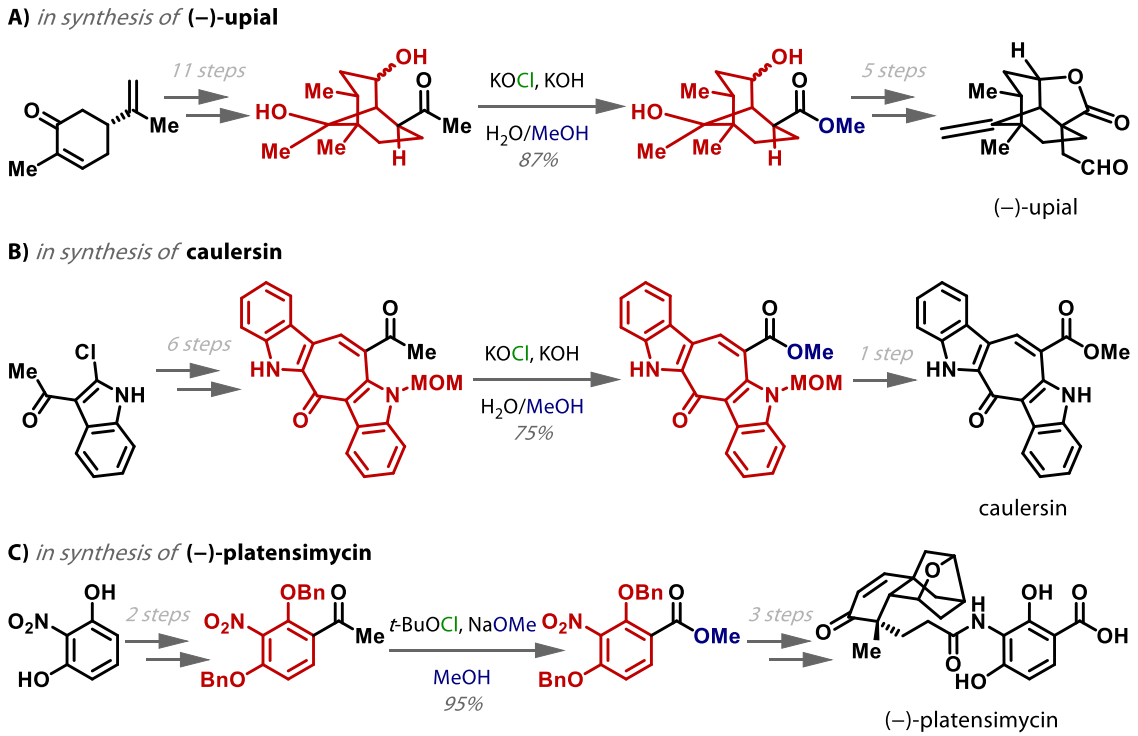
Notably, esters can also be accessed via the haloform reaction. Ester moieties are prevalent in pharmaceuticals and natural products,[76,77] and low-molecular weight esters are used extensively in the flavouring and fragrance industry, due to the strong tastes and smells they can impart.[78] While many methods of ester synthesis exist,[79] most commonly from carboxylic acids (e.g. Fischer[80] and Steglich[81] esterifications), their preparation from ketones is relatively rare.

Although the decomposition of trichloromethyl ketones to esters with sodium alkoxides had been known since 1931,[82] the discovery that esters could be synthesised by a haloform reaction with methyl ketones, if alcohol was employed as a co-solvent, was not made until 1944 (Scheme 1.17).[83] The authors proposed that ester products had not previously been reported due to their facile hydrolysis under the basic reaction conditions, a process which was only avoided in this case by the spontaneous precipitation of the ester.



Scheme 1.17. Discovery that esters can be synthesised via the haloform reaction with alcohol (co-)solvents.

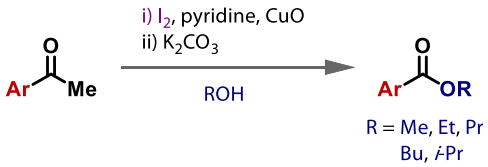
Since then, direct access to esters via the haloform reaction has seen very limited use. Methyl esters were prepared following the original reaction conditions in the syntheses of the natural products (−)-upial (Scheme 1.18A) and caulersin (B).[84,85] In another example from total synthesis, one of the fragments of (−)-platensimycin was prepared under modified reaction conditions (Scheme 1.18C).[86] Using a mixture of *tert*-butyl hypochlorite and sodium methoxide in methanol, high conversion to the methyl ester could be achieved in under a minute. A further report on *"the development and scope of this rapid oxidative esterification of aryl methyl ketones to aryl esters"*, which *"will be published in due course"* is, 9 years on, yet to materialise.



Scheme 1.18. Total synthesis examples of the haloform reaction used to prepare esters.

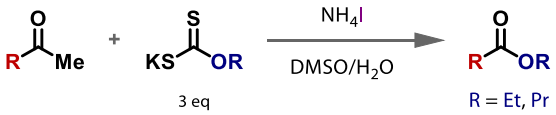
As a result of the limited examples under classical haloform conditions, alternative ester synthesis methods have recently been developed. In 2008, Wu and co-workers reported that esters could be synthesised from acetophenones via a haloform-like reaction with iodine, pyridine and copper(II) oxide in alcohol solvent (Scheme 1.19).[87] The reaction appears to be mechanistically similar to those reported by King and Pearson (see Scheme 1.8 and accompanying text),[45,46] where initial α-iodination is followed by substitution to give a pyridinium-containing intermediate. The method's scope extended

beyond methanol to include several other simple alcohols: ethanol, and, somewhat less successfully (due to steric hinderance), *n*-propanol, *n*-butanol and isopropyl alcohol (*tert*-butanol was also tested, but *tert*-butyl ester formation was not observed). Esters could also be prepared from β-keto esters, 1,3-diketones (i.e. substrates with an electron-withdrawing group pre-installed in the α-position, *cf.* Scheme 1.7 and accompanying text) and propiophenone, albeit with a reduced yield in the latter instance.



Scheme 1.19. Synthesis of simple alkyl esters via haloform reaction with iodine and pyridine.

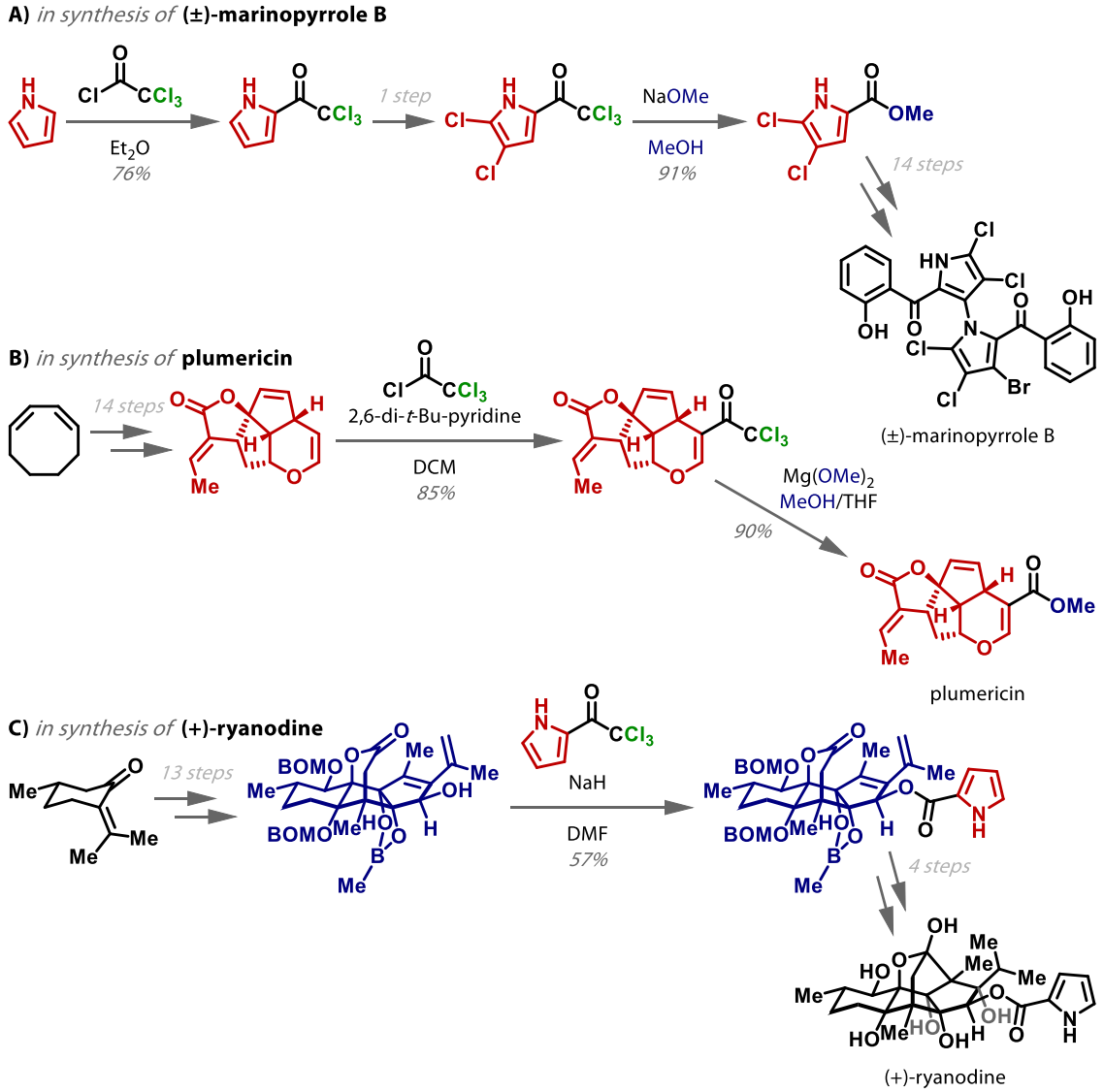
In 2020, Huang and Li reported a method that dispensed with the need for alcohol solvent, instead using potassium xanthates (prepared from alcohols and carbon disulfide) as the alkoxy source (Scheme 1.20).[88] Although mechanistically unproven, a radical mechanism was proposed, which invoked a classical triiodomethyl ketone intermediate en route to the ester. This enabled the synthesis of esters from a range of (predominantly) acetophenones with ammonium iodide in a solvent mixture of DMSO and water. Ethyl and propyl esters were synthesised, although, in principle the method could be extended by preparing xanthates with other alcohols.



Scheme 1.20. Synthesis of ethyl and propyl esters via haloform reaction with xanthates.

A closely-related and more-frequently used alternative to the haloform reaction for the installation of ester moieties is two-step trihalomethyl ketone installation and degradation, first reported in 1931.[82] Typically, this has involved installation of a trichloromethyl ketone, followed by C–C bond cleavage with methoxide, yielding a methyl ester (Scheme 1.21A[89] and B[90]), however, this method has also been used for the coupling of much larger alcohol fragments (Scheme 1.21C[91]).[92–95] Similar approaches have been employed for the preparation of amides[96–103] and carboxylic acids.[104,105] The relative popularity of this method likely stems from the ease of installation of the trichloromethyl ketone group (Scheme 1.21A and B) and commercial availability of trichloroacetyl-containing precursors (Scheme 1.21C). Trichloromethyl ketones are sufficiently stable to be isolated and they can even be carried through other synthetic steps prior to their cleavage (Scheme 1.21A and see reference 105). The obvious disadvantages compared to the classical haloform reaction derive from the

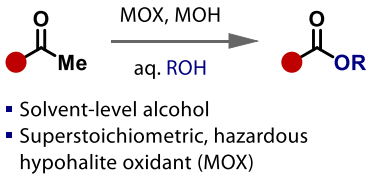
additional step involved in formation of the trihalomethyl ketone species, i.e. reduced overall efficiency, increased reagent and solvent waste, etc.



Scheme 1.21. Examples of two-step trihalomethyl ketone installation and degradation from total synthesis. BOM = Benzyloxymethyl ether.

1.5 Project Background

There are two main issues with the classical haloform reaction as a method for ester synthesis: 1) the requirement for solvent-level alcohol, which severely limits the scope of esters that can be accessed in an economically-viable manner; and 2) the use of superstoichiometric quantities of relatively hazardous hypohalite oxidants (Scheme 1.22).

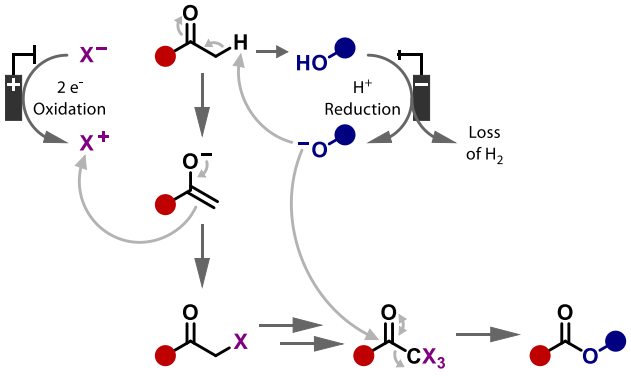


Scheme 1.22. Issues with classical haloform reaction for ester synthesis.

Recent attempts to address these issues have been made, namely by Wu,[87] and Huang and Li (see Scheme 1.19, Scheme 1.20 and associated text).[88] However, these methods are limited to simple, unfunctionalised primary alcohols (with the single exception of isopropyl alcohol) and either still rely on the use of solvent-level alcohol (Wu) or require preformation (and isolation) of a xanthate coupling partner (Huang and Li).

In theory, only 1 equivalent of the nucleophilic reagent is required to cleave each molecule of trihalomethyl ketone formed during the haloform reaction, meaning it should not be necessary to carry out such reactions with solvent-level alcohol. If the amount of alcohol used could be reduced to a stoichiometric level, this would enable the use of more structurally-complex alcohols (i.e. not just simple, unfunctionalised aliphatic alcohols), enabling the installation of a diverse range of ester groups previously inaccessible using the haloform reaction.

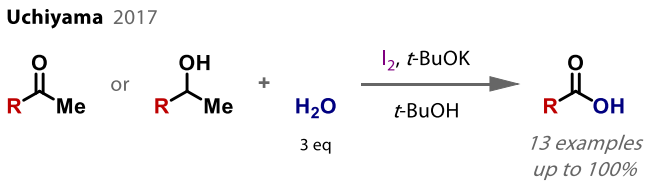
Regarding the use of large excesses of hazardous hypohalite oxidants, electrochemistry can provide an alternative. Halonium ions (X^+), generated by anodic oxidation of inexpensive and comparatively benign halide salts,[106,107] can be employed to halogenate methyl ketones, producing the key trihalomethyl ketone intermediate (Scheme 1.23). Electrodes therefore replace the chemical oxidants otherwise required, demonstrating one of the green chemistry benefits electrochemistry can offer.[108]



Scheme 1.23. Idealised mechanism for electrochemical haloform synthesis of esters.

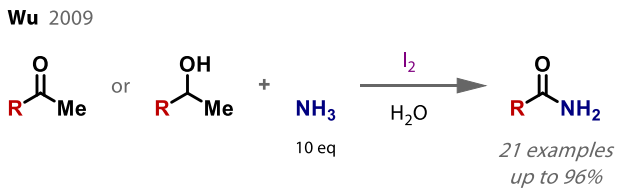
1.5.1 Stoichiometric Nucleophile Haloform Reaction Variants

Although the classical haloform conditions are reliant on solvent-level alcohol (or water, in the case of carboxylic acid synthesis), a handful of methods employing stoichiometric quantities of the nucleophile have been developed. One such example is that reported by Uchiyama and co-workers, in 2017, for the preparation of carboxylic acids with 3 equivalents of water,[35] although in this case, limiting the amount of water used was not actually the aim of the work. Rather, the authors were concerned with the synthesis of succinic acid (see Scheme 1.6 and accompanying text) and found that classical haloform conditions suffered from side-reactions, resulting in poor yields. Employing an alternative system of iodine and potassium *tert*-butoxide in *tert*-butanol, they were able to synthesise a range of aliphatic and aromatic acids in generally good yields from their corresponding methyl ketones or secondary alcohols (via oxidation to methyl ketones; Scheme 1.24).



Scheme 1.24. Haloform reaction with stoichiometric water.

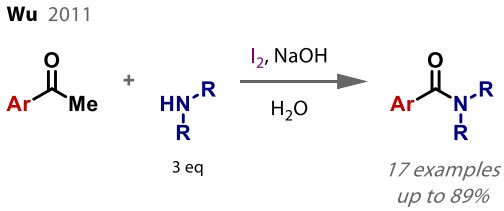
More methods exist for the haloform synthesis of amides using stoichiometric amine. The first of these came from Wu and co-workers in 2009, who reported the synthesis of aryl, heteroaryl and alkenyl (α,β-unsaturated) primary amides, employing aqueous ammonia as the nitrogen source (Scheme 1.25).[62] Since 10 equivalents of ammonia were used, no additional base was required. The method was also successfully applied to a handful of 1-arylethanols, demonstrating that, like in the classical haloform reaction, alcohol oxidation to methyl ketones, prior to the halogenation and cleavage sequence, was possible under the reaction conditions.



Scheme 1.25. Primary amide synthesis via haloform reaction with stoichiometric aqueous ammonia.

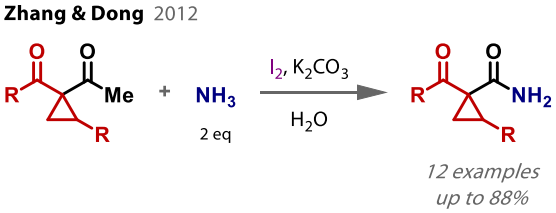
In 2011, the authors extended this methodology to access secondary and tertiary amides (Scheme 1.26).[70] Using iodine and sodium hydroxide in water (presumably resulting in *in situ* hypoiodite formation), aryl and heteroaryl methyl ketones could be coupled with primary and secondary amines, indicating that selective amide synthesis is possible

even under essentially classical haloform conditions. Based on the range of, albeit relatively simple, aliphatic amines that were coupled using this method, this is the most important example of a stoichiometric nucleophile haloform reaction variant reported to date.



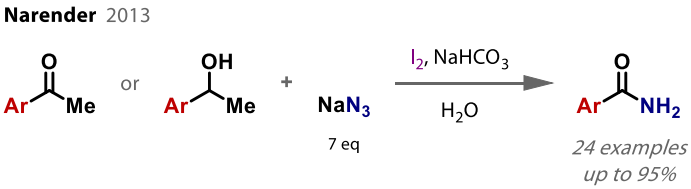
Scheme 1.26. Secondary and tertiary amide synthesis via haloform reaction with stoichiometric amines.

An alternative method for the preparation of primary amides, under similar conditions to those previously employed by Wu, was reported by Zhang, Dong and co-workers in 2012.[66] Addition of potassium carbonate to the reaction enabled the amount of aqueous ammonia needed to be reduced to 2 equivalents, with the efficacy of these conditions demonstrated by the conversion of a series of acetylcyclopropanes to cyclopropyl amides (Scheme 1.27).



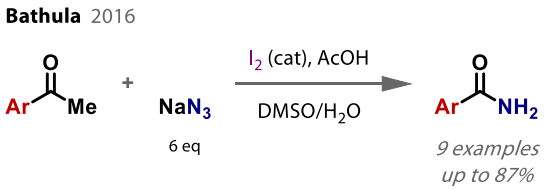
Scheme 1.27. Primary amide synthesis via haloform reaction with stoichiometric aqueous ammonia and additional base.

Narender and co-workers reported in 2013 that sodium azide could be used as an alternative nitrogen source in the synthesis of primary amides (Scheme 1.28).[64] Their reaction system was otherwise unremarkable: a mixture of iodine and sodium bicarbonate in water.



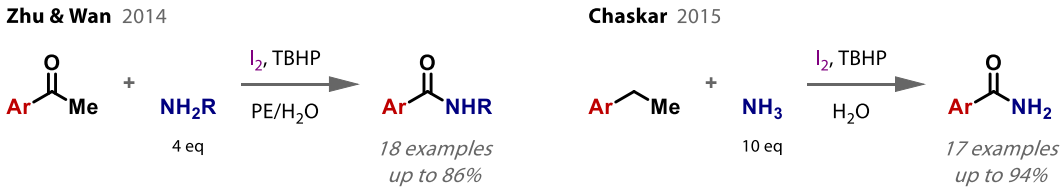
Scheme 1.28. Primary amide synthesis via haloform reaction with stoichiometric azide as nitrogen source.

In 2016, Bathula and co-workers reported an alternative method employing stoichiometric sodium azide (Scheme 1.29).[65] The standout feature of this method is the use of catalytic iodine (just 30 mol% vs ketone), which the authors proposed was regenerated by iodide oxidation with DMSO.



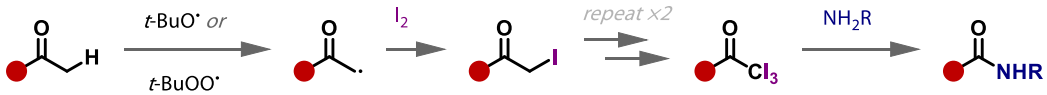
Scheme 1.29. Primary amide synthesis via haloform reaction with catalytic iodine, and stoichiometric azide as the nitrogen source.

Two other, closely-related methods for the synthesis of primary[67] and secondary[72] amides with sub-stoichiometric iodine have also been reported, by Chaskar and co-workers, and Zhu, Wan and co-workers, respectively (Scheme 1.30).



Scheme 1.30. Primary and secondary amide synthesis via haloform reaction with sub-stoichiometric iodine and TBHP. PE = Petroleum ether.

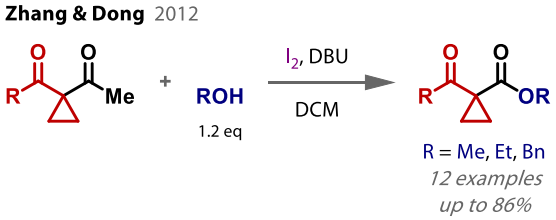
While Chaskar's method utilised ethylarenes,[67] both reactions were proposed to proceed via triiodomethyl ketone intermediates, with Zhu and Wan having confirmed the presence of iodoform as a by-product in their reaction mixtures.[72] Zhu and Wan also suggested that iodination may proceed via a radical pathway (although only circumstantial evidence was provided), with *tert*-butyl hydroperoxide (TBHP) generating a methylene radical, which could then abstract an iodine atom to form an iodomethyl ketone intermediate (Scheme 1.31). Repetition of this process would generate the triiodomethyl ketone, which could be cleaved in the normal manner to yield the amide. Although not discussed in either example, regeneration of iodine (presumably with TBHP) is necessary, as both reactions required just 1.1 equivalents. Without such regeneration, yields would have been restricted to levels lower than those achieved.



Scheme 1.31. Proposed radical pathway for haloform reaction with sub-stoichiometric iodine and TBHP.

Only one example of a haloform reaction with stoichiometric alcohol has been reported to date. This came from Zhang, Dong and co-workers in 2012, who, alongside their amide synthesis method (see Scheme 1.27 and accompanying text), described the conversion of a small group of acetylcyclopropanes to their corresponding cyclopropyl esters with just 1.2 equivalents of alcohol in DCM (Scheme 1.32).[66] Molecular iodine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) replaced the hypohalite of the classical

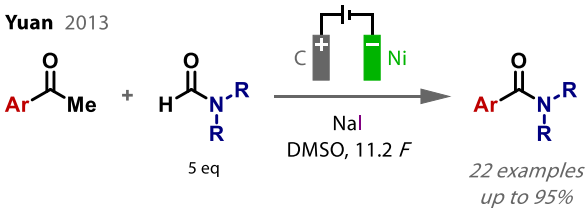
haloform reaction and ester yields were good. This method appears, therefore, to address the issues identified with the classical reaction for ester synthesis, however, the reaction's scope was very limited. Significantly, esters were prepared using just three simple, primary alcohols (methanol, ethanol and benzyl alcohol), each of which could be employed on a solvent-scale under the classical conditions if required. Furthermore, since the authors' interests lay in accessing substituted cyclopropane building blocks, only cyclopropanoate esters bearing β-amido or -keto groups were synthesised. It is therefore unknown whether this method would be compatible with other, less specific methyl ketone substrates.



Scheme 1.32. Haloform reaction with stoichiometric alcohols. Bn = Benzyl.

1.5.2 Electrochemical Haloform Reaction Variants

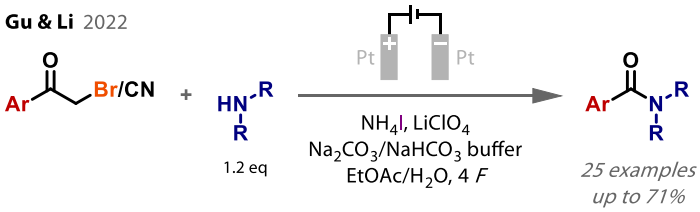
Electrochemical approaches to the haloform reaction have also attracted recent attention, with Yuan and co-workers reporting a methyl ketone-formamide coupling reaction to access secondary or tertiary amides in 2013 (Scheme 1.33).[71] This was an example of a paired electrolysis, since iodide oxidation at a graphite anode is matched by formamide reduction to amine (decarbonylation) at a nickel cathode. Amide formation ensues when the amine attacks the triiodomethyl ketone intermediate generated, since both processes occur in the same solution (in an undivided cell). The relatively low Faradaic efficiency (6 *F* theoretical requirement) was attributed to unproductive DMSO solvent oxidation.



Scheme 1.33. Amide synthesis via electrochemical haloform reaction with formamides.

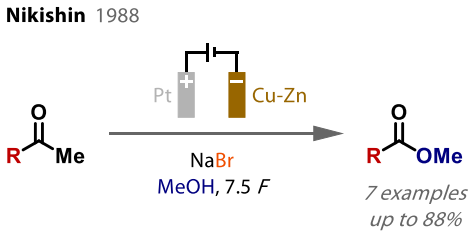
More recently still (2022), Gu and Li reported an alternative electrochemical haloform coupling for amide synthesis.[73] This method employed free amines and only very slight excesses (1.2 equivalents) were needed for coupling with α-bromo- or -cyanomethyl ketones (Scheme 1.34; *cf.* Scheme 1.7 and accompanying text). Through single

examples, 1,3-diketone and β-keto ester substrates were also shown to be viable substrates, albeit with reduced yields. Ketone iodination was achieved via iodide oxidation and facilitated by an aqueous carbonate buffer. This buffer created a biphasic system with the ethyl acetate co-solvent and resulted in significant carboxylic acid formation as a side-reaction (19% with the model substrate). That amides were still the major products, however, combined with Yuan and co-workers' observation that *"a small amount of water was crucial for this reaction"*,[71] demonstrates the relatively facile nature of amide coupling compared to ester coupling.



Scheme 1.34. Amide synthesis via electrochemical haloform reaction with amines.

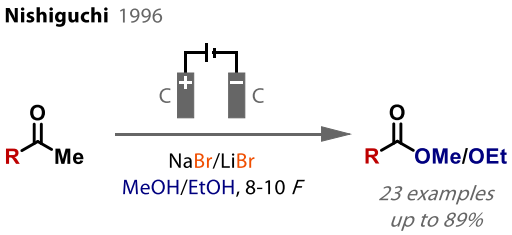
The first example of an electrochemical haloform reaction was, however, an ester synthesis; Nikishin and co-workers reported the preparation of methyl esters via bromide oxidation in methanol in 1988.[109–111] Sodium bromide (1.5 equivalents) was found to be the best halide source, which, oxidised in an undivided cell at a platinum anode (with a brass cathode), enabled the conversion of aryl, alkyl and alkenyl methyl ketones to their corresponding methyl esters in good yields (Scheme 1.35). The reaction was able to proceed with catalytic (i.e. <3 equivalents) bromide, as it was regenerated from the bromoform by-product by reaction with methoxide or, to a lesser extent, cathodic reduction. A modest excess of charge was required to obtain optimal yields (only 6 *F* would have been required at 100% Faradaic efficiency).



Scheme 1.35. Methyl ester synthesis via electrochemical haloform reaction.

Nishiguchi and co-workers reported a very similar method of electrochemical ester synthesis in 1996, in this case preparing both methyl and ethyl esters and with an expanded ketone scope, which included cyclic 1,3-diketones (Scheme 1.36).[112] Sodium bromide was, again, used as the bromination source in methanol, but lithium bromide was preferred for electrolyses in ethanol, due to its superior solubility. The conditions employed by Nishiguchi were otherwise broadly similar to those used by Nikishin,

although *"carbon rods"* were employed as electrodes and slightly more charge (8-10 *F*) was passed. Notably, the authors emphasised the need for anhydrous alcohol solvent to prevent the formation of carboxylic acid side-products.

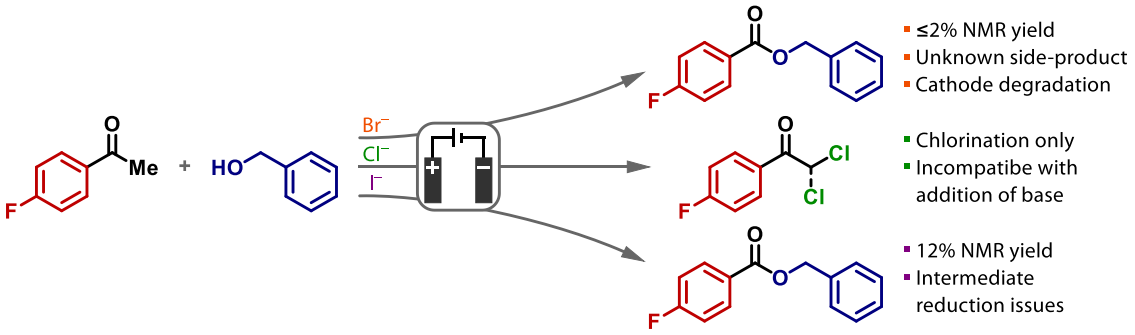


Scheme 1.36. Synthesis of methyl and ethyl esters via electrochemical haloform reaction.

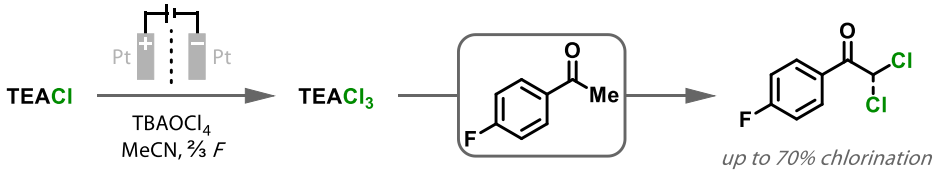
Chapter 2:
Towards Electrochemical Haloform Coupling

Abstract

Two significant issues preclude the adoption of the classical haloform reaction as a method of ester synthesis: the need for solvent-level alcohol, which severely limits the scope of esters that can be economically prepared; and the use of superstoichiometric quantities of hazardous hypohalite oxidants. A method based on electrochemical halide oxidation in the presence stoichiometric quantities of methyl ketone and alcohol was proposed as a solution. Initial attempts to develop this electrochemical haloform coupling via bromide oxidation, drawing on literature electrochemical haloform reactions in alcohol solvents, were unsuccessful. Switching to chloride oxidation was similarly unsuccessful, resulting in only mono- and dichlorination of the acetophenone substrate. This issue likely stemmed from insufficient cathodic alkoxide generation with stoichiometric alcohol, necessitating addition of base and a switch to iodide oxidation. Iodide oxidation was moderately successful, with ester yields of up to 12%, but suspected cathodic reduction of iodinated reaction intermediates hindered the achievement of higher yields. Attempts to tackle this issue were unsuccessful, impeding further progress in the development of the reaction.



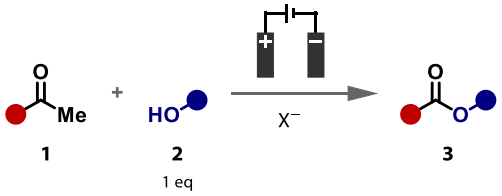
Although haloform coupling could not be achieved via electrochemical chloride oxidation, this spurred the development of an electrochemical synthesis of tetraethylammonium trichloride ($TEACl_3$), a useful, non-commercial reagent, whose classic synthesis requires chlorine gas. Up to 70% yields of $TEACl_3$ were achieved via divided electrolysis, although further work is needed to address repeatability issues and conclude optimisation of the reaction.



- $TEACl_3$ is valuable, but non-commerical reagent
- Ex-cell chlorination as indirect measure of $TEACl_3$ yield

2.1 Project Aim

The aim of this project was to develop a general electrochemical haloform coupling reaction with stoichiometric alcohol for the transformation of methyl ketones to esters (Scheme 2.1). Anodic halide oxidation, paired with cathodic alcohol reduction, would obviate the hazardous hypohalite oxidants used in the classical haloform reaction, and by requiring only one equivalent of (as opposed to solvent-level) alcohol, a wide range of complex alcohols should be employable, enabling the construction of structurally-complex esters that have been previously inaccessible via the haloform reaction.



Scheme 2.1. Envisaged electrochemical haloform coupling with stoichiometric alcohol.

Clear precedent exists for both stoichiometric nucleophile and electrochemical variants of the haloform reaction (see 1.5). The aim is therefore to merge and improve on these, to address the need for solvent-level alcohol in the electrochemical methods and the very narrow alcohol and methyl ketone scopes demonstrated in the only 'chemical' stoichiometric alcohol method.

2.2 Initial Attempts via Bromide Oxidation

2.2.1 Reproduction of Previously Reported Results

Firstly, reproduction of the results reported by Nikishin[109–111] and Nishiguchi[112] for electrochemical haloform reactions in solvent-level alcohol (see 1.5.2) was targeted. 4'-Fluoroacetophenone **1a** was chosen as the model methyl ketone substrate to enable ^{19}F NMR to be used for yield calculations and reaction monitoring. Although **1a** was not tested by Nikishin or Nishiguchi, the latter did report successful conversion of several similar acetophenone substrates (including 4'-chloroacetophenone in 71% yield). Nishiguchi's use of "*carbon rods*" (assumed to mean graphite) as cheap and readily-available electrodes was also considered more practical than the platinum and brass electrodes described by Nikishin, and therefore the conditions reported by Nishiguchi and co-workers were chosen as the starting point for reproduction of the literature results with **1a**.

While these conditions provided a good starting point for establishing a benchmark yield with solvent-level alcohol, some aspects of the electrochemical set-up were insufficiently detailed. For example, while a current density of 25-30 mA cm^{-2} was reported, there was no indication of the current applied or the surface areas of the electrodes used. Similarly, the charge passed was described as *"8~10 F mol^{-1}"*, with no further detail provided for individual substrates. As such, some experimentation was required to establish suitable electrolysis conditions for the development of a method with stoichiometric alcohol.

To establish a suitable current to apply, it was first necessary to measure the oxidation potential of the bromide source, sodium bromide. Cyclic voltammetry (CV) measurements in methanol **2a** demonstrated that bromide could be oxidised in the presence of acetophenone **1a**, methyl 4-fluorobenzoate **3aa** (the haloform reaction product) and 4,4'-difluorobiphenyl (which was to be used as an internal standard, IS), with an oxidation peak at 0.73 V (onset ~0.40 V; Figure 2.1). In the absence of sodium bromide, oxidation of 4,4'-difluorobiphenyl was observed at 1.50 V (onset ~1.25 V), so care was taken to ensure these potentials were not reached during bulk electrolyses. A brief chronoamperometry (constant potential) experiment at 0.73 V produced a current of 6.0 mA, so this was used in subsequent chronopotentiometry (constant current) reactions.

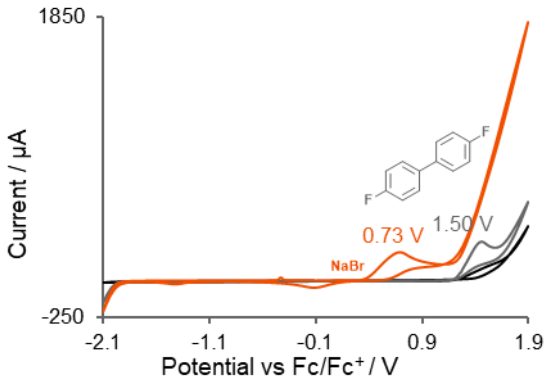
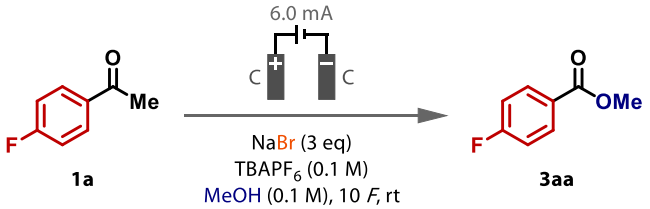


Figure 2.1. CVs of a blank solution (black; $TBAPF_6$ in MeOH), a solution containing NaBr (orange; NaBr, **1a**, **3aa**, 4,4'-difluorobiphenyl and $TBAPF_6$ in MeOH) and a solution without NaBr (grey; **1a**, **3aa**, 4,4'-difluorobiphenyl and $TBAPF_6$ in MeOH).

Applying 6.0 mA to an electrolysis mixture of **1a** and sodium bromide with tetrabutylammonium hexafluorophosphate ($TBAPF_6$) supporting electrolyte in methanol for 10 *F* resulted in a 70% ^{19}F NMR yield of methyl ester **3aa** (Table 2.1, entry 1). When only 8 *F* were passed (the lower end of the range reported by Nishiguchi), the yield was markedly lower at 50% (entry 2), whereas doubling the charge passed to 20 *F* further increased the yield of **3aa** to 80% and led to almost complete conversion of **1a** (entry 3). Doubling the concentration of NaBr (entry 4) or excluding additional supporting

electrolyte ($TBAPF_6$; entry 5) had little to no impact on yield. Having matched the yields achieved by Nishiguchi and co-workers with similar substrates, the 10 *F* electrolysis was repeated on a smaller scale (but with the same volume of methanol; entry 6). While this resulted in lower yields of **3aa**, the shorter reaction time was a practical advantage. This reaction was performed in duplicate, with the two yields demonstrating good repeatability. These yields were considered a benchmark and the conditions therefore an acceptable starting point for progressing to investigations with stoichiometric alcohol.

Table 2.1. Influence of electrolysis conditions on the yield of methyl ester **3aa** in an electrochemical haloform reaction in methanol.[a]



Entry	Change from conditions above	**1a**[b] / %	**3aa**[b] / %	MB[b],[c] / %
1	–	25	70	99
2	8 *F*	42	50	100
3	20 *F*	2	80	92
4	6 equiv. NaBr	23	71	101
5	No $TBAPF_6$	36	67	108
6[d]	0.06 M **1a**	48, 45	47, 50	100, 98

[a] On 0.400 mmol scale; undivided cell with graphite rod electrodes. [b] Calculated by ^{19}F NMR vs 4,4'-difluorobiphenyl IS. [c] Calculated as the integral of all signals (excluding IS and $^{-}PF_6$). [d] Reaction performed on 0.247 mmol scale, in duplicate. rt = Room temperature. MB = Mass balance.

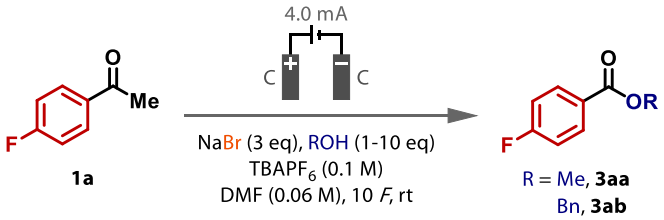
2.2.2 Preliminary Investigations with Stoichiometric Alcohol

In order to lower the amount of methanol required from solvent level to stoichiometric, an alternative reaction solvent was required. This needed to be an aprotic, non-nucleophilic solvent, with a suitable potential window and which would be capable of dissolving all the reaction components. DMF appeared to fit these criteria and was therefore selected for initial investigation.

CV measurements in DMF confirmed that bromide could be selectively oxidised in the presence of acetophenone **1a**, methanol **2a**, the ester product **3aa** and 4,4'-difluorobiphenyl. However, unlike in methanol, two bromide oxidation peaks were observed, at 0.33 V (onset ~0.05 V) and 0.93 V (onset ~0.65 V), corresponding to the formation of tribromide (Br_3^-) and bromine (Br_2), respectively.[107] Since tribromide is known to be a competent bromonium (Br^+) source in the haloform reaction,[55] a potential of 0.40 V was targeted, which could be achieved by applying 4.0 mA (determined by chronoamperometry).

This current was therefore applied to a series of electrolyte solutions containing 1, 5 or 10 equivalents of methanol **2a** in DMF (Table 2.2, entries 1-3). While the conversions of **1a** were much higher than those achieved in methanol, the amount of methanol added had no impact on the yields of methyl ester **3aa**, all of which were very low (2-3%). The higher conversions were instead a result of the formation of two unknown species with overlapping ^{19}F NMR signals at −118.8 ppm (in DMF). It was hypothesised that (at least one of) these signals could correspond to unreacted tribromoacetophenone intermediate **4a** or carboxylic acid **5a** (either in its protonated or carboxylate form), but comparison to NMR data from authentic samples disproved this. The two unknown species were isolated from one of the reaction mixtures by chromatography, but could not be separated from each other, suggesting that their structures may be very similar, or even that the signals observed by ^{19}F NMR may correspond to two conformers of a single compound. ^{1}H NMR analysis showed that the compounds were isolated in a ~5:1 ratio (matching that observed by ^{19}F NMR), with each appearing to contain only *para*-fluorophenyl and methyl moieties. This suggested these compounds' structures were likely closely related to acetophenone **1a**, perhaps adducts of **1a** with another species. Characterisation by mass spectrometry was inconclusive.

Table 2.2. Influence of alcohol on the results of electrolyses in DMF.[a]



Entry	Alcohol (equiv.)	**1a**[b] / %	**3**[b] / %	Unknown Species[b],[c] / %	MB[b],[d] / %
1	MeOH **2a** (1)	2	3	90	102
2	MeOH **2a** (5)	1	2	101	109
3	MeOH **2a** (10)	1	3	89	98
4[e]	BnOH **2b** (1)	3	trace	68	82
5[e]	BnOH **2b** (5)	1	2	65	91
6[e]	BnOH **2b** (10)	1	1	49	88
7[f]	None	2	–	78	95

[a] On 0.247 mmol scale; undivided cell with graphite rod electrodes. [b] Calculated by ^{19}F NMR vs 4,4'-difluorobiphenyl IS. [c] Unknown compound(s) with overlapping ^{19}F NMR signals at −118.8 ppm (in DMF). [d] Calculated as the integral of all signals (excluding IS and $^{-}PF_6$). [e] Reaction performed on 0.200 mmol scale. [f] Reaction performed at 5.0 mA.

When methanol was substituted for benzyl alcohol **2b**, high conversions to the unknown compounds were, again, observed (with relatively low yields of benzyl ester **3ab**; Table 2.2, entries 4-6), suggesting that the alcohol is not involved in the formation of these species. This was confirmed by electrolysis of acetophenone **1a** under the same conditions, but in the absence of alcohol (entry 7).

Another issue encountered during these electrolyses was that of severe degradation of the graphite cathodes (counter-electrodes), potentially due the extremely low reduction potential of DMF (onset ~2.80 V) and the scarcity of more readily-reduced alternatives (e.g. alcohol). Combined, these issues meant that switching to a different reaction solvent would be necessary before further progress could be made.

2.3 A Change in Approach; Chloride Oxidation

Recognising that what worked with solvent-level alcohol, might not under the significantly different circumstances of using stoichiometric alcohol, the focus shifted to identifying the optimal combination of solvent and oxidant (i.e. halonium species) for the reaction. DCM appeared to be a good choice, fulfilling the criteria by which DMF had been selected and having been successfully employed in ester-forming haloform reactions previously (see Scheme 1.32 and accompanying text).[66] To avoid solubility issues, this necessitated a switch from the inorganic halide salts used by Nikishin[109–111] and Nishiguchi[112] to organic tetraalkylammonium salts.

2.3.1 Cyclic Voltammetry

To determine which halide would be most suitable, CVs of the tetrabutylammonium (TBA) salts of chloride, bromide and iodide were recorded in DCM. As expected,[107] chloride had the highest oxidation potential (Figure 2.2A). Furthermore, CVs of tribromo- **4a**, trichloro- **6a** and trifluoroacetophenone **7a** showed that the C–X bonds in the trihaloacetophenone intermediates were relatively easily reduced, in the order C–Br > C–Cl > C–F, i.e. **4a** is the least reductively stable and **7a** the most (Figure 2.2B). The analogous mono- and dichloro- and bromoacetophenones (not shown) were less readily reduced, meaning that the trihaloacetophenone species should be the most easily reduced intermediate in an electrochemical haloform reaction. Since reduction of reaction intermediates was undesirable and considering that generation of the highest potential oxidising species (i.e. trichloride, via one-electron chloride oxidation) should promote methyl ketone halogenation, chloride oxidation was selected for further investigation.

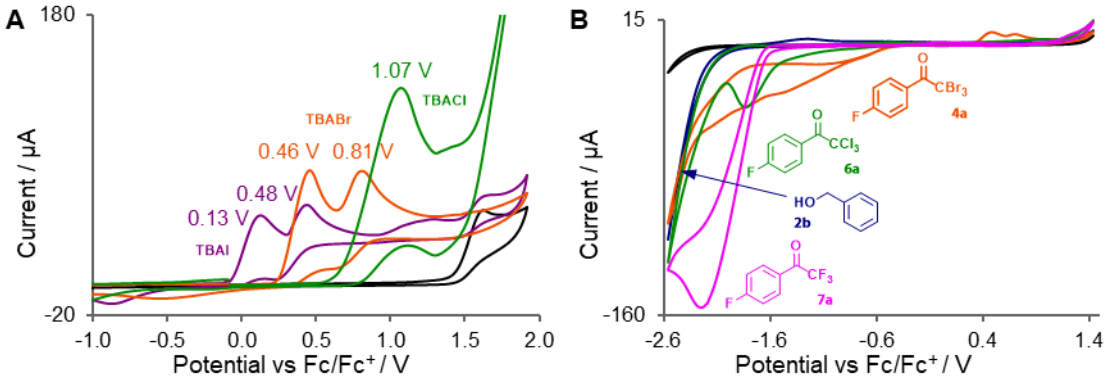


Figure 2.2. A) CVs of a blank solution (black; $TBAPF_6$ in DCM), a solution containing TBAI (purple; TBAI and $TBAPF_6$ in DCM), a solution containing TBABr (orange; TBABr and $TBAPF_6$ in DCM) and a solution containing TBACl (green; TBACl and $TBAPF_6$ in DCM). **B)** CVs of a blank solution (black; $TBAPF_6$ in DCM), a solution containing benzyl alcohol **2b** (blue; **2b** and $TBAPF_6$ in DCM), a solution containing tribromoacetophenone **4a** (orange; **4a** and $TBAPF_6$ in DCM), a solution containing trichloroacetophenone **6a** (green; **6a** and $TBAPF_6$ in DCM) and a solution containing trifluoroacetophenone **7a** (pink; **7a** and $TBAPF_6$ in DCM).

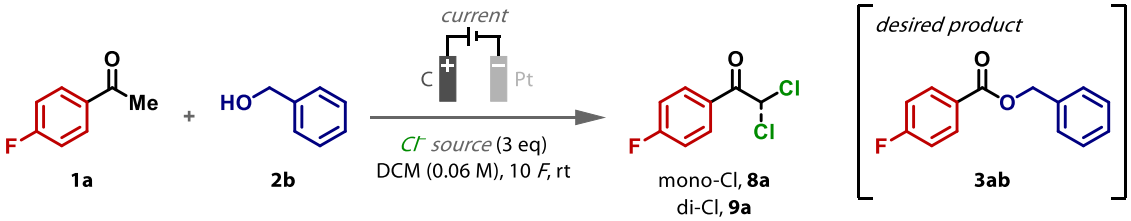
2.3.2 Bulk Electrolysis

Having found graphite anodes to be effective for halide oxidation (see 2.2) and since platinum cathodes are known to have a low overpotential for proton reduction,[113] these were selected as the working and counter electrodes, respectively. A silver/silver nitrate reference electrode was also used, to enable the anodic potential to be recorded. Electrolyses were carried out in an undivided cell, since this has been shown to be adequate for haloform reactions in alcohol by Nikishin and Nishiguchi.[109–112]

Targeting an anodic potential of 1.07 V (i.e. the first oxidation potential of chloride), a current of 2.5 mA was applied to a solution of acetophenone **1a**, TBACl and benzyl alcohol **2b** in DCM and, based on previous results and literature precedent,[109–112] excess charge (10 *F*) was passed. Although a small amount of chlorination to chloroacetophenone **8a** was observed, no ester **3ab** was obtained and the majority of **1a** remained unreacted (Table 2.3, entry 1). Addition of tetrabutylammonium hexafluorophosphate as supporting electrolyte increased the amount of **8a** obtained and led to the formation of dichloroacetophenone **9a**, but **3ab** was still not observed (entry 2). The additional supporting electrolyte did also allow a higher current (4.0 mA) to be applied without affecting the anodic potential, resulting in faster electrolyses. Under the assumption that cathodic reduction of benzyl alcohol **2b** to generate alkoxide base was required for the reaction, it was hypothesised that addition of a greater excess of **2b** would increase reduction efficiency and decrease the likelihood of undesired reduction of chlorinated intermediates. However, increasing the amount of **2b** used from 2 equivalents to 10 made little difference (entry 3). Substituting tetrabutylammonium chloride with its tetraethylammonium analogue as the chloride source led to a slight

increase in chloro- **8a** and dichloroacetophenone **9a** production, but ester formation remained elusive (entry 4).

Table 2.3. Attempts at formation of ester **3ab** by chloride oxidation in the presence of acetophenone **1a** and benzyl alcohol **2b**.[a]



Entry	Additional supporting electrolyte (conc)	Current / mA	**2b** equiv.	Cl^- source	**1a**[b] / %	**8a**[b] / %	**9a**[b] / %	**3ab**[b] / %	MB[b],[c] / %
1	–	2.5	2	TBACl	78	8	0	0	93
2	$TBAPF_6$ (0.1 M)	4.0	2	TBACl	37	29	2	0	83
3	$TBAPF_6$ (0.1 M)	4.0	10	TBACl	58	21	1	0	91
4	$TBAPF_6$ (0.1 M)	4.0	10	TEACl	39	36	4	0	96

[a] On 0.247 mmol scale; undivided cell with graphite rod anode, platinum coil cathode. [b] Calculated by ^{19}F NMR vs 4,4'-difluorobiphenyl IS. [c] Calculated as the integral of all signals (excluding IS and $^-PF_6$). conc = Concentration.

2.3.3 Base Additives

Electrochemical haloform reactions carried out in alcohol solvents do not require addition of base, as demonstrated by Nikishin and Nishiguchi, presumably since alkoxide (generated by alcohol reduction) can effect the necessary deprotonations. With near-stoichiometric alcohol, however, this appeared to no longer hold true, since, while the first two chlorinations can be achieved via enolisation,[114] formation of trichloroacetophenone **6a**, and ultimately esters, is not possible without base.[115] Addition of external base was therefore investigated.

Since DBU had proven effective in Zhang and Dong's ester-forming haloform reaction (see Scheme 1.32 and accompanying text),[66] this was the obvious candidate to test. However, comparison of the CVs of DBU and chloride in DCM suggested that DBU would be unsuitable (Figure 2.3A). The overlapping oxidation potentials of the two reductants suggested that selective chloride oxidation was unlikely to be achievable in a mixture containing both. No such issues were predicted with pyridine (pyr) or 2,6-lutidine (lut), however, since their oxidation potentials were significantly higher than that of chloride (Figure 2.3A). Furthermore, the conjugate acids of pyridine and 2,6-lutidine (pyr.H and lut.H, respectively) were both more easily reduced than trichloroacetophenone **6a** (Figure 2.3B), meaning that proton reduction should be the most facile reductive process in haloform reaction mixtures containing these species.

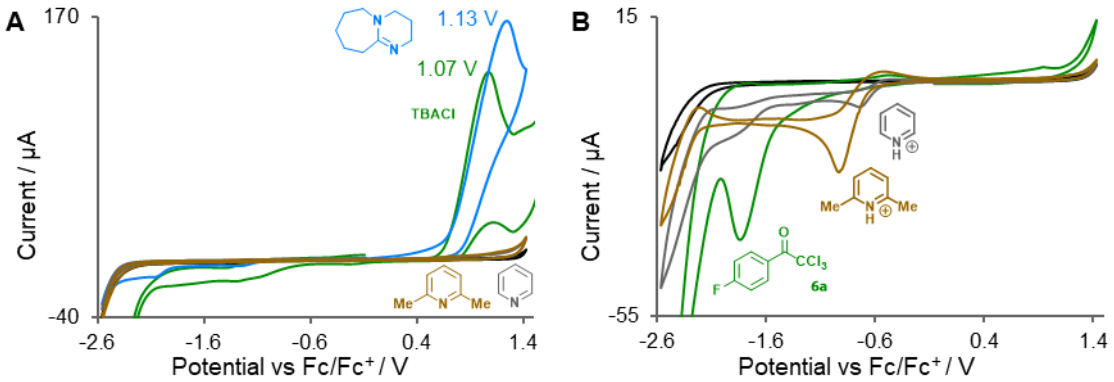
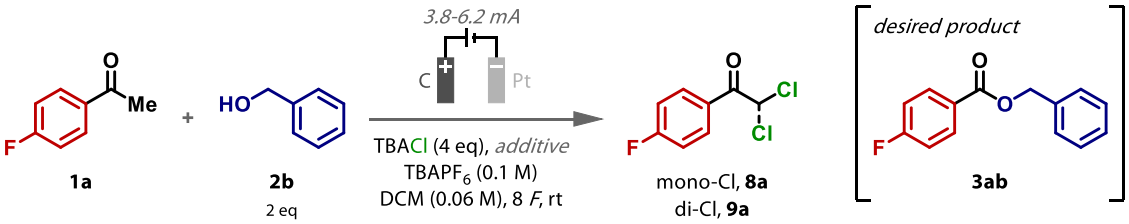


Figure 2.3. A) CVs of a blank solution (black; $TBAPF_6$ in DCM), a solution containing DBU (blue; DBU and $TBAPF_6$ in DCM), a solution containing pyridine (grey; pyridine and $TBAPF_6$ in DCM), a solution containing 2,6-lutidine (brown; 2,6-lutidine and $TBAPF_6$ in DCM) and a solution containing TBACl (green; TBACl and $TBAPF_6$ in DCM). **B)** CVs of a blank solution (black; $TBAPF_6$ in DCM), a solution containing pyridine.HBF_4 (grey; pyridine.HBF_4 and $TBAPF_6$ in DCM), a solution containing lutidine.HBF_4 (brown; lutidine.HBF_4 and $TBAPF_6$ in DCM) and a solution containing trichloroacetophenone **6a** (green; **6a** and $TBAPF_6$ in DCM).

Pyridinium and 2,6-lutidinium tetrafluoroborate were therefore added (separately) to electrolyses, in the hope that their reduction would minimise unwanted reduction of chlorinated reaction intermediates and in the process liberate the base needed to access trichloroacetophenone **6a**. This was not the case, however: acetophenone **1a** conversion was very low, and the chloro- and dichloroacetophenone intermediates were the only products observed (Table 2.4, entries 1 and 2), but in much lower concentrations than before (*cf.* Table 2.3). Considering the possibility that the acidity of the electrolysis solutions may have been responsible for the low conversions of **1a**, the electrolyses were repeated with 2:1 pyridine:pyridinium tetrafluoroborate and 2,6-lutidine:2,6-lutidinium tetrafluoroborate buffer systems, to ensure that basic conditions were maintained throughout the electrolyses. Again, however, essentially no conversion of **1a** was achieved (entries 3 and 4).

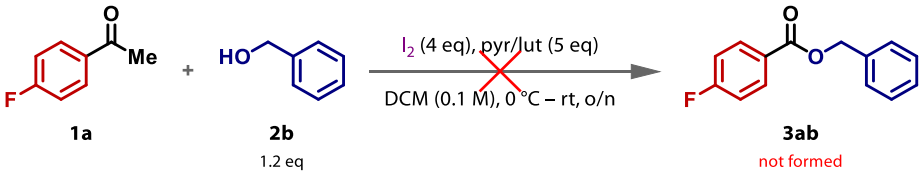
Table 2.4. Impact of the addition of base and conjugate acid additives on the formation of ester **3ab** by chloride oxidation in the presence of acetophenone **1a** and benzyl alcohol **2b**.[a]



Entry	Additive (equiv.)	Current[b] / mA	**1a**[c] / %	**8a**[c] / %	**9a**[c] / %	**3ab**[c] / %
1	pyr.HBF_4 (5)	4.4	98	2	trace	0
2	lut.HBF_4 (5)	3.8	100	trace	0	0
3	pyr:pyr.HBF_4 (10:5)	6.2	101	trace	trace	0
4	lut:lut.HBF_4 (10:5)	4.9	101	0	0	0

[a] On 0.247 mmol scale; undivided cell with graphite rod anode, platinum coil cathode. [b] Current to apply determined by brief chronoamperometry experiment at 1.07 V prior to chronopotentiometry. [c] Calculated by ^{19}F NMR, as a mole fraction of all signals (excluding $^{-}BF_4$ and $^{-}PF_6$).

It was suspected that the reason for these results was that pyridine and 2,6-lutidine were insufficiently strong bases to effect the necessary deprotonations. This was confirmed by substituting DBU with pyridine and 2,6-lutidine (separately) in 'chemical' haloform reactions with iodine (Chapter 3 details the development of this reaction; Scheme 2.2). Neither reaction yielded any ester; with pyridine, no conversion of acetophenone **1a** was observed at all, whereas with 2,6-lutidine, a small amount (6%) of an unidentified species was produced, but **1a** remained the major fluorinated compound in solution.



Scheme 2.2. Unsuccessful 'chemical' haloform reactions with pyridine and 2,6-lutidine.

This prompted a search for other bases which could be suitable additives in an electrochemical haloform coupling with chloride. A shortlist of candidate bases was assembled based on the requirements that the base should be: sufficiently basic to effect the necessary deprotonations; oxidatively stable at the potential required for chloride oxidation (i.e. 1.07 V vs Fc/Fc^+); non-nucleophilic; and relatively inexpensive and readily available. CVs revealed that none of the amine bases initially identified were suitable, since their oxidation onset potentials were significantly below the oxidation potential of chloride (Table 2.5, entries 4-13). The five remaining, inorganic bases were oxidatively stable, potentially due to insolubility in DCM, but were unable to effect a haloform reaction in conjunction with iodine (entries 14-18). Although small amounts (≤2%) of chloroacetophenone **8a** were produced in each case (apart from with caesium carbonate, entry 15), no conversion to ester **3ab** was observed, suggesting that the bases were either insufficiently basic and/or that heterogenous deprotonation (due to poor solubility in DCM) was ineffective.

Table 2.5. Bases tested for suitability in an electrochemical haloform reaction via chloride oxidation.

Entry	Base	Oxidatively stable?[a]	Effects haloform reaction?[b]
1	DBU	No (onset ~0.4 V)	Yes[66]
2	Pyridine	Yes	No
3	2,6-Lutidine	Yes	No
4	Diisopropylamine (DIPA)	No (onset ~0.3 V)	–
5	*N*,*N*-Diisopropylethylamine (DIPEA)	No (onset ~0.1 V)	–
6	Triethylamine (TEA)	No (onset ~0.2 V)	–
7	4-Dimethylaminopyridine (DMAP)	No (onset ~0.6 V)	–
8	1,1,3,3-Tetramethylguanidine (TMG)	No (onset ~0.3 V)	–
9	1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)	No (onset ~0.0 V)	–
10	1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)	No (onset ~0.0 V)	–
11	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)	No (onset ~0.1 V)	–
12	1,4-Diazabicyclo[2.2.2]octane (DABCO)	No (onset ~0.3 V)	–
13	Quinuclidene	No (onset ~0.4 V)	–
14	NaH	Yes	No
15	Cs_2CO_3	Yes	No
16	K_3PO_4	Yes	No
17	K_2HPO_4	Yes	No
18	MTBA PO_4Bu_2	Yes	No

[a] At the potential required for chloride oxidation (1.07 V vs Fc/Fc^+). [b] Reaction conditions: acetophenone **1a** (0.412 mmol, 1 equiv.), benzyl alcohol **2b** (1.2 equiv.), iodine (4 equiv.) and base (5 equiv.) in anhydrous DCM (4.1 mL), under nitrogen atmosphere in Schlenk flask, 0 °C – rt, 16 h. MTBA = Methyltributylammonium.

2.4 Iodide Oxidation

Since no bases were identified which could both effect a haloform reaction and were oxidatively stable at the potential required for chloride oxidation, the selection of chloride as the electrochemical reductant was re-examined. The relatively high oxidation potential of chloride (1.07 V vs Fc/Fc^+) made it incompatible with many otherwise conceivably suitable amine bases, so it was proposed that switching to bromide (0.46 and 0.81 V) or iodide oxidation (0.13 and 0.48 V) might avert this issue. In particular, the oxidation potentials of iodide are sufficiently low that it should be compatible with DBU (Figure 2.4), which has been shown to be capable of achieving haloform reactions with elemental iodine.[66]

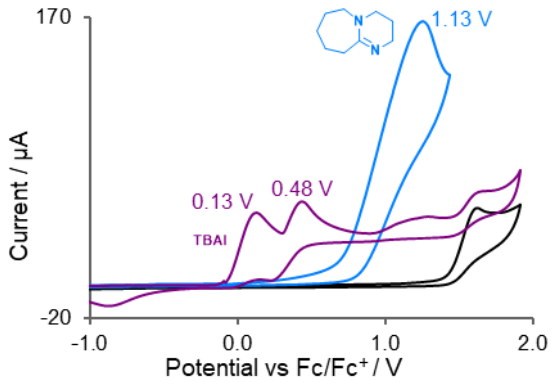
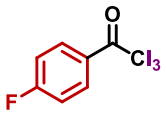


Figure 2.4. CVs of a blank solution (black; $TBAPF_6$ in DCM), a solution containing DBU (blue; DBU and $TBAPF_6$ in DCM) and a solution containing TBAI (purple; TBAI and $TBAPF_6$ in DCM).

A current of 8.0 mA (resulting in an anodic potential of ~0.48 V, i.e. the second oxidation potential of iodide) was therefore applied to a solution of acetophenone **1a**, TBAI and benzyl alcohol **2b** in DCM, under similar conditions to those previously used for chloride oxidation. By contrast to chloride oxidation, this led to appreciable formation of ester **3ab**, although the disparity between the mole fraction (19%) and NMR yield (12% vs 4,4'-difluorobiphenyl IS; both calculated by ^{19}F NMR) indicated a relatively low mass balance (61%; Table 2.6, entry 1).

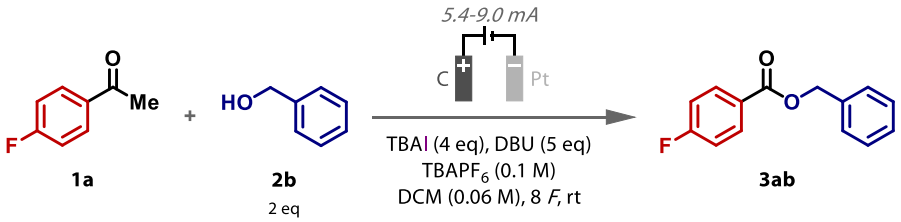


10a

Figure 2.5. 2,2,2-Triiodo-4'-fluoroacetophenone **10a**.

A review of the trend in trihaloacetophenone reduction potentials (Figure 2.2B) suggests that the analogous triiodoacetophenone **10a** (Figure 2.5) would be the most easily reduced, possibly at a potential as high as ~0 V. Depletion of this intermediate by cathodic reduction may therefore be a key reason for the relatively low yield of ester **3ab**. In an attempt to avert this, electrolysis was repeated in a divided cell. As the anodic and cathodic compartments were separated by a glass frit, migration of triiodoacetophenone **10a** to the cathode, where it could be reduced, should have been minimised. In practice, however, both acetophenone **1a** and ester **3ab** were found in the cathodic compartment after electrolysis (albeit in lower concentrations), suggesting that preventing all diffusion is not possible. Ultimately, formation of **3ab** (measured in the anodic compartment) was lower than in the undivided cell, although more unreacted **1a** remained (29%; Table 2.6, entry 2).

Table 2.6. Ester formation via electrochemical haloform reaction with iodide oxidation.[a]



Entry	Change from conditions above	Current[b] / mA	**1a**[c] / %	**3ab**[c] / %
1	–	8.0	4 (2)	19 (12)
2	Divided cell	5.4	29	10
3	Ex-cell (2-step)	7.0	83	5
4	DBU.HBF$_4$ additive (6 equiv.)	9.0	8	15

[a] On 0.247 mmol scale; undivided cell with graphite rod anode, platinum coil cathode. [b] Current to apply determined by brief chronoamperometry experiment at 0.48 V prior to chronopotentiometry. [c] Calculated by ^{19}F NMR, as a mole fraction of all signals (excluding $^{-}$BF$_4$ and $^{-}$PF$_6$); figures in parentheses calculated vs 4,4'-difluorobiphenyl IS.

As an alternative method for preventing triiodoacetophenone **10a** reduction, a two-step, 'ex-cell' approach was tested,[116] in which iodide was oxidised in isolation and the

remaining reaction components (**1a**, **2b** and DBU) were added at the end of the electrolysis. However, the low production of ester **3ab** (5%) and large amount of unreacted **1a** remaining (83%; entry 3) suggest that either: iodide oxidation was unselective; or triiodide and iodine produced can be reduced if not engaged in other reactions upon generation. The first explanation seems unlikely to be correct, since CV data have shown that iodide is significantly more readily oxidised than DCM or $TBAPF_6$ (Figure 2.4). However, iodide oxidation is also irreversible according to CV data, so the latter theory is also unsupported. In any case, an ex-cell approach was clearly not a viable solution. Addition of $DBU.HBF_4$ to the electrolysis mixture, with the aim of providing an alternative oxidant, and thus preventing triiodoacetophenone **10a** reduction, made little difference (entry 4); ester **3ab** formation was comparable to that in the absence of DBU.H. A comparison of a CV of $DBU.HBF_4$ to those of the series of trihaloacetophenones provides the likely reason: triiodoacetophenone **10a** is likely much more readily reducible than DBU.H, whose reduction onset potential is more akin to that of relatively reductively-stable trifluoroacetophenone **7a** (Figure 2.6).

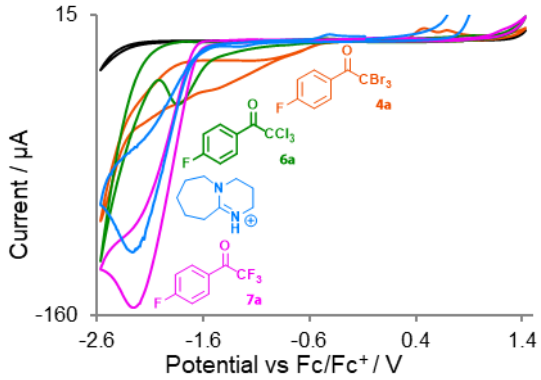


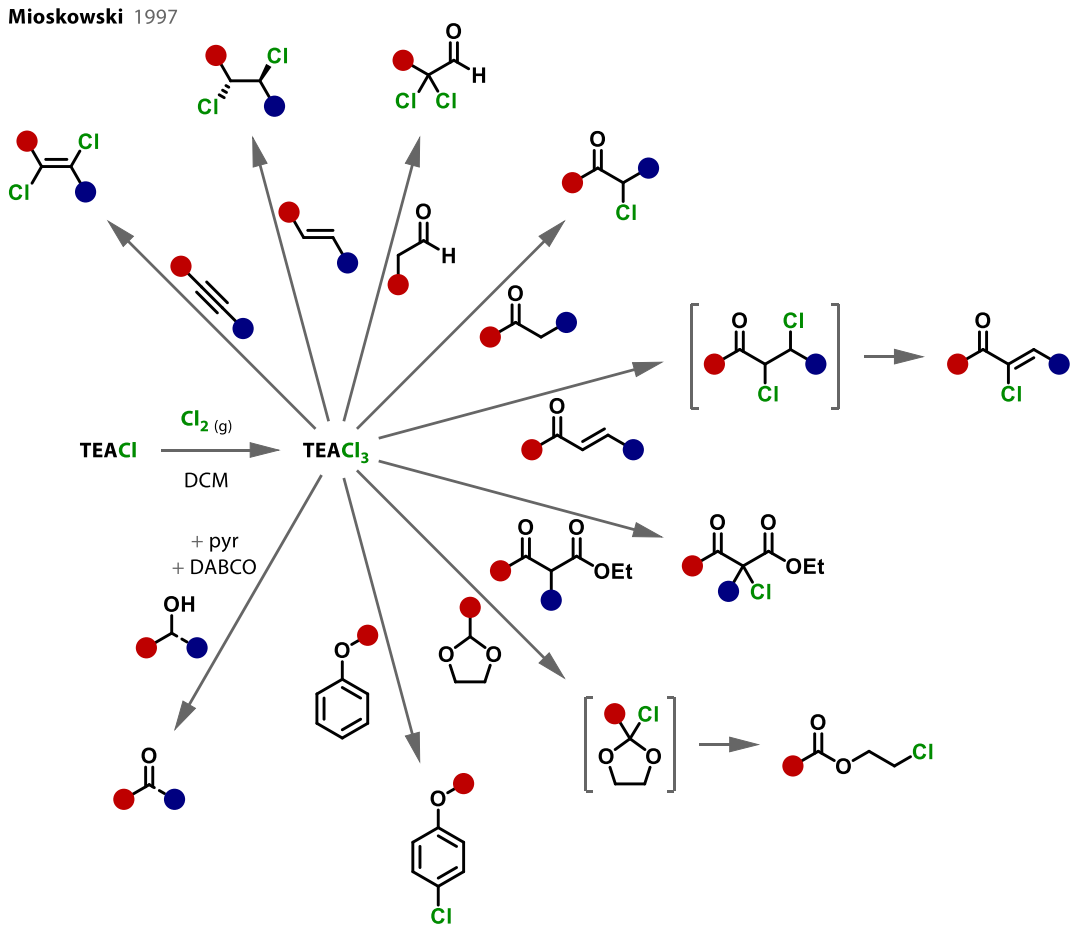
Figure 2.6. CVs of a blank solution (black; $TBAPF_6$ in DCM), a solution containing $DBU.HBF_4$ (blue; $DBU.HBF_4$ and $TBAPF_6$ in DCM), a solution containing tribromoacetophenone **4a** (orange; **4a** and $TBAPF_6$ in DCM), a solution containing trichloroacetophenone **6a** (green; **6a** and $TBAPF_6$ in DCM) and a solution containing trifluoroacetophenone **7a** (pink; **7a** and $TBAPF_6$ in DCM).

Since none of the mitigation strategies resulted in even a slight improvement in ester yield, there was no clear solution to the suspected issue at hand, i.e. that of cathodic reduction of iodinated reaction intermediates. Furthermore, electrochemical generation of iodonium was deemed to offer little benefit, since the use of elemental iodine presents no practical issues, being relatively non-hazardous, as well as inexpensive and readily available. Efforts were therefore redirected to the development of a ‘chemical’ haloform coupling with iodine to achieve the project’s original aims (see Chapter 3).

2.5 Preparation of Tetraalkylammonium Trichlorides

2.5.1 Background

Although haloform coupling could not be achieved via electrochemical chloride oxidation (see 2.3), the oxidation of chloride to form trichloride was not the problem, as evidenced by the presence of chloro- **8a** and dichloroacetophenone **9a** among the reaction products. This was of interest, as, while tetraalkylammonium tribromide and triiodide salts are commercially available, the analogous trichlorides are not. This is not a result of their being unknown, however.

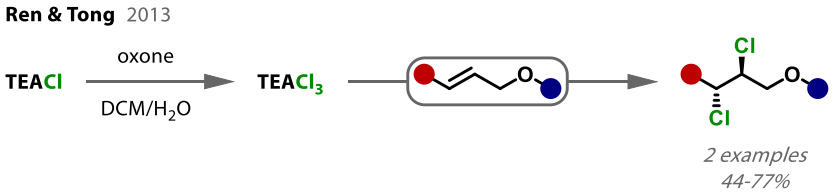


Scheme 2.3. Synthesis and applications of $TEACl_3$ reported by Mioskowski and co-workers.

Tetraethylammonium trichloride ($TEACl_3$), a yellow solid, synthesised by streaming elemental chlorine over TEACl, was first reported in 1923, by Chattaway and Hoyle.[117] Synthesis of $TEACl_3$ was subsequently re-reported by Mioskowski and co-workers in 1997, who demonstrated its stability (*"several months"* under an inert atmosphere), and utility in chlorination and alcohol oxidation reactions (Scheme 2.3).[118,119] This popularised the use of $TEACl_3$ (often referred to as Mioskowski's reagent) and, since then, it has been employed as a chlorine source in natural product synthesis,[120–123] and the

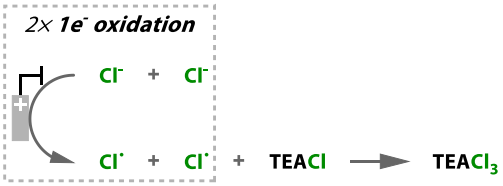
syntheses and *in situ* application of two related trichloride salts, tetrabutylammonium and triethylmethylammonium trichloride, have also been reported.[124,125]

Tetraalkylammonium trichloride salts represent an appealing alternative to using elemental chlorine in synthesis, owing to the practical challenges associated with the latter, namely the difficulty in measuring its stoichiometry, its incompatibility with many common functional groups and, not least, its highly hazardous nature. However, trichloride salts are themselves prepared using chlorine gas, making a chlorine-free synthesis of tetraalkylammonium trichlorides an attractive target. Ren and Tong purportedly achieved precisely that in 2013, having prepared $TEACl_3$ from TEACl using oxone as the oxidant.[126] In this case, $TEACl_3$ was not isolated, being instead used directly for alkene dichlorination (Scheme 2.4).



Scheme 2.4. Chlorine-free synthesis and *in situ* use of $TEACl_3$.

It is proposed that electrochemistry could provide an alternative method for $TEACl_3$ synthesis (and that of other tetraalkylammonium trichloride salts; Scheme 2.5), obviating the use of chlorine gas (required in the classical methods) and stoichiometric oxidants (reported more recently by Ren and Tong[126]). The synthesis of chloro- **8a** and dichloroacetophenone **9a** from acetophenone **1a** via electrochemical oxidation of TBACl demonstrated in 2.3 serves as proof of this concept. The aim was therefore to develop conditions for efficient chloride oxidation in the absence of a chlorination substrate, such that the trichloride salt formed could be isolated and employed as a reagent in subsequent reactions, potentially even including the haloform reaction, as demonstrated by Mioskowski and co-workers.[118]

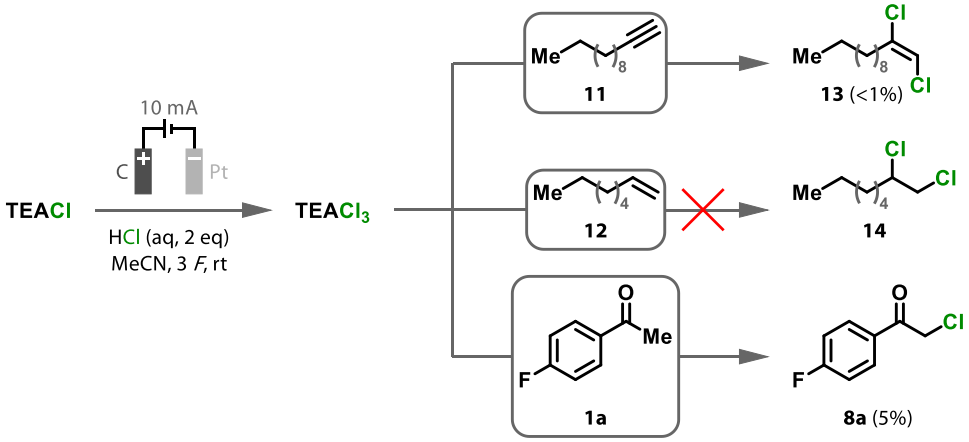


Scheme 2.5. Proposed synthesis of $TEACl_3$ via electrochemical chloride oxidation.

2.5.2 Towards Electrochemical $TEACl_3$ Synthesis

With the idea of simplifying eventual $TEACl_3$ isolation from the electrolysis mixture, idealised conditions were used as the starting point for $TEACl_3$ electrosynthesis.

Therefore, based on conditions reported for the electrochemical chlorination of quinones and other, similar heterocycles,[127] a 2:1 mixture of TEACl:12 M aq. HCl was electrolysed in acetonitrile in an undivided cell for 3 *F* (Scheme 2.6). However, with no direct method for measuring the amount of trichloride produced, this had to be calculated indirectly. This was achieved by addition of the electrolysis mixture (split approximately three ways) to three substrates which should be chlorinated by $TEACl_3$ (essentially an ex-cell chlorination procedure[116]), according to the results of Mioskowski and co-workers.[118] While only a small amount of chlorination (0.5-1 mol% by ^{1}H NMR) was observed with 1-dodecyne **11** and no evidence of chlorination was detected at all with 1-octene **12**, 5% chlorination was achieved with acetophenone **1a** (mole fraction, by ^{19}F NMR). Since the chlorination substrate only serves as a tool for estimating the amount of $TEACl_3$ produced, a non-challenging substrate (ideally one that would give 100% yield based on the amount of trichloride used) was desired. Therefore, as the most readily chlorinated of the three substrates tested, acetophenone **1a** was chosen as the model substrate for indirect calculation of trichloride yields.



Scheme 2.6. Electrochemical synthesis of $TEACl_3$ under idealised conditions and chlorinations achieved with the electrolysis mixture.

Comparison of the CVs of TEACl in the presence of aqueous HCl, and $HCl.Et_2O$ showed that chloride oxidation occurs at a slightly lower potential in the presence of $HCl.Et_2O$ than aqueous HCl (Figure 2.7), suggesting that chloride oxidation might be more selective or efficient in the presence of $HCl.Et_2O$. However, when the electrolysis of TEACl was repeated in the presence of (2 equivalents of) $HCl.Et_2O$ rather than aqueous HCl, no chlorination of **1a** was achieved with the electrolysis mixture (Table 2.7, entry 2).

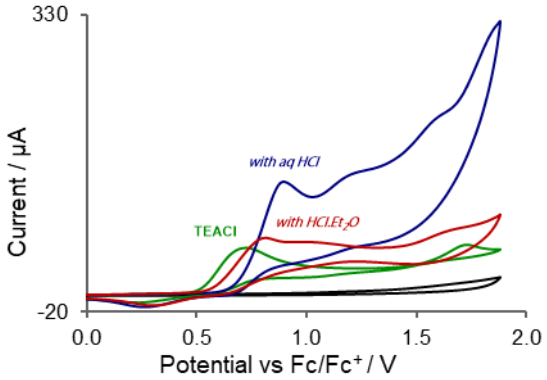
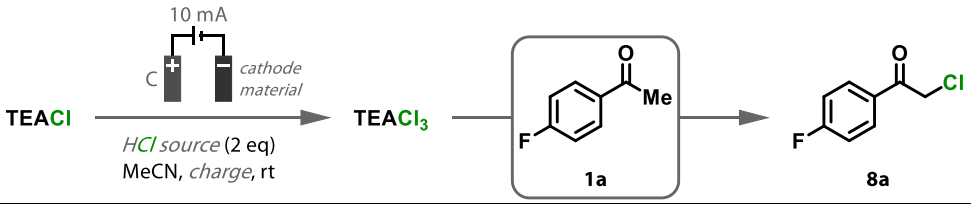


Figure 2.7. CVs of a blank solution (black; $TBAPF_6$ in MeCN), a solution containing TEACl (green; TBACl and $TBAPF_6$ in MeCN), a solution containing TEACl and aq. HCl (blue; TEACl, aq. HCl and $TBAPF_6$ in MeCN) and a solution containing TEACl and $HCl.Et_2O$ (red; TEACl, $HCl.Et_2O$ and $TBAPF_6$ in MeCN).

The platinum cathode was substituted with nickel, resulting in a 7% yield of chloroacetophenone **8a** (Table 2.7, entry 3). Aiming to simplify the set-up from the three-neck round-bottom flask which had been used as the electrolysis cell to this point (in which the electrodes were almost perpendicular to one another), an electrolysis was carried out in a (single-neck) round-bottom flask (in which the electrodes were parallel). This resulted in a drop of the eventual yield of **8a** to 1% (entry 4) and when the charge passed was lowered to 2 *F* (the theoretical charge required), subsequent chlorination of **1a** was not achieved at all (entry 5). Since it is implausible that trichloride formation only took place during the final third of the 3 *F* electrolyses, an alternative explanation for this result was sought. Closer examination of the CVs of TEACl revealed that small reduction peaks are present, suggesting that chloride oxidation is (at least quasi-)reversible (Figure 2.7). This would mean that any $TEACl_3$ formed could be reduced under the electrolysis conditions, explaining the low and inconsistent yields observed.

Table 2.7. Influence of electrolysis conditions on the production of $TEACl_3$, measured by chlorination of acetophenone **1a** with the resulting electrolysis mixture.[a]



Entry	HCl source	Cathode material	Charge / *F*	Electrolysis cell	**1a**[b] / %	**8a**[b] / %
1[c]	aq HCl	Pt sheet	3	3-neck RBF	95	5
2	$HCl.Et_2O$	Pt sheet	3	3-neck RBF	100	0
3	aq HCl	Ni foil	3	3-neck RBF	93	7
4	aq HCl	Ni foil	3	RBF	99	1
5	aq HCl	Ni foil	2	RBF	100	0

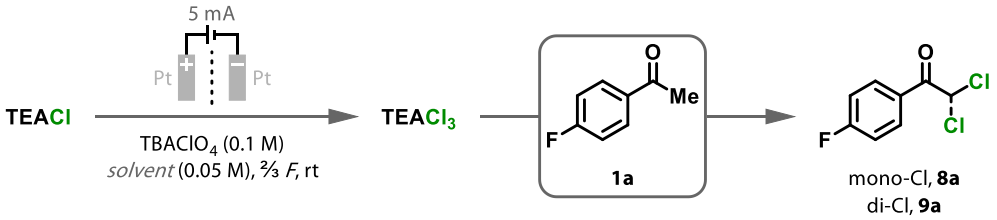
[a] On 0.300 mmol scale; undivided cell with carbon-felt anode. Post-electrolysis: electrodes removed and acetophenone **1a** (0.300 mmol, 1 equiv. vs theoretical $TEACl_3$ yield) added. [b] Calculated by ^{19}F NMR, as a mole fraction of all signals. [c] Electrolysis mixture divided three ways, so only 0.100 mmol acetophenone **1a** added. RBF = Round-bottom flask.

The use of nickel cathodes created an additional problem: suspected nickel(II) chloride formation in solution (even prior to electrolysis), evidenced by the bright green colour of

the solutions. With these issues in mind, changes to the reaction set-up were made to incorporate a divided cell and alternative electrodes.

Drawing inspiration from Nonaka and co-workers' reports on electrochemical preparation and utilisation of other polyhalides,[128–132] $TEACl_3$ synthesis was attempted by oxidation of a solution of TEACl in DCM in a divided H-cell with platinum-coil electrodes (Table 2.8). Addition of ⅓ equivalent of acetophenone **1a** (i.e. 1 equivalent relative to the theoretical yield of $TEACl_3$) to the anolyte solution after electrolysis yielded 11% chloroacetophenone **8a** (entry 1). Performing the electrolysis in acetonitrile enabled a significantly higher yield (44%) of **8a** to be obtained, as well as ~2% of the dichlorinated product **9a**, giving a total of 49% 'chlorination' (i.e. 49% chlorine atom incorporation, which should correspond to the amount of $TEACl_3$ produced; entry 2).

Table 2.8. Influence of solvent choice on the production of $TEACl_3$ in a divided cell, measured by chlorination of acetophenone **1a** with the resulting electrolysis mixture.



Entry	Solvent	**1a**[b] / %	**8a**[b] / %	**9a**[b] / %	Chlorination[c] / %
1	DCM	89	11	trace	12
2	MeCN	54	44	2	49

[a] On 0.300 mmol scale; divided H-cell with platinum-coil electrodes. Post-electrolysis: anolyte solution transferred to a vial and acetophenone **1a** (0.100 mmol, 1 equiv. vs theoretical $TEACl_3$ yield) added. [b] Calculated by ^{19}F NMR, as a mole fraction of all signals. [c] Calculated as: **8a** % + 2 × **9a** %; reflects total chlorine atom incorporation.

When electrolysis (in acetonitrile) was repeated in a different, but visually-identical H-cell, however, only 26% chlorination was achieved with its anolyte solution (Figure 2.8, cell 2), indicating a potential repeatability issue. A selection of other 'identical' H-cells were therefore also tested, resulting in 14 to 70% chlorination of acetophenone **1a** (cells 3-7). Repeatability with a single H-cell appeared be less problematic, as 70% and 63% chlorination yields were recorded from two electrolyses with the best-performing cell (cell 3). This suggested that differences between the cells themselves, rather than other variables in the electrolyses, were responsible for the inconsistent results.

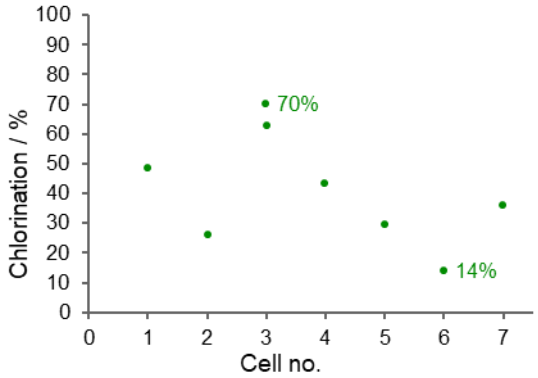


Figure 2.8. Percentage of chlorine incorporation achieved with $TEACl_3$ prepared in different H-cells.

The glass frits dividing the H-cells were identified as a likely source of the repeatability issues, as, although visually identical, the H-cells were of varying ages and had different histories of use. This may have led to differences in frit porosities, which, since frit porosity affects cell resistance and the ease with which reaction species can migrate between compartments during electrolysis, may have influenced electrolysis efficiency. It should also be noted that, since the H-cells were custom-made, the volumes of the two compartments were not always perfectly equal, such that the level of solvent on one side of the cell was often initially higher than on the other. The resulting levelling of the solvent may have provided a driving force for migration of reaction species and may therefore also have contributed to poor repeatability.

2.5.3 Future Work

The repeatability of chloride oxidation in the divided cell set-up ought to be addressed as a priority. If this were not done, electrolyses would need to be carried out in a single H-cell to enable fair comparisons to be made and results would be unlikely to be reproducible anyway. Investigation of alternative membranes, such as Nafion, to separate the two compartments may be fruitful. Alternatively, electrolysis in an undivided cell with a sacrificial oxidant, such as a pyridinium salt, which is more readily reduced than the trichloride, could be tested.

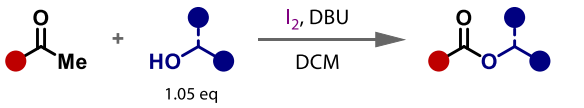
Once the repeatability issues have been resolved, optimisation of the electrolysis conditions for $TEACl_3$ production could be resumed. Particular efforts should be made to investigate the impact of: increasing the current at which electrolyses are carried out; removing the additional $TBAClO_4$ supporting electrolyte, possibly in conjunction with increasing the concentration of TEACl; and substituting the platinum electrodes for cheaper, more readily available alternatives.

The isolation of $TEACl_3$ should be considered throughout the optimisation process. For example, while addition of $TBAClO_4$ supporting electrolyte may increase $TEACl_3$ production, it may hinder $TEACl_3$ isolation. Ideally, a procedure would be developed by which pure $TEACl_3$, analytically indistinguishable from that prepared by combining TEACl with elemental chlorine, could be isolated and stored for subsequent use. However, if, for example, the combination of salts present makes isolation of $TEACl_3$ too challenging, the method could still be a convenient means of *in situ* $TEACl_3$ production for immediate use. In this case, it could be considered an ex-cell chlorination or oxidation method for substrates which would be incompatible with in-cell reactions (where the substrate is added prior to electrolysis).[116]

Chapter 3:
Chemical Haloform Coupling

Abstract

Since elemental iodine is readily and inexpensively available, and relatively non-hazardous, its use was proposed as an alternative to electrochemical halide oxidation in the development of a stoichiometric haloform coupling for ester synthesis. Literature conditions were tested to find a starting point in this endeavour, with iodine and DBU in DCM found to be effective for the synthesis of esters with primary alcohols. Just 1.05 equivalents of the alcohol coupling partner were required. Re-optimisation of the reaction was necessary for secondary alcohols, however. Higher concentrations of iodine and DBU ensured complete conversion to ester and strict anhydrous conditions, including the addition of molecular sieves to reactions, minimised the formation of carboxylic acid side-products. Under these complementary sets of conditions, methyl ketones were successfully coupled with a wide variety of primary and secondary alcohols in good yields. Furthermore, several esters were synthesised with complex, natural product alcohols, whose use in excess, let alone on a solvent scale, would not be viable. Given that previous haloform methods have only been demonstrated with a handful of simple, aliphatic primary alcohols, this general coupling method could therefore be considered a novel method of ester synthesis. Mechanistic investigations into the nucleophilicity differences between primary and secondary alcohols revealed unexpected impacts on reactivity beyond the nucleophilic substitution step and may explain the need for additional iodine and DBU with secondary alcohols.



- Compatible with 1° & 2° alcohols
- Selective ester formation
- Demonstrated with complex natural product alcohols

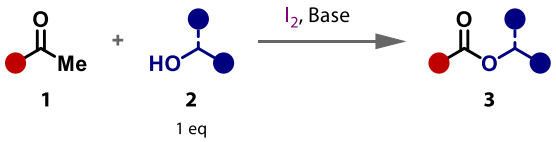
Contributions:

David Heard synthesised esters **3ce**, **3cf**, **3cg**, **3ch**, **3cj**, **3ck**, **3mc**, **3cv**, **3cw**, **3cx**, **3cz**, **3caa**, **3cab**, **3cac** and **3cad**, and attempted the synthesis of **3gl**, **3cn**, **3co**, **3cp**, **3cq**, **3gc**, **3ec**, **3fc**, **3caf**, **3cag** and **3caj**.

Stephen Sweeting performed DFT calculations (see Figure 3.5).

3.1 Adjustment of Project Aims

Recognising the significant challenge associated with further development of an electrochemical haloform coupling and the minimal advantage it would offer over a method utilising elemental iodine, the project aim was adjusted accordingly. The revised goal was: to develop a general, iodine-mediated haloform coupling reaction with stoichiometric alcohol for the transformation of methyl ketones to esters (Scheme 3.1). By limiting the amount of the alcohol coupling partner required to as close to stoichiometric levels as possible, a wide range of complex alcohols, including secondary alcohols, should be viable as substrates. Since previously only unfunctionalised, aliphatic, primary alcohols have been employed, the significant expansion in the scope of esters accessible via the haloform reaction this would enable would effectively render this a new method of ester synthesis.



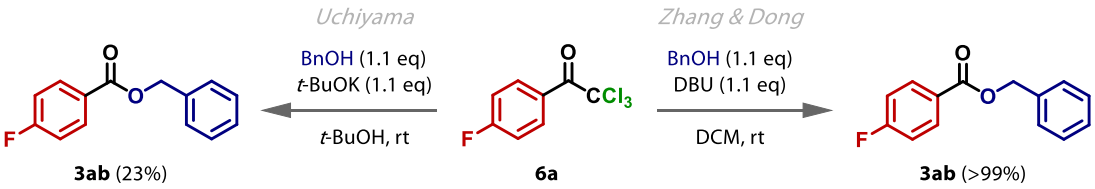
Scheme 3.1. Envisaged haloform coupling with stoichiometric alcohol.

3.2 Preliminary Investigations

To establish a starting point from which to progress, the haloform reaction methods published by Uchiyama,[35] and Zhang and Dong[66] (see 1.5.1) were investigated.

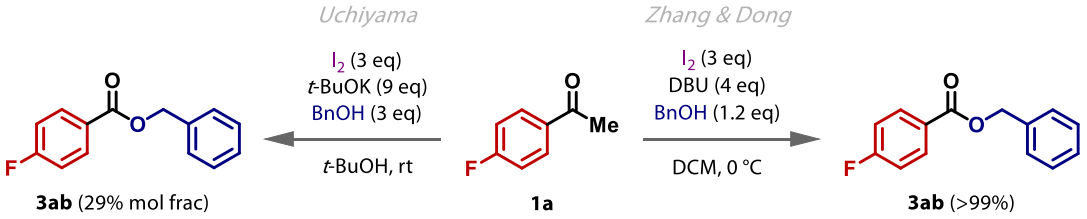
The final, ester-forming step of the haloform reaction was considered in isolation first, comparing the efficiency of C–C bond cleavage under the two sets of conditions-specifically the bases and solvents used (Scheme 3.2). Zhang and Dong's conditions (DBU in DCM) were very efficient, with 1.1 equivalents of benzyl alcohol **2b** proving sufficient for clean, quantitative conversion of trichloroacetophenone **6a** to ester **3ab** within 10 minutes. By contrast, using potassium *tert*-butoxide in *tert*-butanol (Uchiyama's conditions), only 23% **3ab** was obtained (both ^{19}F NMR yields vs 4,4'-difluorobiphenyl IS). A low mass balance (42%, including 18% unreacted **6a**) was recorded in the latter case, likely due to formation of 4-fluorobenzoic acid **5a** as a side-product, which has poor solubility in *tert*-butanol. A ^{19}F NMR signal corresponding to 1% of the mass balance was observed at the shift expected for **5a** (−112.1 ppm in *tert*-butanol) and a cloudy reaction mixture was obtained. Water in the reaction mixture (required for **5a** formation) may have been introduced by insufficiently dry potassium *tert*-butoxide or *tert*-butanol, however, when the reaction was repeated using rigorously dried *tert*-butanol (dried over calcium hydride) and potassium *tert*-butoxide stored and added to the reaction in a

nitrogen glovebox, only 2% **3ab** was obtained. While complete conversion of **6a** was achieved (using 2 equivalents of **2b** and *tert*-butoxide), it is hypothesised that this was almost exclusively to benzoic acid **5a**, since a mass balance of just 3% was recorded. This suggests that it may be difficult to avoid forming benzoic acid side-products in a full haloform reaction under Uchiyama's conditions (a problem they did not encounter, since these were the targeted products in their work).[35]



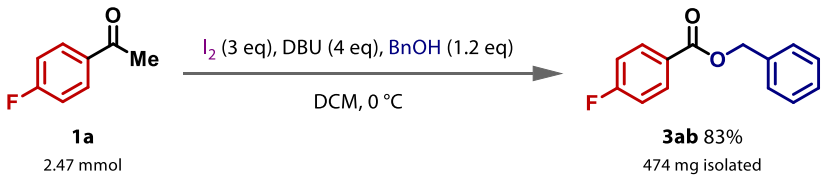
Scheme 3.2. Comparison of nucleophilic substitutions of trichloroacetophenone **6a** under literature conditions. ^{19}F NMR yields shown.

Despite this, both Uchiyama's, and Zhang and Dong's haloform reaction conditions were tested for the conversion of acetophenone **1a** to ester **3ab** with benzyl alcohol **2b** (Scheme 3.3). Uchiyama's method resulted in a poor conversion of **1a**: just 29% **3ab** was observed, even after 5 days (by ^{19}F NMR mole fraction). Using Zhang and Dong's method (iodine and DBU in DCM), however, ester **3ab** was obtained in quantitative yield (by ^{19}F NMR vs 4,4'-difluorobiphenyl IS) within 6 hours.



Scheme 3.3. Comparison of literature haloform reaction methodologies. ^{19}F NMR yield and mole fraction shown. Mol frac = Mole fraction.

To verify this result, the reaction was repeated on a larger scale (2.47 mmol); after work-up (following the reported procedure), 474 mg (83%) of ester **3ab** was isolated without issues (Scheme 3.4).



Scheme 3.4. Scaled-up haloform reaction for the synthesis of benzyl ester **3ab** from acetophenone **1a**. Isolated yield shown.

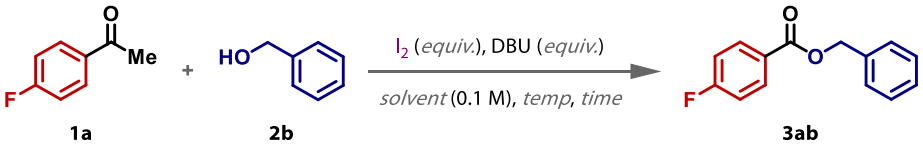
3.3 Reaction Optimisation

3.3.1 Primary Alcohols

Having found the haloform reaction conditions reported by Zhang and Dong to be highly effective for the synthesis of ester **3ab**, it appeared likely that, while the original scope was only demonstrated with acetylcyclopropanes,[66] these conditions could be applicable to a much wider range of methyl ketones. However, since no optimisation data was reported, a review of the reaction conditions was undertaken to explore the potential for improvements.

Under the literature conditions, near-complete conversion of acetophenone **1a** was achieved and 105% yield of benzyl ester **3ab** was recorded (Table 3.1, entry 1). It should be clarified that this and subsequent ^{19}F NMR yields >100% potentially resulted from an inadequate relaxation delay during spectral acquisition (this issue was overcome in subsequent studies by increasing the relaxation delay) and, in reality, they were somewhat lower. The mole fraction of **3ab** in reaction mixtures (93% in this case; also calculated by ^{19}F NMR) was therefore also considered. Complete conversion of **1a**, resulting in an increase in the yield and mole fraction of **3ab** could be achieved using modest excesses of each of the reagents (including benzyl alcohol **2b**; for convenience, reactions were carried out overnight, 16 h, and allowed to warm towards room temperature; entry 2). However, since stoichiometric **2b** was desired (but accepting that a slight excess may be necessary to maintain a maximal yield), the equivalents of **2b** used were reduced to 1.05. This had no negative affect on **3ab** production (entry 3). Aiming to similarly minimise the amounts of iodine and DBU employed, these were reduced to 3.03 and 4.04 equivalents, respectively. While the resulting 'near-quantitative' yield of **3ab** might suggest this change had no impact, this ignores the notable drop in the mole fraction of **3ab**, due to increased side-product formation (entry 4), and, in hindsight, it would have been preferable to proceed using higher concentrations of these reagents. However, this was not considered at the time, so the lower concentrations were taken forward.

Table 3.1. Influence of changes to literature haloform reaction conditions on the yield of benzyl ester **3ab**.[a]



1a + **2b** (equiv.) → **3ab**

Entry	I_2 equiv.	DBU equiv.	**2b** equiv.	Solvent	Temp	Time / h	**1a**[b] / %	**3ab** / % Yield[b]	**3ab** / % Mol frac[c]
1	3	4	1.2	DCM	0 °C	6	3	105	93
2	3.5	4.5	2	DCM	0 °C – rt	16	0	114	98
3	3.5	4.5	1.05	DCM	0 °C – rt	16	0	113	96
4	3.03	4.04	1.05	DCM	0 °C – rt	16	0	97	82
5	3.03 (Br_2)	4.04	1.05	DCM	0 °C – rt	16	0	11	10
6	3.03	4.04	1.05	Et_2O	0 °C – rt	16	65	9	12
7	3.03	4.04	1.05	DMSO	0 °C – rt	16	35	17	22
8	3.03	4.04	1.05	MeCN	0 °C – rt	16	0	77	83
9	3.03	4.04	1.05	THF	0 °C – rt	16	9	65	73
10	3.03	4.04	1.05	DCM	0 °C – rt	8	6	87	94

[a] With 0.412 mmol acetophenone **1a**. [b] Calculated by ^{19}F NMR vs 4,4'-difluorobiphenyl IS. NB: Yields >100% were possible, due to inadequate d_1 (= 1 s) used in ^{19}F NMR (see page 47 for full discussion). [c] Calculated by ^{19}F NMR, as a proportion of all signals (excluding IS). Temp = Temperature.

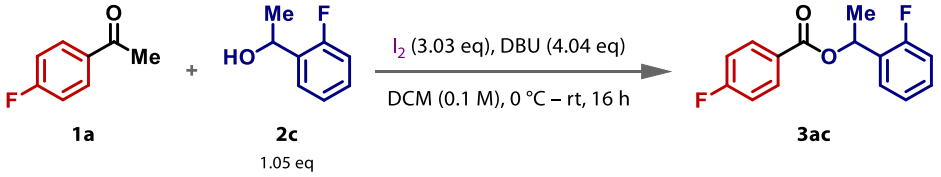
Substituting iodine with elemental bromine resulted in poor selectivity for **3ab** formation (Table 3.1, entry 5). A small solvent screen was also carried out, with the aim of finding a viable, 'greener' alternative to DCM. Low conversion of **1a** was observed in diethyl ether (entry 6), potentially due to poor iodine solubility. Conversion was also an issue in DMSO, as was selectivity (several unidentified side-products were observed; entry 7). Although the mole fraction of **3ab** obtained in acetonitrile was comparable to that in DCM, this was a result of the lower mass balances recorded in the other solvents, so the corresponding yield was considerably lower (entry 8). Moderately successfully coupling was also achieved in THF (entry 9), but, ultimately, none of the solvents tested were as effective as DCM. Under the modified conditions, incomplete conversion of **1a** was observed after 8 h and, consequently, a lower yield of ester **3ab** was obtained (entry 10) than when the reaction was continued overnight (entry 4). Since **3ab** was found to be stable under the reaction conditions overnight (99% recovery vs 4,4'-difluorobiphenyl after 16 h), this was considered a practical choice.

The key discovery of this review of the reaction conditions was that the equivalents of the alcohol coupling partner used could be reduced from 1.2 to 1.05 (a 12.5% improvement). That reactions could be performed overnight, with no need to maintain a 0 °C temperature throughout was also a practical benefit. Although slightly higher equivalents of iodine and DBU would have been beneficial, as noted, the reaction conditions selected (Table 3.1, entry 4) were, overall, considered an improvement on the literature conditions (entry 1).

3.3.2 Secondary Alcohols

While the modified haloform reaction conditions could be successfully employed in the synthesis of esters with primary alcohols (see 3.4.2 for an exploration of the reaction scope), they were much less efficient for coupling secondary alcohols. This was attributed to the higher steric hinderance of secondary alcohols reducing their nucleophilicities. Re-optimisation of the coupling conditions for use with secondary alcohols was therefore necessary.

Table 3.2. Effect of reaction temperature, concentration and reagent addition rates on ester yield in haloform coupling with secondary alcohol.[a]



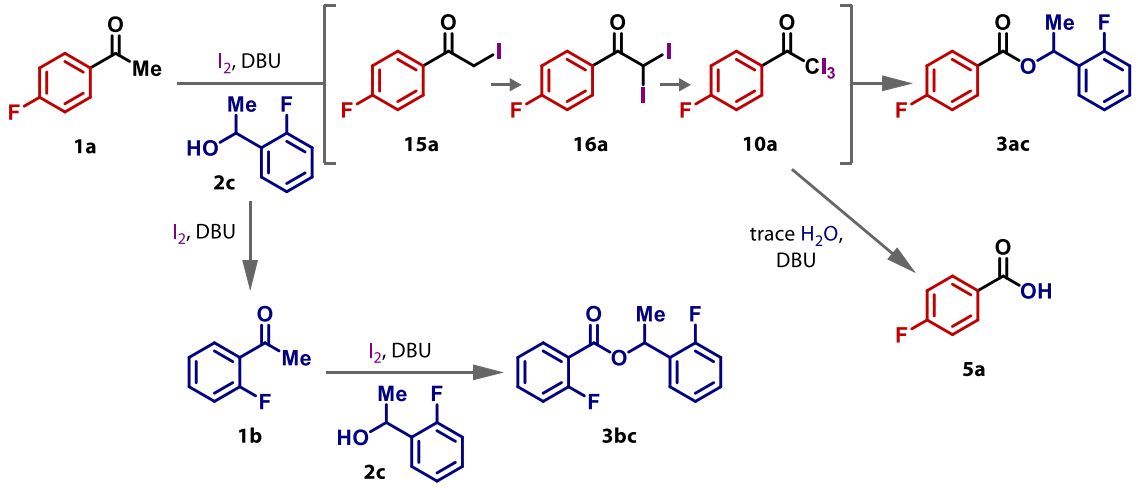
1a **2c** (1.05 eq) **3ac**

Entry	Change from conditions above	**1a**[b] / %	**15a**[b],[c] / %	**16a**[b],[c] / %	**2c**[b] / %	**1b**[b],[c] / %	**3bc**[b],[c] / %	**5a**[b],[c] / %	**3ac**[b] / %
1	–	trace	13	trace	59	0	trace	1	**32**
2	−20 °C – rt	0	0	0	52	0	0	15	**40**
3	rt	0	27	trace	60	0	trace	trace	**23**
4	0.05 M	1	19	0	58	0	trace	trace	**34**
5	0.2 M	0	12	trace	55	0	trace	1	**35**
6[d]	**2c** added over 2 h	0	9	2	72	0	trace	1	**31**
7[d]	DBU added over 5 h	98	0	0	56	52	0	trace	**trace**

[a] On 0.412 mmol scale. [b] Calculated by ^{19}F NMR vs 4,4'-difluorobiphenyl IS. [c] See Scheme 3.5 (page 50) for overview of all reaction species. [d] Controlled addition of reagent with syringe pump as DCM solution.

Fluorinated benzyl alcohol **2c** was chosen as the model secondary alcohol. While structurally similar to primary benzyl alcohol **2b**, the fluorine handle of **2c** enabled the fate of both coupling partners to be monitored. When acetophenone **1a** and alcohol **2c** were subjected to the primary alcohol coupling conditions, ester **3ac** was obtained in 32% yield (Table 3.2, entry 1). Conversion to the key triiodoacetophenone intermediate **10a** was incomplete, evidenced by unreacted iodoacetophenone **15a** in the reaction mixture (see Scheme 3.5 for an overview of side-product formation). Alternative reaction temperatures (entries 2 and 3) and concentrations (entries 4 and 5) had little impact on yield, although starting the reaction at −20 °C did result in complete conversion of acetophenone **1a** and no iodinated intermediates were observed (entry 2). Controlled addition of reagents (via syringe pump) was also explored, with addition of alcohol **2c** over 2 h having essentially no impact (entry 6; *cf.* entry 1). Addition of DBU over 5 h, however, resulted in completely different reactivity: instead of ester formation, alcohol **2c** was oxidised to acetophenone **1b** (an oxidation known to take place under similar conditions;[133] Scheme 3.5), with 98% recovery of **1a** (entry 7). Controlled addition of an iodine solution was also attempted, but was unsuccessful, due to the precipitation of

iodine (a result of the relatively low solubility of iodine in DCM combined with the slow addition rate) blocking the needle before addition was completed.

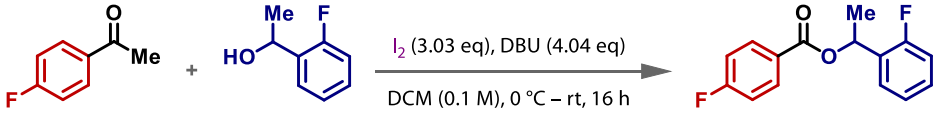


Scheme 3.5. Overview of routes to possible side-products in haloform coupling reaction.

Doubling the concentration of alcohol **2c** in the coupling (to 2 equivalents) increased the yield of ester **3ac** to 58%, but did not achieve complete conversion of acetophenone **1a**, with both iodo- **15a** and diiodoacetophenone **16a** also observed (Table 3.3, entry 2). Furthermore, a small amount of ester **3bc**, from a haloform coupling with acetophenone **1b** (via oxidation of alcohol **2c**) was observed (Scheme 3.5) and 160% **2c** (i.e. 1.6 equivalents) remained. When the iodine concentration was doubled (to 6 equivalents), alcohol oxidation (producing **1b**) was favoured over haloform coupling (entry 3), suggesting that selectivity between these competing reactions can be achieved by controlling the ratio of iodine:DBU (excess iodine favouring alcohol oxidation and vice versa). Doubling the concentrations of iodine and **2c** simultaneously simply resulted in additional alcohol oxidation (entry 4). Although complete conversion of acetophenone **1a** could be achieved by doubling the concentration of DBU (to 8 equivalents), the yield of **3ac** was not improved (entry 5), due to increased carboxylic acid **5a** formation (from competitive nucleophilic attack of triiodoacetophenone **10a** by trace water, Scheme 3.5). Doubling the concentrations of **2c** and DBU simultaneously had a similar outcome (entry 6). Simultaneously doubling the concentrations of iodine and DBU, however, resulted in a significant increase in the yield of **3ac** to 77%, although ester **3bc** and carboxylic acid **5a** side-products were also observed (entry 7). A further yield improvement to 86% was achieved by also doubling the concentration of alcohol **2c** (on top of those of iodine and DBU; entry 8). However, a substantial amount of side-product ester **3bc** (6%) was also produced, and with 85% **2c** (i.e. 0.85 equivalents) remaining, there was a practical as well as an economic impetus to limit the alcohol employed to a stoichiometric amount. Aiming to increase the effective concentrations of iodine and

DBU without using excess amounts of these reagents, controlled addition of a mixture of acetophenone **1a** and alcohol **2c** to a mixture of iodine and DBU was tested. However, this gave broadly similar results to adding **1a** and **2c** in one portion at the start of the reaction (entries 9-11, *cf.* entry 1).

Table 3.3. Effect of varying reagents, equivalents and addition rates on ester yield in haloform coupling with secondary alcohol.[a]



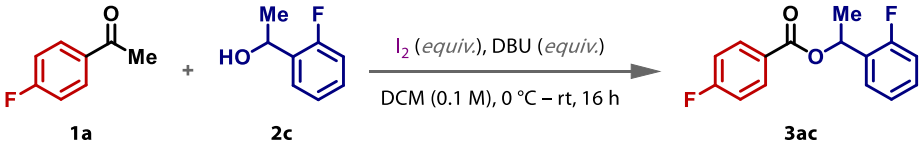
1a **2c** (1.05 eq) **3ac**

Entry	Change from conditions above	**1a**[b] / %	**15a**[b],[c] / %	**16a**[b],[c] / %	**2c**[b] / %	**1b**[b],[c] / %	**3bc**[b],[c] / %	**5a**[b],[c] / %	**3ac**[b] / %
1	–	trace	13	trace	59	0	trace	1	**32**
2	2 equiv. **2c**	2	11	1	160	0	1	1	**58**
3	6 equiv. I_2	74	14	11	4	59	0	0	**trace**
4	2 equiv. **2c**, 6 equiv. I_2	84	5	4	57	94	2	0	**1**
5	8 equiv. DBU	0	0	0	95	0	trace	12	**29**
6	2 equiv. **2c**, 8 equiv. DBU	0	0	0	157	0	0	8	**25**
7	6 equiv. I_2, 8 equiv. DBU	0	trace	0	12	0	2	11	**77**
8	6 equiv. I_2, 8 equiv. DBU, 2 equiv. **2c**	0	0	0	85	0	6	10	**86**
9[d]	**1a** and **2c** added over 2 h	1	17	trace	69	0	trace	1	**27**
10[d]	**1a** and **2c** added over 5 h	0	7	0	51	0	trace	8	**42**
11[d]	**1a** and **2c** added over 8 h	18	8	0	76	0	trace	4	**22**
12	$TBAI_3$ instead of I_2	0	15	0	70	0	1	1	**24**
13	Br_2 instead of I_2	75	N/A	N/A	18	23	1	0	**1**
14	$TBABr_3$ instead of I_2	3	N/A	N/A	24	0	2	16	**68**
15	$TBABr_3$ (6 equiv.) instead of I_2, 8 equiv. DBU	0	N/A	N/A	11	0	7	16	**69**

[a] On 0.412 mmol scale. [b] Calculated by ^{19}F NMR vs 4,4'-difluorobiphenyl IS. [c] See Scheme 3.5 (page 50) for overview of all reaction species. [d] Controlled addition of reagents with syringe pump as DCM solution.

Alternative halonium sources were also investigated. Substituting iodine with tetrabutylammonium triiodide gave a similar product distribution, but a lower yield of ester **3ac** (Table 3.3, entry 12). Bromine was much worse, resulting in predominantly alcohol oxidation (entry 13), whereas tetrabutylammonium tribromide gave a promising 68% yield of **3ac** (entry 14). This could not, however, be further increased by doubling the concentration of tribromide (as well as that of DBU; entry 15), so iodine was preferred.

Table 3.4. Finalising reaction conditions for optimal ester yield in haloform coupling with secondary alcohol.[a]



Entry	I_2 equiv.	DBU equiv.	Additive	**15a**[b],[c] / %	**2c**[b] / %	**3bc**[b],[c] / %	**5a**[b],[c] / %	**3ac**[b] / %
1	3.03	4.04	–	13	59	trace	1	**32**
2	3.3	4.4	–	7	54	trace	1	**42**
3	3.6	4.8	–	trace	39	trace	5	**57**
4	3.9	5.2	–	0	33	trace	9	**64**
5	4.2	5.6	–	0	31	trace	15	**69**
6	4.5	6	–	0	23	1	13	**75**
7	6	8	–	trace	12	2	11	**77**
8	7.5	10	–	trace	12	2	10	**79**
9[d]	4.5	6	3 Å MS	0	13	1	trace	**82**
10[d]	4.8	6.4	3 Å MS	0	11	1	trace	**85**
11[d]	5.1	6.8	3 Å MS	0	11	1	trace	**85**
12[d]	5.4	7.2	3 Å MS	0	13	1	1	**81**
13[d]	5.7	7.6	3 Å MS	trace	11	1	1	**86**
14[d]	6	8	3 Å MS	trace	11	1	2	**84**
15[d],[e]	4.8	6.4	3 Å MS	0	10	1	2	**81**

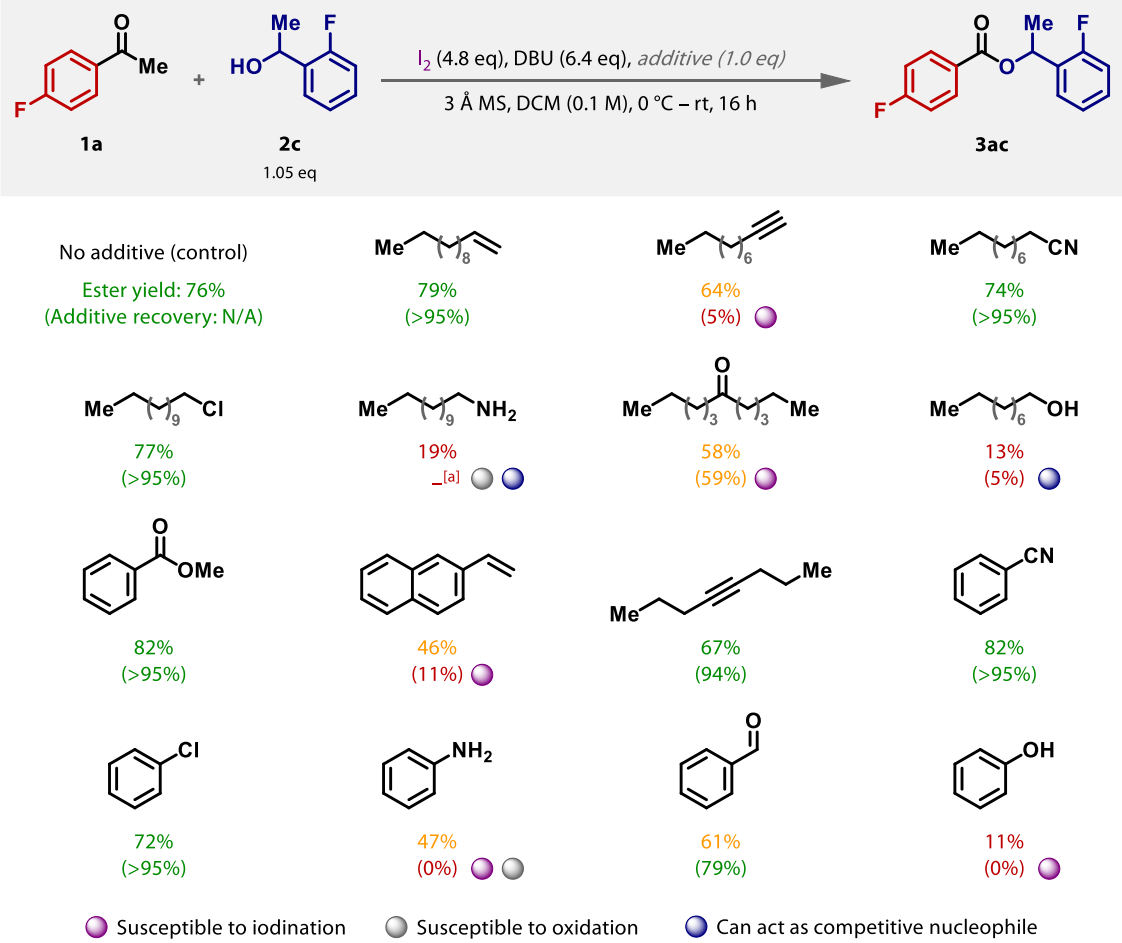
[a] On 0.412 mmol scale. [b] Calculated by ^{19}F NMR vs 4,4'-difluorobiphenyl IS. [c] See Scheme 3.5 (page 50) for overview of all reaction species. [d] 410 mg activated 3 Å molecular sieves added to reaction. [e] With 1.00 equiv. alcohol **2c**. MS = Molecular sieves.

An excess of iodine and DBU appeared to be critical to ensuring an efficient haloform coupling and there was a positive correlation between their concentrations and the yield of ester **3ac**. However, this correlation plateaued at around 4.5 and 6 equivalents of iodine and DBU, respectively (1.5× their original concentrations; Table 3.4, entries 1-6), with further increases in their concentrations resulting in only slight improvements in the yield of **3ac** (entries 7 and 8). Under these conditions (4.5 and 6 equivalents of iodine and DBU, respectively), carboxylic acid **5a** was the only major side-product and it was found that this could be all but eliminated by the addition of molecular sieves to the reaction, increasing the yield of **3ac** to 82% (entry 9). A further increase to 85% was achieved with marginally higher concentrations of iodine and DBU (4.8 and 6.4 equivalents, respectively, i.e. 1.6× their original concentrations; entry 10). Yields of **3ac** plateaued, or even declined slightly, as a result of increased carboxylic acid **5a** formation (presumably due to the introduction of more water with the additional iodine and DBU), when their concentrations were increased beyond this (entries 11-14). Finally, since there was always unreacted alcohol **2c** left at the end of the reaction, its stoichiometry was reduced to 1.00 (relative to acetophenone **1a**). However, this led to a drop in **3ac** yield to 81%, accompanied by an increase in carboxylic acid **5a** formation (due to the effective increase in the ratio of water:**2c**), ironically, resulting in essentially the same amount of unreacted **2c** remaining at the end of the reaction (entry 15). It was therefore decided to proceed with 1.05 equivalents of alcohol, maintaining methyl ketone as the limiting coupling partner.

3.4 Reaction Scope

3.4.1 Robustness Screen

With optimised conditions for haloform couplings using both primary and secondary alcohols in hand, the reaction's applicability was investigated. A robustness screen was first employed for a rapid and objective assessment of the reaction's functional group tolerance. This was carried out under the secondary alcohol coupling conditions, since these were the more challenging substrates, requiring more forcing conditions.



Scheme 3.6. Robustness screen to assess functional group tolerance. GC-MS yields and additive recoveries shown. [a] Additive recovery could not be quantified, due to co-elution with DBU.

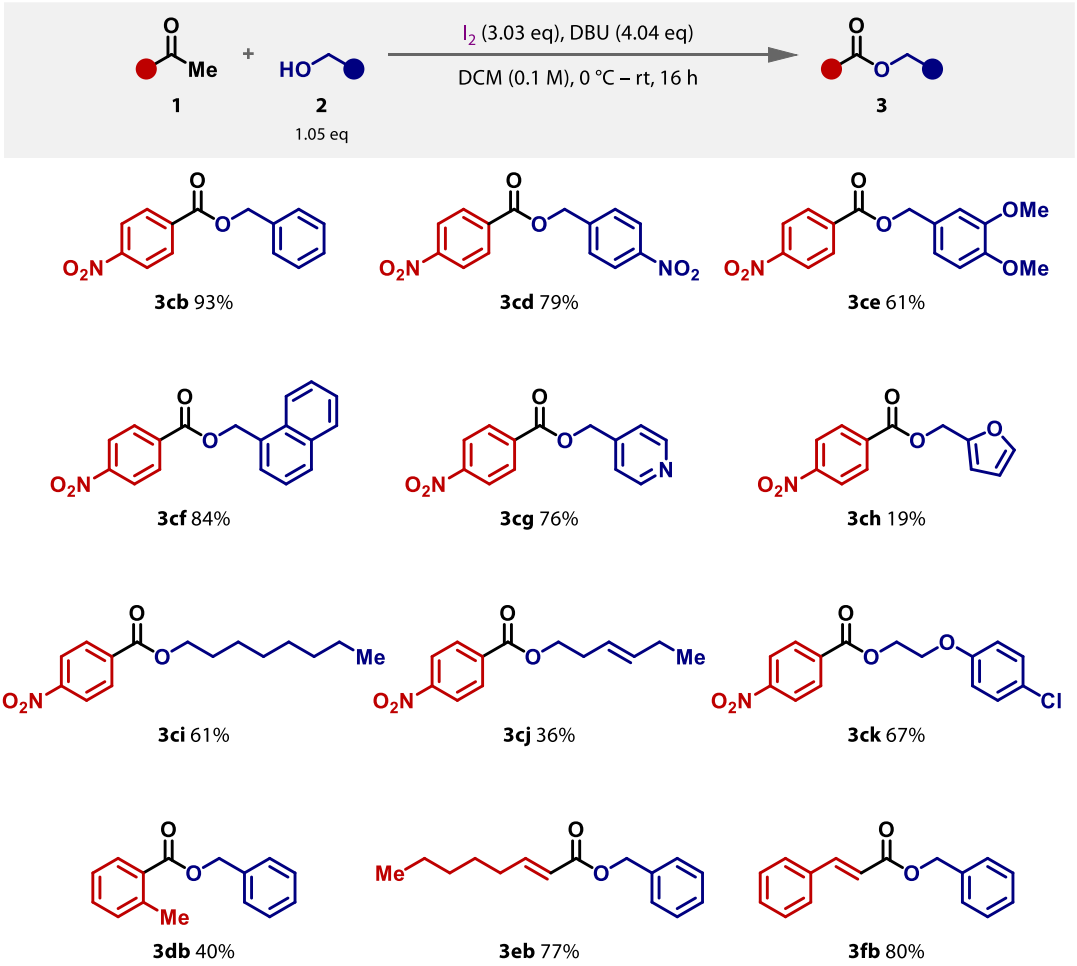
The model haloform coupling of acetophenone **1a** and secondary alcohol **2c** was therefore repeated with the addition of various functionalised additives, with their impact on reaction outcomes recorded, following a procedure reported by Glorius and co-workers.[134,135] The majority of additives had little to no negative impact on reaction yield and were themselves stable to the reaction conditions: an aliphatic alkene, nitrile and chloride, electron-poor aromatics (ester, nitrile and chloride), benzaldehyde and an internal alkyne (Scheme 3.6). Non-tolerated additives were foreseeably so and fell into

at least one of three categories: those susceptible to iodination; those susceptible to oxidation; and those which can act as competitive nucleophiles.

The additives susceptible to iodination were a terminal alkyne, ketone, conjugated alkene, and electron-rich aromatics (aniline and phenol). Recoveries of these additives were almost universally very low (6-undecanone being the only exception), but ester yields were less severely impacted, due to the excess iodine and DBU used. Aniline was also oxidised under the reaction conditions (to azobenzene), as was an aliphatic amine (to the corresponding nitrile). The aliphatic amine, being a competent nucleophile, also led to formation of an amide side-product, just as addition of an aliphatic alcohol resulted in formation of a second ester. The yield of **3ac** was very low in these cases and the additives themselves were almost completely consumed.

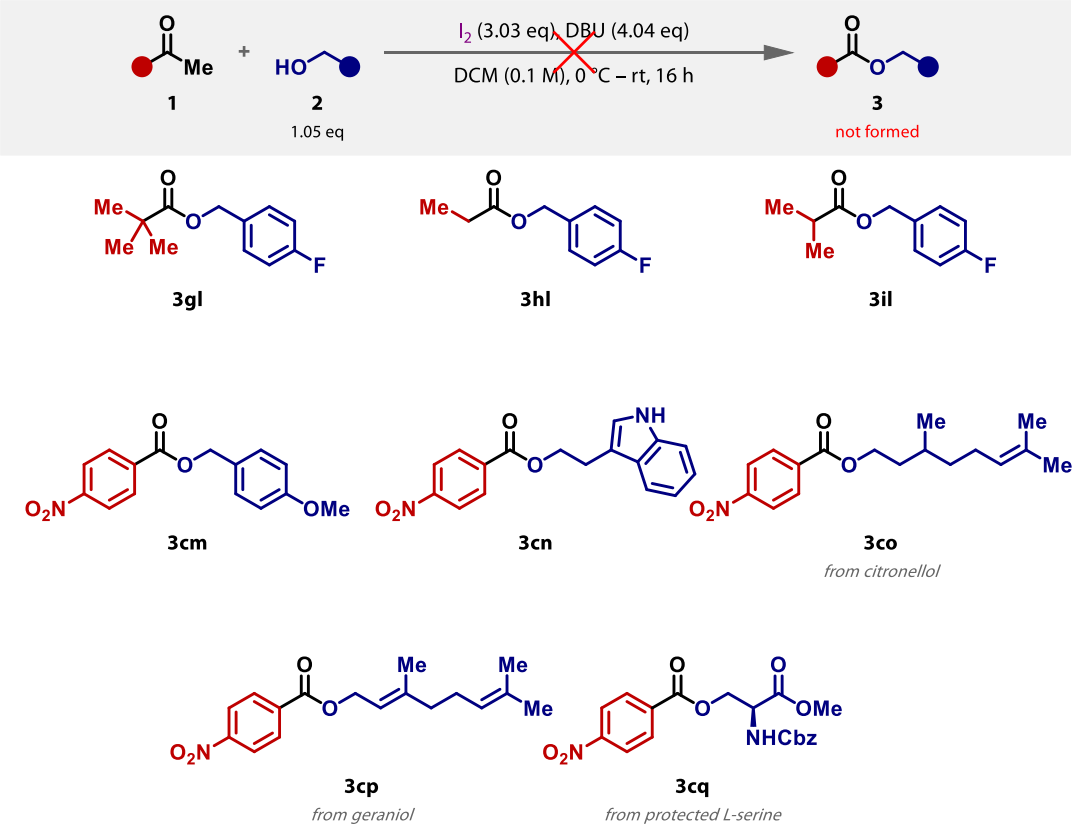
3.4.2 With Primary Alcohols

Having established the functional group tolerance of the coupling reaction, the scope of compatible substrates was explored, starting with primary alcohols (Scheme 3.7). *para*-Nitroacetophenone **1c** was employed as the methyl ketone coupling partner, as this enabled higher yields than the model acetophenone **1a**, accentuating the differences between alcohols. Neutral (**3cb**), electron-poor (**3cd**), electron-rich (**3ce**) and conjugated (**3cf**) primary benzyl alcohols were all coupled in good yields. Both *N*- and *O*-heterocyclic alcohols were also tolerated (**3cg**-**ch**), as were aliphatic primary alcohols (**3ci**-**ck**). Benzyl alcohol **2b** was also successfully coupled with sterically-hindered *ortho*-methylacetophenone (**3db**) and two α,β-unsaturated methyl ketones (**3eb**-**fb**).



Scheme 3.7. Scope of haloform coupling with primary alcohols. Isolated yields shown. Esters **3ce**, **3cf**, **3cg**, **3ch**, **3cj** and **3ck** synthesised by David Heard.

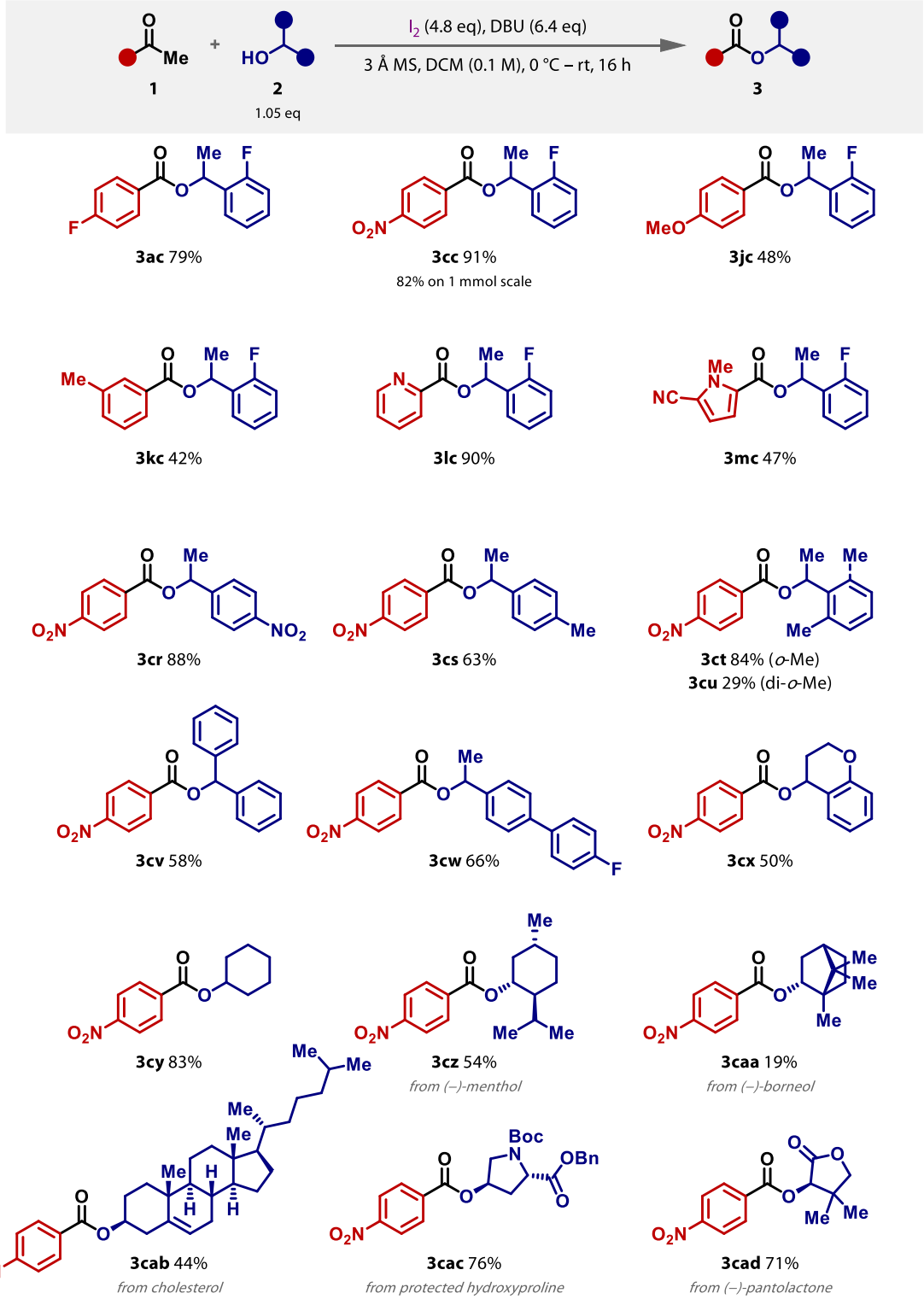
Not all substrates tested were compatible. *tert*-Butyl methyl ketone was too sterically-encumbered (Scheme 3.8, **3gl**) and couplings with less hindered alkyl methyl ketones were also unsuccessful, likely due to unselective α-iodination (since they contain two competing positions for α-deprotonation; **3hl**-**il**). *para*-Methoxy benzyl alcohol was too electron-rich and suffered aromatic iodination (**3cm**). Several other, mainly natural product, primary alcohols were also tested, but were found to be incompatible with the reaction conditions (**3cn**-**cq**).



Scheme 3.8. Esters which could not be synthesised by a haloform coupling under primary alcohol conditions. Synthesis of esters **3gl**, **3cn**, **3co**, **3cp** and **3cq** attempted by David Heard. Cbz = Carbobenzyloxy.

3.4.3 With Secondary Alcohols

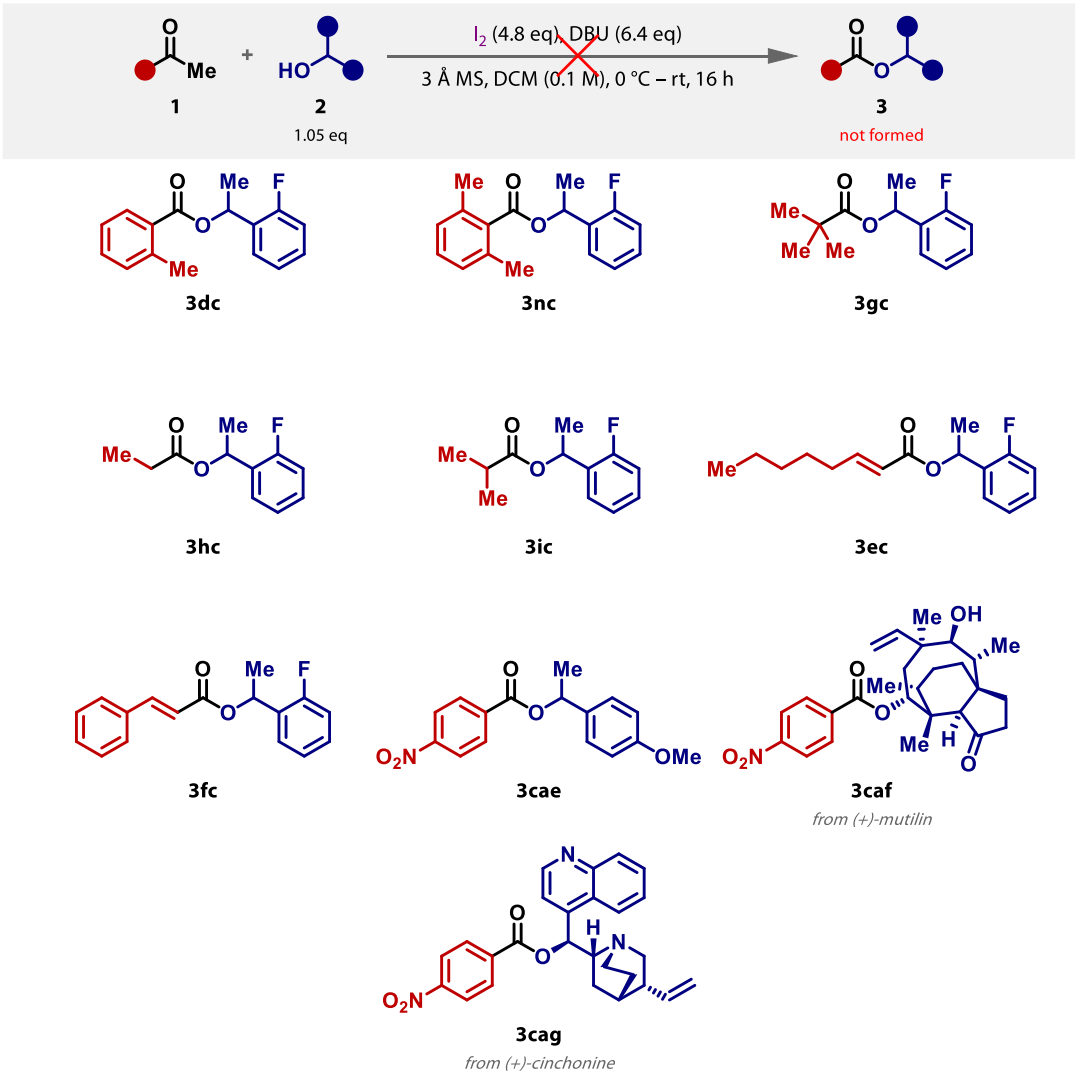
The exploration of the coupling reaction's scope with secondary alcohols was more extensive, with an emphasis on finding the steric and electronic limitations of viable substrates (Scheme 3.9). Acetophenones with a range of electronic properties were tolerated, with a trend of higher yields with more electron-rich acetophenones (**3ac**, **3cc** and **3jc**). Although significantly sterically-hindered acetophenones were not compatible (see Scheme 3.10), *meta*-substituted acetophenone **1k** was successfully esterified (**3kc**). As well as acetophenones, *N*-heterocyclic methyl ketones were tolerated, as demonstrated by pyridine- and pyrrole-based substrates (**3lc**-**mc**). To demonstrate the coupling's scalability, the synthesis of **3cc** was repeated on a 1 mmol scale (0.4 mmol scale originally), resulting in only a small drop in yield (91% to 82%).



Scheme 3.9. Scope of haloform coupling with secondary alcohols. Isolated yields shown. Esters **3mc**, **3cv**, **3cw**, **3cx**, **3cz**, **3caa**, **3cab**, **3cac** and **3cad** synthesised by David Heard. Boc = *tert*-Butoxycarbonyl.

Both more electron-poor (Scheme 3.9, **3cr**) and electron-rich (**3cs**) benzyl alcohols (than the model alcohol **2c**) were compatible, as were sterically-hindered benzyl alcohols (**3ct**-**cu**). Similarly, diphenylmethanol (**3cv**), an alcohol with extended conjugation (**3cw**) and a bicyclic benzyl alcohol (**3cx**) were all coupled in good yields. Aliphatic secondary

alcohols were also tested. Steric hinderance around the alcohol moiety led to less efficient coupling, evidenced by the successively lower yields of the esters derived from cyclohexanol (**3cy**) and the natural products (−)-menthol (**3cz**) and (−)-borneol (**3caa**). A reasonable yield was also obtained with the large natural product cholesterol (**3cab**). A protected hydroxyproline (**3cac**) and (−)-pantolactone (**3cad**) were also well-tolerated, demonstrating the compatibility of *N*- and *O*-heterocyclic alcohols, respectively. The latter two examples also highlight the stability of other (non-ketone) carbonyl functionalities (lactone, carbamate, ester) to the coupling conditions.



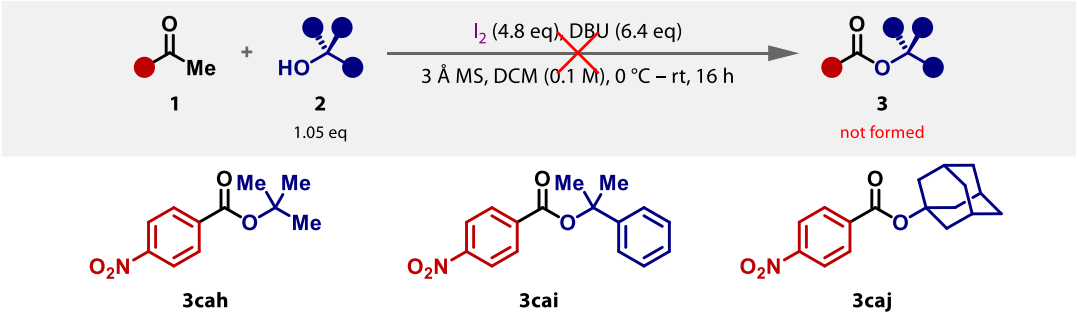
Scheme 3.10. Esters which could not be synthesised by a haloform coupling under secondary alcohol conditions. Synthesis of esters **3gc**, **3ec**, **3fc**, **3caf** and **3cag** attempted by David Heard.

Unsurprisingly,[7] *ortho*-substituted acetophenones were too sterically-hindered (Scheme 3.10, **3dc** and **3nc**), as was *tert*-butyl methyl ketone (**3gc**). As observed under the primary alcohol coupling conditions, less bulky alkyl methyl ketones were also incompatible, presumably due to a lack of control during iodination (**3hc**-**ic**). In contrast to under the primary alcohol conditions, however, α,β-unsaturated methyl ketones were

not tolerated, likely as a result of the higher concentrations of iodine and DBU (**3ec**-**fc**). Several alcohols also proved problematic. As with its primary alcohol analogue, aromatic iodination issues were encountered with a *para*-methoxy substituted benzyl alcohol (**3cae**), and the natural products (+)-mutilin and (+)-cinchonine could not be coupled (**3caf**-**cag**), possibly owing to a combination of steric hinderance and incompatible functionalities on the substrates.

3.4.4 With Tertiary Alcohols

Coupling acetophenone **1c** with tertiary alcohols (under the secondary alcohol conditions) was also attempted, but was unsuccessful (Scheme 3.11). This was almost certainly as a consequence of steric hinderance and could be anticipated, given that *tert*-butanol has been used as a reaction solvent in the haloform synthesis of carboxylic acids.[35] This was therefore not pursued further.

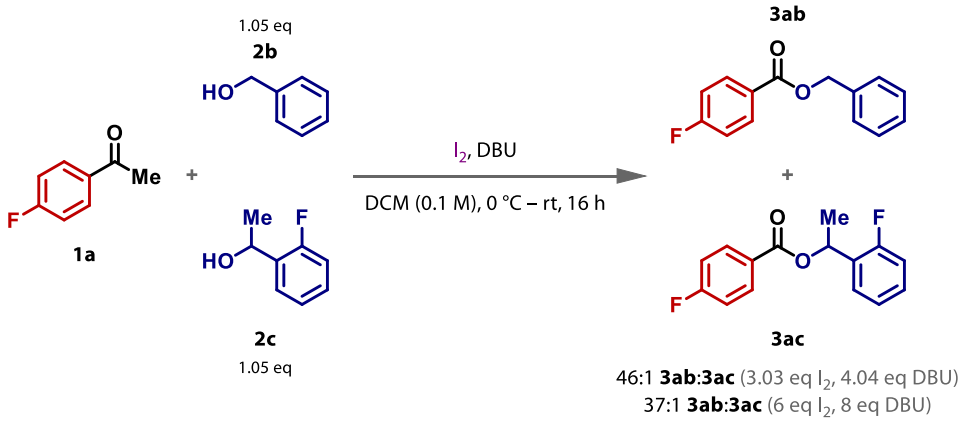


Scheme 3.11. Esters could not be synthesised by a haloform coupling with tertiary alcohols. Synthesis of ester **3caj** attempted by David Heard.

3.5 Mechanistic Insight

3.5.1 Alcohol Reactivity Differences

The difference in reactivity observed between primary and secondary alcohols (near-quantitative ^{19}F NMR yield of **3ab** with primary benzyl alcohol **2b** versus just 32% **3ac** with secondary benzyl alcohol **2c** under the same conditions) was probed in a competition experiment. Under the primary alcohol coupling conditions (3.03 equivalents iodine, 4.04 equivalents DBU), a 46:1 ratio of **3ab**:**3ac** was obtained, dropping to 37:1 with excess reagents (6 and 8 equivalents of iodine and DBU, respectively; Scheme 3.12). Preferential formation of **3ab** suggested that the relative nucleophilicities of the alcohols had a significant influence on the product ratio (the primary alcohol **2b** being the less sterically-hindered of the two electronically-similar alcohols).



Scheme 3.12. Competition experiment between primary and secondary alcohols. Product ratios shown calculated by ^{19}F NMR.

This hypothesis was supported by ^{19}F NMR-monitored reactions between trichloroacetophenone **6a** (as a proxy for the non-isolable triiodoacetophenone **10a**) and the alcohols, which enabled the rate of the ester-forming, substitution step of the haloform coupling to be studied in isolation. On addition of DBU to a mixture containing primary alcohol **2b**, complete conversion of **6a** to ester **3ab** was effected within 25 s (when the first spectrum was acquired), whereas with secondary alcohol **2c** the substitution was significantly slower (Figure 3.1).

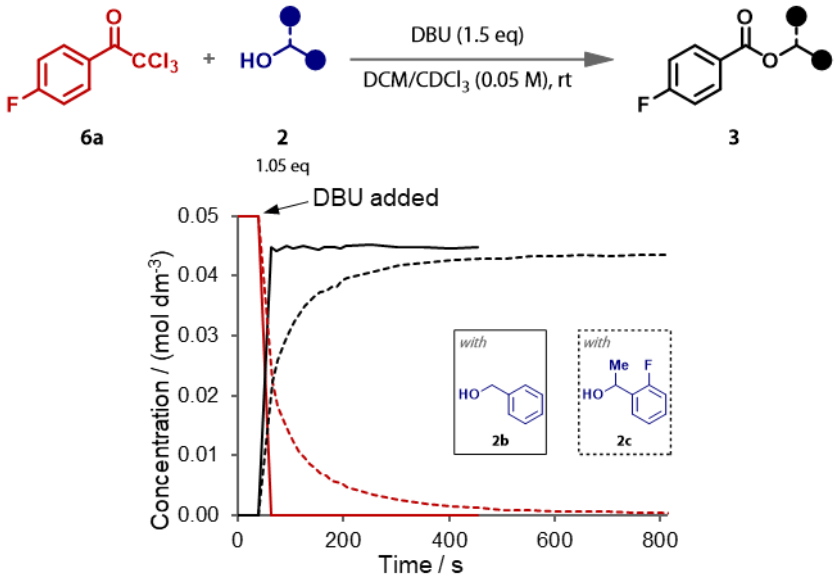


Figure 3.1. ^{19}F NMR-monitored substitution reactions with primary and secondary alcohols.

It seems likely, therefore, that reduced nucleophilicity, due to increased steric hinderance, is responsible for the lower reactivities of secondary alcohols in the overall transformation. This does not, however, explain the low yield of **3ac** obtained under primary alcohol conditions (see Table 3.2, entry 1), since alcohol nucleophilicity 'should' only affect the rate, rather than the extent, of reactions (i.e. only the kinetics) in the absence of competing nucleophiles.

3.5.2 Kinetics Studies

To investigate this further, the reactions of acetophenone **1a** with primary alcohol **2b** and secondary alcohol **2c** were monitored (by ^{19}F NMR). With primary alcohol **2b**, the rate of ester formation was approximately equal to that of acetophenone consumption (at least early in the reaction; Figure 3.2A). With secondary alcohol **2c**, the rate of ester formation was significantly lower than that of acetophenone consumption (Figure 3.2B), as expected based on the previous conclusions about the relative nucleophilicities of the alcohols. Less predictable, however, was the observation of all three iodinated acetophenone intermediates, i.e. not just triiodoacetophenone **10a** (iodoacetophenone **15a** and diiodoacetophenone **16a** were confirmed by comparison to authentic samples; triiodoacetophenone **10a**, which could not be synthesised and isolated, was assumed based on the signals' ^{19}F NMR shifts and their occurrences). Only low concentrations of intermediates were observed with primary alcohol **2b** and one might therefore have expected with secondary alcohol **2c**, based on the difference in their nucleophilic substitution rates, to observe an initial accumulation of triiodoacetophenone **10a**, the concentration of which would then decrease over time, as it was converted to ester **3ac**. That this was not the case suggests that the iodinated intermediates were in equilibrium. This was confirmed by a reaction in which no alcohol was added, where, since ester formation was not possible, the equilibrium concentrations of each of the intermediates, once established, remained constant (Figure 3.2C).

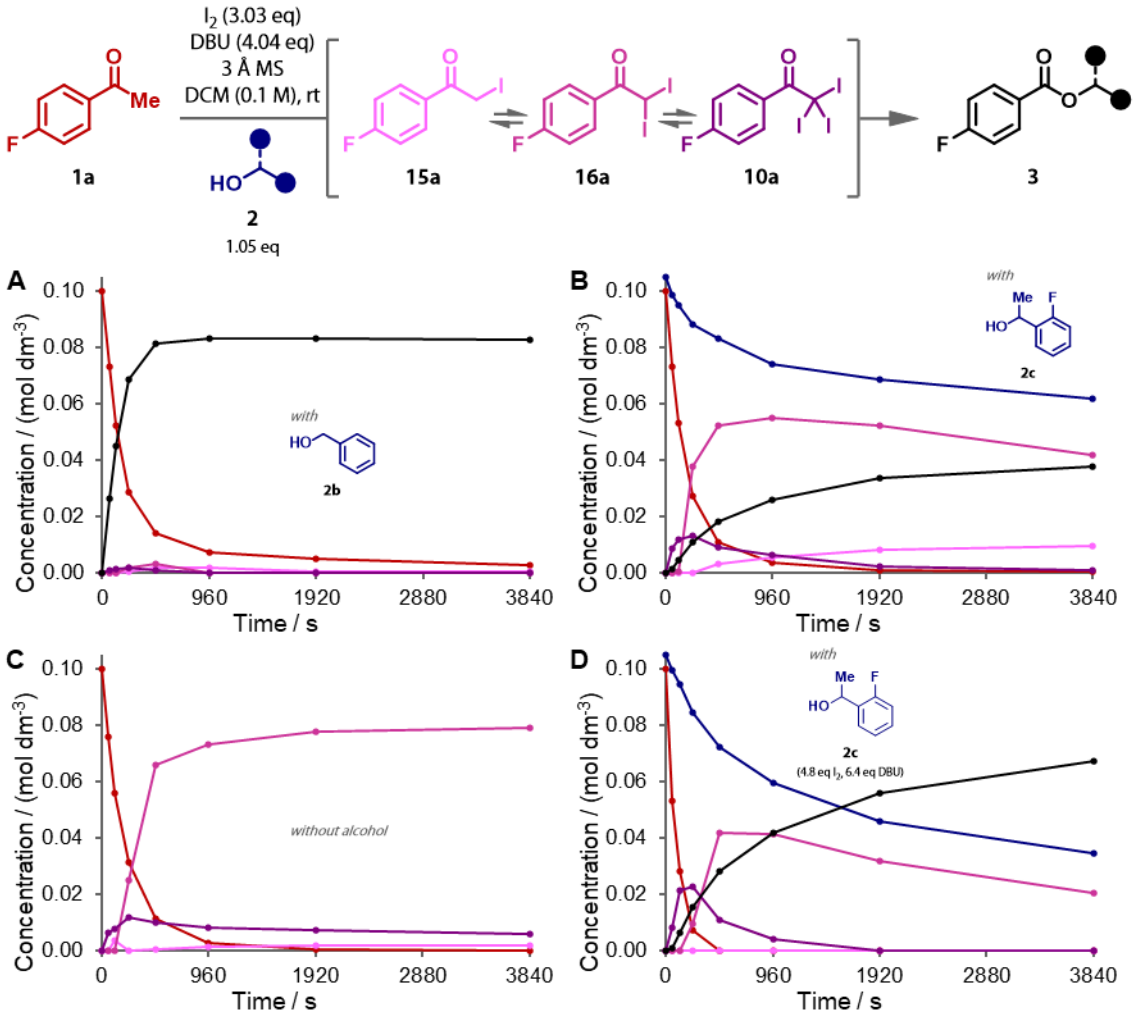
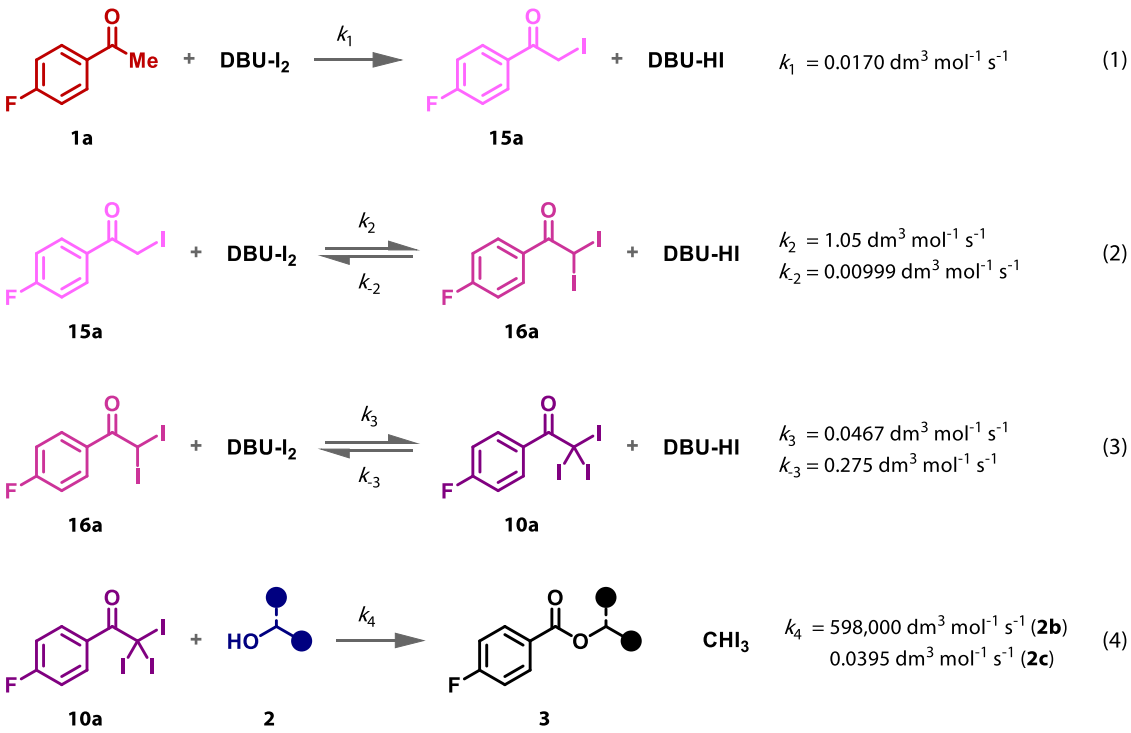


Figure 3.2. ^{19}F NMR-monitored haloform couplings with: **A)** primary alcohol **2b**; **B)** secondary alcohol **2c**; **C)** no alcohol; and **D)** secondary alcohol **2c** under optimised secondary alcohol conditions.

The other key observation was that ester formation with secondary alcohol **2c** plateaued as the reaction progressed (Figure 3.2B), at a level significantly below that observed with primary alcohol **2b** (Figure 3.2A). This trend correlated with the low yield previously achieved under these conditions (see Table 3.2, entry 1) and was assumed to be a result of the much slower nucleophilic substitution step with **2c**. Under the optimised secondary alcohol conditions (4.8 and 6.4 equivalents of iodine and DBU, respectively), the yield plateauing was overcome, possibly simply because the rates of the forward reactions (dependent on iodine and DBU) were increased, resulting in a higher concentration of triiodoacetophenone **10a** and therefore an increased rate of ester formation (Figure 3.2D).

A simplified kinetics-based model of the haloform coupling was created and fit to the ^{19}F NMR monitoring data using COPASI, an open-source application for reaction simulation and analysis.[136] This model was based on four elementary reactions:



Scheme 3.13. Elementary reactions used in the COPASI model and calculated rate constants.

The 'DBU-I_2' term in these reactions represents a DBU-iodine complex, which, based on shifting signals in the ^{1}H NMR spectrum of DBU on addition of iodine, is believed to form in solution and is proposed to be the active iodination agent. Incidentally, this might explain why very low selectivity for haloform coupling was observed when the concentration of iodine exceeded that of DBU (see Table 3.2, entry 7, and Table 3.3, entries 9 and 10), since free iodine may promote alcohol oxidation. The concentration of the DBU-iodine complex was inputted as that of iodine (i.e. the limiting reagent). Enolisation and iodination were modelled as a single elementary reaction, since reactions were monitored by analysing acid-quenched aliquots, such that enolates would have been protonated. The final elementary reaction (reaction 4) was also simplified by disregarding the need for alcohol deprotonation. Reaction 1 was modelled as irreversible, with k_1 (shown in Scheme 3.13) calculated from the initial rate of acetophenone **1a** consumption in the reaction without alcohol (Figure 3.2C). Reactions 2 and 3 were assumed to be reversible, such that an equilibrium between the iodinated intermediates could be established. Reaction 4 was modelled as irreversible, since the substitution step involves C–C bond cleavage, which was considered unlikely to be in equilibrium.

The rate constants in reactions 2 and 3 were calculated by the software for the best fit of the model to the experimental concentration data in the alcohol-free reaction (Figure 3.2C). Of the resulting constants (shown in Scheme 3.13), k_2 was the largest and was two orders of magnitude greater than k_1. This means that, once formed,

iodoacetophenone **15a** is rapidly converted to diiodoacetophenone **16a** and, since k_{-2} is small, the position of equilibrium in reaction 2 lies significantly towards **16a**. Since k_3 is an order of magnitude smaller than k_{-3}, the equilibrium in reaction 3 also lies towards **16a**, explaining why this is the dominant species at equilibrium. The rate constant in reaction 4 is dependent on the alcohol coupling partner, so this was calculated separately for primary alcohol **2b** and secondary alcohol **2c**. In each case, the other rate constants were held constant, with k_4 calculated for the best fit of the model to the experimental data (Figure 3.2A and B). The value of k_4 calculated with **2b** was considerably larger (seven orders of magnitude) than that with **2c**, reflecting the difference in the nucleophilicities of the alcohols.

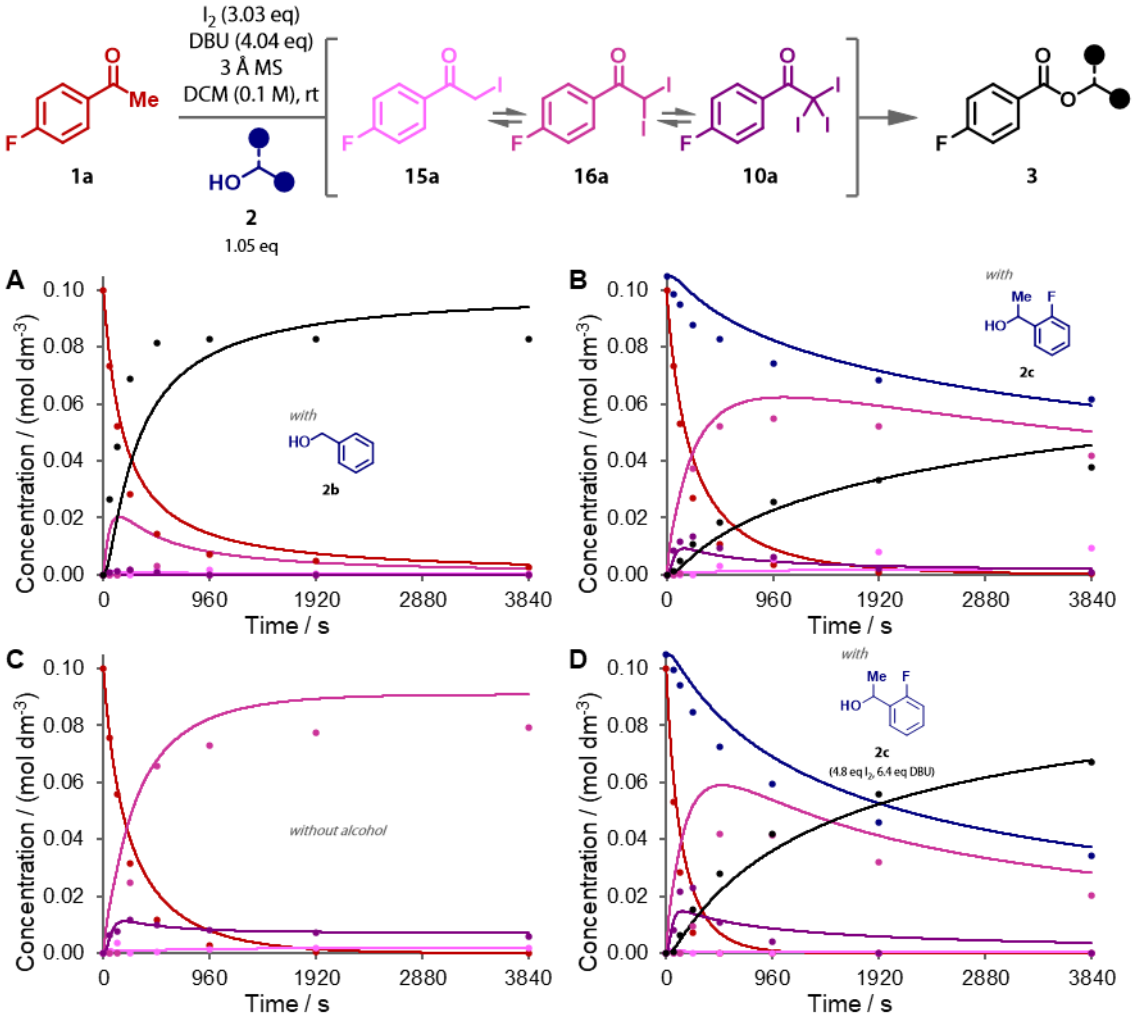


Figure 3.3. Comparison of COPASI predictions (lines) with experimentally-recorded (balls) concentrations of species in haloform couplings with: **A)** primary alcohol **2b**; **B)** secondary alcohol **2c**; **C)** no alcohol; and **D)** secondary alcohol **2c** under optimised secondary alcohol conditions.

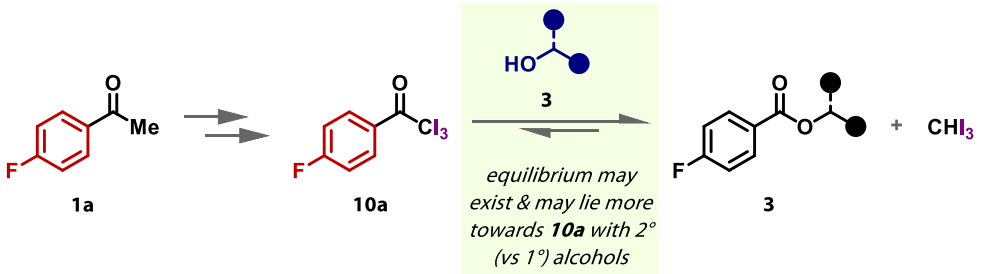
Crudely, the model fits the experimental data for the reactions with primary alcohol **2b** (Figure 3.3A), secondary alcohol **2c** (Figure 3.3B) and without alcohol (Figure 3.3C) fairly well, with a handful of exceptions (e.g. poor fits to experimental diiodoacetophenone **16a**

concentrations in Figure 3.3A and iodoacetophenone **15a** concentrations in Figure 3.3B). The model also maintained a reasonable fit when the starting concentration of the DBU-iodine complex was increased to 0.48 mmol dm^{-3} to reflect the situation under the optimised secondary alcohol conditions (Figure 3.3D). Crucially though, the model failed to predict the stalling production of ester **3ac** under the primary alcohol conditions (Figure 3.3C), suggesting that this was not simply a consequence of the equilibria between the iodinated intermediates, as initially speculated.

3.5.3 Investigation into Reaction Attenuation with Secondary Alcohol

The reason behind the plateauing yield effect observed with secondary alcohol **2c** under primary alcohol coupling conditions (Figure 3.2B) remained unclear. Resolving this was essential to understanding the need for additional iodine and DBU under the optimised secondary alcohol conditions to overcome the plateau and enable high yields to be obtained (with secondary alcohols; see 3.4.3). The COPASI model created to fit the experimental data failed to predict that the ester concentration would stall in this manner, suggesting that the explanation lay in a process which was either not considered or modelled incorrectly.

Since the concentrations of triiodoacetophenone **10a**, alcohol **2** and ester **3** plateaued as the reaction progressed (see Figure 3.2B), the existence of an equilibrium between these species, which lay more towards **10a** with secondary alcohols (than primary) was considered (Scheme 3.14). This would mean that ester formation was not irreversible, as originally modelled. The COPASI model was therefore adjusted, such that reaction 4 (see Scheme 3.13) was reversible, but this did not improve the model's fit to the plateauing ester concentration, since the rate constant of the reverse reaction (k_{-4}) was determined to be extremely small. Nevertheless, reversibility of the ester-forming, substitution step remained a compelling theory, so it was also investigated experimentally.



Scheme 3.14. Hypothesised equilibrium between triiodoacetophenone **10a** and ester **3**.

The impact of adding a stoichiometric amount of iodoform to a coupling between acetophenone **1a** and secondary alcohol **2c** under the primary alcohol conditions was studied first. If the proposed equilibrium between triiodoacetophenone **10a** and ester **3ac** existed, addition of iodoform (the by-product of ester formation) should shift the position of equilibrium towards **10a**. One would therefore expect to see the concentration of ester **3ac** plateau at a lower level than in the absence of additional iodoform, which was indeed observed (Figure 3.4A, *cf.* Figure 3.4B). However, no accompanying increase in the concentration of triiodoacetophenone **10a** (or iodo- **15a** and diiodoacetophenone **16a**, since these species are in equilibrium) was observed. Instead, the positions of the equilibria between the iodinated intermediates appeared to shift. These steps are not dependent on iodoform, suggesting that another factor, such as the introduction of additional moisture by addition of insufficiently-dry iodoform, was responsible for the observed changes. Therefore, while addition of iodoform did affect the reaction, it is not clear that this was as a result of shifting the proposed triiodomethyl ketone-ester equilibrium.

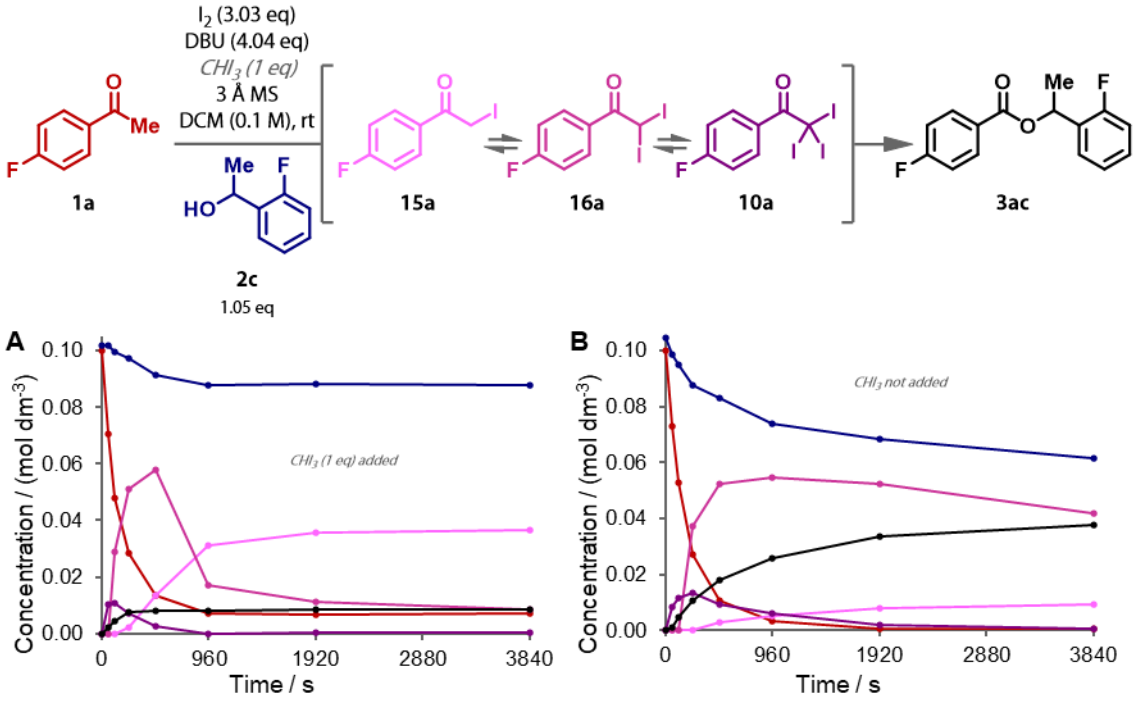
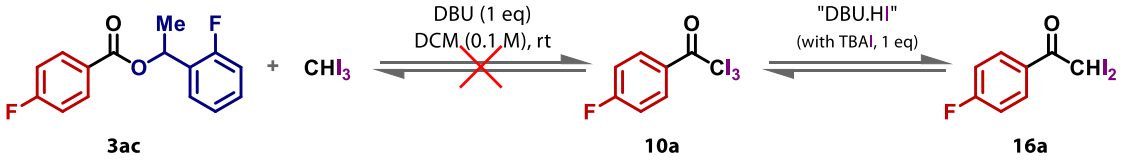


Figure 3.4. Comparison between: **A)** Haloform coupling with 1 equivalent of iodoform added; and **B)** Standard reaction.

The reversibility of the ester-forming step was also probed directly. Ester **3ac** was stirred in a mixture of iodoform and DBU, with the idea that this could enable nucleophilic attack of iodoform on **3ac** and establish an equilibrium between **3ac** and triiodoacetophenone **10a** (Scheme 3.15). An iodide source (TBAI) was also added in attempt to facilitate formation of diiodoacetophenone **16a**, since the equilibrium between **16a** and **10a** was

shown to lie towards the former under the haloform coupling conditions (Figure 3.2B). However, complete recovery of ester **3ac** was observed (by ^{19}F NMR) after 1 h, with no traces of **10a** or **16a** detected. Even if the proposed equilibrium lay significantly toward **3ac** under these conditions, a drop in the recovery of **3ac** would be expected, due to carboxylic acid formation (by attack of trace water on **10a**). That this did not occur suggests that no such equilibrium was established.



Scheme 3.15. Unsuccessful equilibration of ester **3ac** with triiodomethyl ketone **10a**.

A computational assessment of the reversibility of ester formation was also made. Using DFT, energies were calculated for a simple model reaction between triiodoacetophenone **10o** and methoxide (primary alcohol) or isopropoxide (secondary alcohol; Figure 3.5). In each case, the tetrahedral intermediate **17** formed was significantly lower in energy than the reactants. The esters were even lower in energy, resulting in equilibrium constants of 1.5×10^{26} and 4.1×10^{25} for ester formation (from **10o**) with methoxide and isopropoxide, respectively, and meaning that ester formation is predicted to be effectively irreversible.

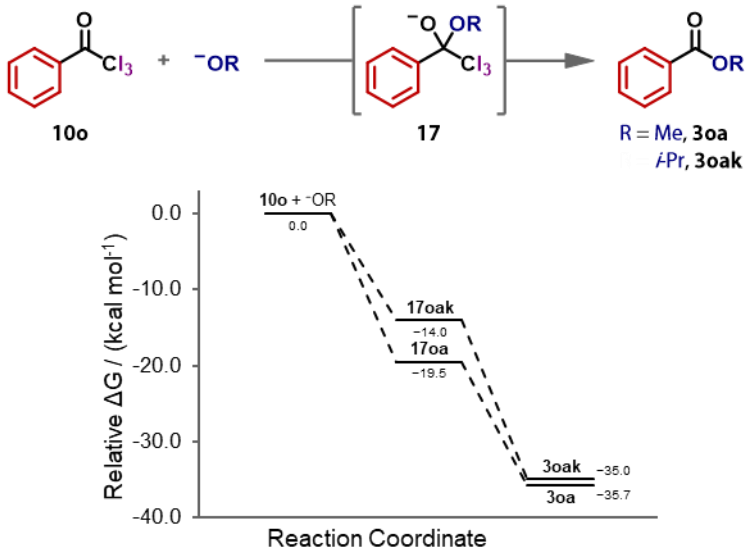
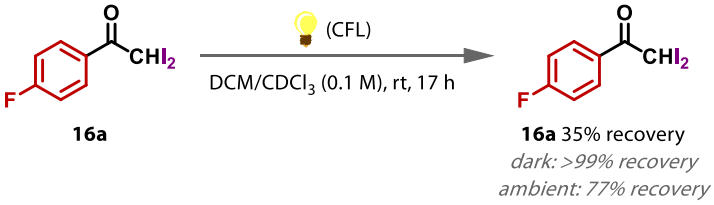


Figure 3.5. DFT-calculated energies for nucleophilic attack of methoxide and isopropoxide on acetophenone **10o**. Calculations performed by Stephen Sweeting.

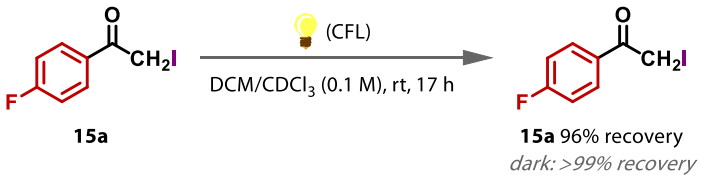
While, in isolation, none of these experiments provide definitive proof that the ester-forming, substitution step of the haloform coupling is irreversible, considered collectively, this is a reasonable conclusion.

During the course of these investigations, it became apparent that diiodoacetophenone **16a** was light-sensitive. This was confirmed by irradiation of a solution of **16a** with a compact fluorescent lamp (CFL): after irradiation overnight, just 35% of **16a** was recovered (by ^{19}F NMR), compared to >99% recovery in a sample that was protected from light (Scheme 3.16). Notably, decomposition was also observed under normal, 'ambient' laboratory lighting, where recovery of **16a** was just 77% overnight. Of the many decomposition products observed by ^{19}F NMR, a small amount (2%) of iodoacetophenone **15a** was the only compound which could be identified. This indicates that decomposition likely occurs via photolytic cleavage of one of the relatively weak C–I bonds.[137–139]



Scheme 3.16. Photodecomposition of diiodoacetophenone **16a**.

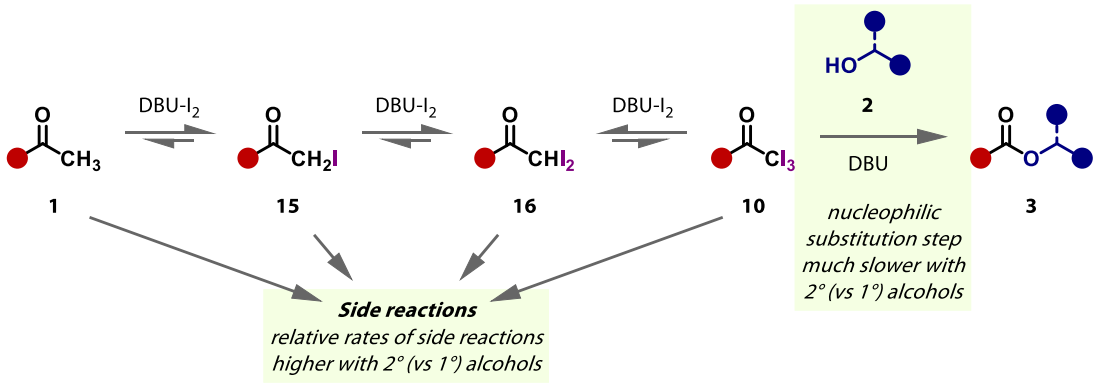
Iodoacetophenone **15a** proved to be more stable: 96% recovery of **15a** was recorded after irradiation overnight (Scheme 3.17), reflecting the relative strength of the C–I bond in **15a** compared to those in **16a**. Extrapolation of this trend suggests that triiodoacetophenone **10a** would be the most light-sensitive intermediate. Considering also that photolysis of diiodoacetophenone **16a** was observed under the ambient lighting conditions in which the haloform couplings were typically performed, it is conceivable that photolytic decomposition of the iodinated intermediates could have had a detrimental effect on reaction yields.



Scheme 3.17. Photodecomposition of iodoacetophenone **15a**.

This discovery led to the formulation of the current hypothesis for explaining the stunted formation of esters with secondary alcohols under primary alcohol coupling conditions and the mechanism by which the optimised conditions overcome this. The explanation is based on the mechanistic insights gleaned and the impact that side-reactions, both photolytic deiodination and other unidentified reactions (e.g. deiodination of iodinated intermediates by iodoform may be possible, based on analogous findings in the bromoform reaction[140]), could be having on the haloform coupling.

The key reactivity difference between primary and secondary alcohols is their differing nucleophilicities, arising from the greater steric bulk of the latter (see 3.5.1). While in a perfect reaction system with no side-reactions, this would only affect the rate of ester formation, not the yields achievable with secondary alcohols, in reality, side-reactions do occur, the rates of which are independent of alcohol nucleophilicity (unless they involve the alcohol). Since the rate of the ester-forming, substitution step of the reaction is much lower with secondary alcohols (than with primary alcohols), the relative rates of side-reactions are therefore much higher (Scheme 3.18). Non-productive consumption of reactants (coupling partners, intermediates) and/or reagents (iodine, DBU) reduces the amount available for ester formation, limiting the ester yield and ultimately producing the 'unexpected' plateauing effect observed (Figure 3.2B). With primary alcohols, because the substitution step is much faster, the reaction reaches completion more quickly (see Figure 3.2A) and, since ester formation is irreversible (see above in 3.5.3), there is less opportunity for side-reactions to affect yields.



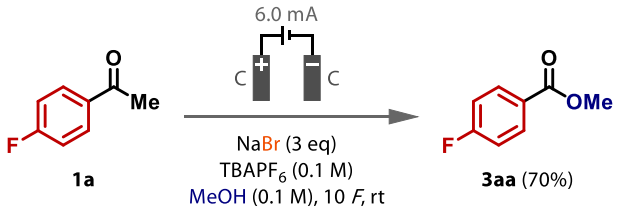
Scheme 3.18. Mechanism of haloform coupling, showing impact of alcohol nucleophilicity on side-reaction rates.

Increasing the concentrations of iodine and DBU (as under the optimised secondary alcohol conditions) has two effects. Firstly, the rates of the iodination steps are increased (the equilibria in Scheme 3.18 are shifted to the right), resulting in a higher equilibrium concentration of triiodoacetophenone **10**, which, in turn, increases the rate of the ester-forming step, reducing the relative rates of any side-reactions not dependent on iodine and DBU (e.g. photolytic deiodination). Secondly, it ensures that sufficient iodine and DBU are present to enable complete conversion to triiodoacetophenone **10**, making up for any net loss of these reagents to other processes (i.e. side-reactions). Combined these effects explain how the issue of stalling ester formation is overcome under the optimised secondary alcohol conditions, enabling higher yields to be achieved.

Chapter 4: Conclusions

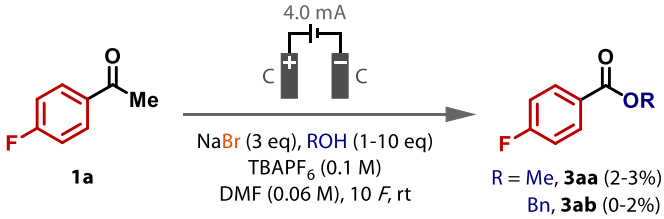
4.1 Electrochemical Haloform Coupling

Following the method reported by Nishiguchi and co-workers,[112] 4'-fluoroacetophenone **1a** was converted to methyl ester **3aa** via an electrochemical haloform reaction in methanol **2a** (Scheme 4.1). The 70% yield achieved by passing 10 *F* (up to 80% was possible with more charge) is comparable to those reported by Nishiguchi for similar acetophenone substrates.



Scheme 4.1. Electrochemical haloform reaction with acetophenone **1a** in methanol yielded methyl ester **3aa**. ^{19}F NMR yield shown.

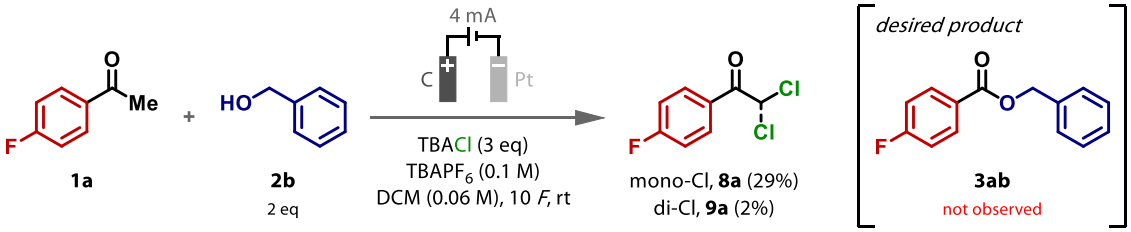
This result could not, however, be translated into a method requiring only stoichiometric alcohol. Under as similar electrolysis conditions as possible, but with 1-10 equivalents of methanol **2a** or benzyl alcohol **2b** in DMF, only very low yields of the corresponding esters **3** could be achieved (Scheme 4.2). Formation of two unknown, seemingly structurally-related species dominated with both **2a** and **2b**, as well as in the absence of any alcohol. These unknown species could not be identified and, since severe cathode degradation was also an issue in DMF, an alternative approach was needed.



Scheme 4.2. Low-yielding electrochemical haloform coupling between acetophenone **1a** and methanol or benzyl alcohol in DMF. ^{19}F NMR yields shown.

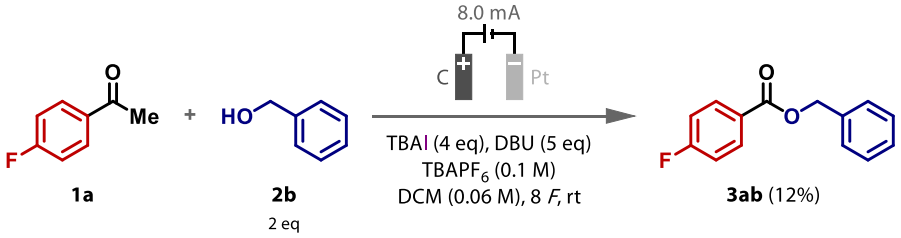
The focus shifted to identifying the optimal solvent-oxidant (i.e. halonium species) combination. DCM was identified as a promising solvent, having previously been employed in ester-forming haloform reactions,[66] and chloride oxidation was chosen (in preference to iodide or bromide oxidation), since chloronium (Cl^+) is the most oxidising halonium species. Trichloroacetophenone **6a** was also found to be the most reductively-stable trihaloacetophenone intermediate. However, oxidation of chloride in a mixture containing acetophenone **1a** and benzyl alcohol **2b** in DCM did not result in the formation of benzyl ester **3ab**, with chloro- **8a** and dichloroacetophenone **9a** being the only identifiable products (Scheme 4.3). This may have been a result of the lack of

alcohol in the electrolysis mixture compared to previously reported electrochemical haloform methodologies (where alcohol was used as the solvent), meaning that alkoxide generation via cathodic reduction was less likely, especially with other relatively readily reducible species (chlorinated reaction intermediates) present. Addition of base to the electrolysis mixture was proposed as a solution, but no suitable non-nucleophilic base could be found that was both oxidatively-stable and strong enough to facilitate the haloform reaction.



Scheme 4.3. Unsuccessful electrochemical haloform coupling via chloride oxidation. ^{19}F NMR yields shown.

Due to its lower oxidation potential, selective oxidation of iodide should be possible in the presence of several of the bases that were incompatible with chloride oxidation. When iodide was oxidised in a mixture of **1a**, benzyl alcohol **2b** and DBU in DCM, ester **3ab** was obtained in 12% yield (Scheme 4.4).

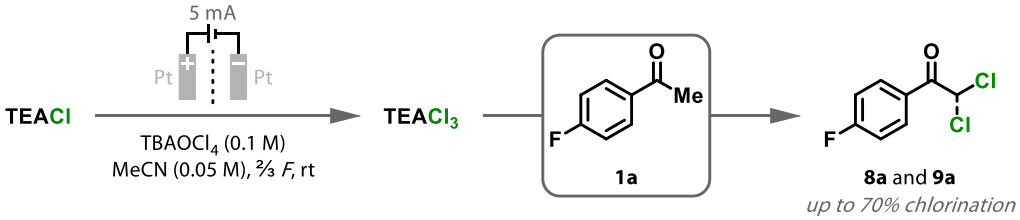


Scheme 4.4. Electrochemical haloform coupling via iodide oxidation. ^{19}F NMR yield shown.

Cathodic reduction of iodinated acetophenone intermediates was suspected to be limiting reaction efficiency, and thus yield. Several mitigation strategies were tested: electrolysis in a divided cell, such that intermediates were physically separated from the cathode; ex-cell oxidation, whereby iodide oxidation was carried out prior to addition of the other reagents; and addition of DBU.HBF_4 as an alternative oxidant to protect intermediates from reduction. None of these increased the yield of ester **3ab**, however.

Although a method for efficient electrochemical haloform coupling via halide oxidation was not realised, the formation of chlorinated acetophenones via chloride oxidation highlighted the potential for an electrochemical synthesis of $TEACl_3$, a non-commercially available reagent, whose utility has been demonstrated in chlorination and alcohol oxidation reactions. This would constitute an attractive, chlorine- and oxidant-free

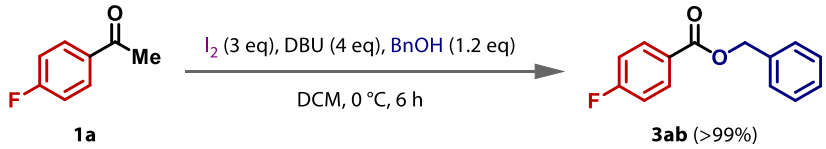
alternative to existing synthetic methods.[117,118,126] $TEACl_3$ formation in undivided cells was rather limited, possibly due to the reversibility of chloride oxidation (via cathodic reduction of $TEACl_3$). This problem was largely overcome by switching to divided electrolysis, where $TEACl_3$ yields of up to 70% were achieved, as determined by ex-cell chlorination of acetophenone **1a** (Scheme 4.5). Repeatability was a significant issue, however, with the extent of $TEACl_3$ formation seemingly dependent on the electrolysis cell used, potentially as a result of the varying porosities of the glass frits separating the cell compartments. Resolution of this issue is necessary before optimisation of the electrochemical conditions can be resumed.



Scheme 4.5. $TEACl_3$ synthesis via electrochemical chloride oxidation in a divided cell. Chlorination calculated from ^{19}F NMR mole fractions as **8a** % + 2 × **9a** %, to reflect total chlorine incorporation.

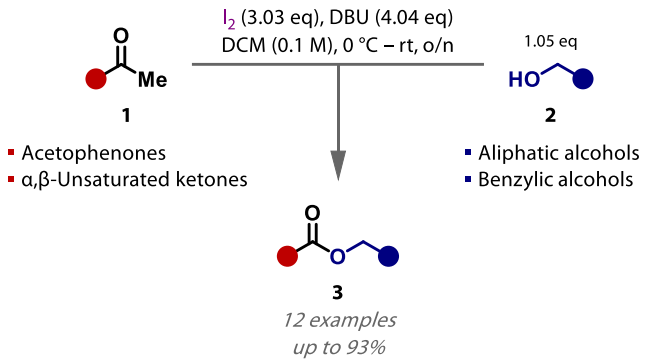
4.2 Chemical Haloform Coupling

Having set the electrochemical efforts aside, two sets of literature conditions were tested with acetophenone **1a** and benzyl alcohol **2b** to find a starting point from which to develop a 'chemical' haloform coupling with iodine.[35,66] Of these, the method featuring a combination of iodine and DBU was found to be highly effective for the synthesis of ester **3ab** (Scheme 4.6). Further optimisation of these conditions enabled the amount of alcohol required to be reduced to 1.05 equivalents with no impact on yield, and a practical procedure where couplings could be performed overnight was developed.



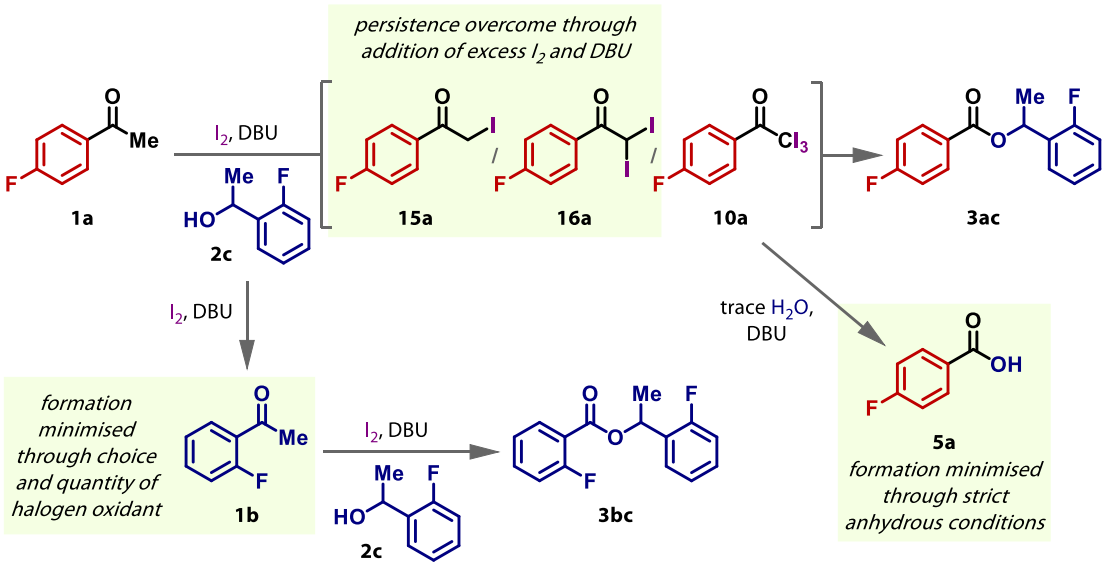
Scheme 4.6. Literature conditions for ester synthesis; starting point for development of a general haloform coupling reaction.

These conditions enabled the haloform coupling of acetophenones and α,β-unsaturated methyl ketones **1** with a range of aliphatic and benzylic primary alcohols **2** in generally good yields (Scheme 4.7).



Scheme 4.7. Summary of haloform coupling scope with primary alcohols.

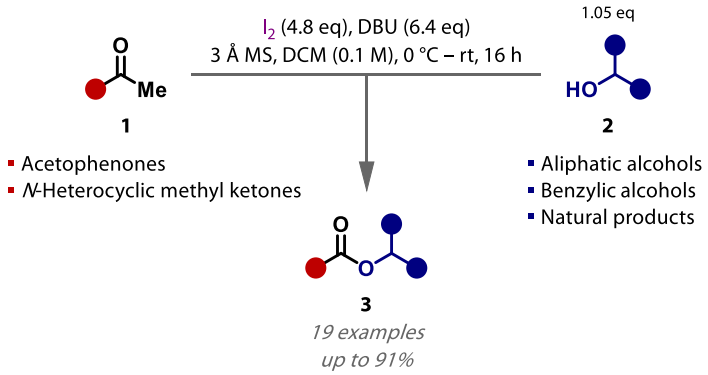
Significantly lower yields were obtained when the coupling conditions were applied to secondary alcohols, however. This prompted a re-optimisation of the reaction conditions with acetophenone **1a** and secondary alcohol **2c**. An excess of iodine and DBU was found to be critical to ensuring complete conversion to the key triiodoacetophenone intermediate **10a**, and without which iodo- **15a** and diiodoacetophenone **16a** were observed in the reaction mixture (Scheme 4.8). This excess had to be moderated though, as higher concentrations of iodine and DBU also led to increased rates of **2c** oxidation to acetophenone **1b**, which could also undergo haloform coupling with **2c** (Scheme 4.8). This was particularly true if the concentration of iodine exceeded that of DBU, so the original ratio of iodine:DBU (3:4) was maintained (4.8 and 6.4 equivalents of iodine and DBU, respectively, under the optimised conditions). Substitution of iodine with bromine also promoted alcohol oxidation (to the extent that haloform coupling was barely observed), presumably due to its higher oxidation potential. The same was true, albeit to a much lesser extent, of tetrabutylammonium tribromide. The final major side-product encountered was carboxylic acid **5a**, resulting from competitive nucleophilic attack of the triiodoacetophenone intermediate by trace water (Scheme 4.8). Formation of **5a** could be minimised by implementing strict anhydrous conditions, including the addition of molecular sieves to reactions.



Scheme 4.8. Formation of side-products controlled by optimising reaction conditions.

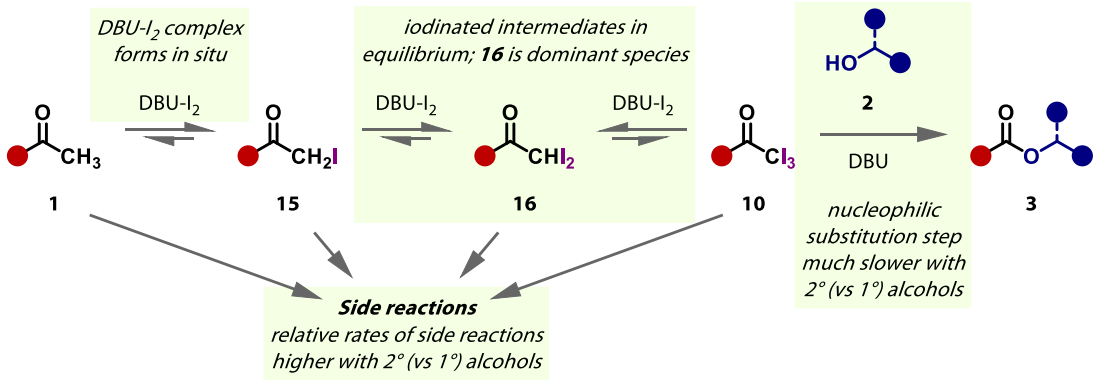
The functional group tolerance of the optimised haloform coupling with secondary alcohols was assessed using a robustness screen, in which the impact of various functionalised additives on reaction outcomes was measured.[134,135] Most of the additives tested had little impact on reaction yield and were themselves stable to the reaction conditions, with a few notable, but foreseeable exceptions, namely: additives susceptible to iodination; those susceptible to oxidation; and those which could act as competitive nucleophiles.

These findings were complemented by an exploration of the coupling's scope with secondary alcohols. Haloform couplings were achieved with a range of acetophenone substrates, as well as *N*-heterocyclic methyl ketones. However, unlike with primary alcohols, α,β-unsaturated methyl ketones could not be employed, likely due to unselective iodination (because of the excess iodine and DBU used under the secondary alcohol conditions; Scheme 4.9). Secondary benzyl alcohols with a range of steric and electronic properties could be coupled, as could aliphatic alcohols. With the latter, yields tended to decrease with increased steric bulk around the alcohol moiety. Nevertheless, among several esters prepared with complex natural product alcohols, relatively congested (−)-menthol and (−)-borneol were both coupled in reasonable yields. As this trend suggested might be the case, haloform couplings with tertiary alcohols were not possible.



Scheme 4.9. Summary of haloform coupling scope with secondary alcohols.

Probing the reactivity differences between primary and secondary alcohols, it was determined that the greater nucleophilicity of the former, owing to the greater steric hinderance of the latter, resulted in a considerably faster ester-forming substitution step with primary alcohols (Scheme 4.10). The iodinated intermediates involved in the haloform coupling were found to be in equilibrium and, because of the lower rate of triiodomethyl ketone **10** conversion to ester **3**, this was more noticeable with the secondary alcohol. Diiodomethyl ketone **16** was observed in the highest concentration at equilibrium and was concluded to be the dominant species.



Scheme 4.10. Proposed mechanism of the haloform coupling.

The other consequence of slower nucleophilic substitution with secondary alcohols is that the relative rates of side-reactions (e.g. photodecomposition of iodinated intermediates has been confirmed) are higher than with primary alcohols (Scheme 4.10). Since this can involve consumption of reactants (methyl ketone **1** and intermediates **15**, **16** and **10**) and/or reagents (iodine and DBU), incomplete conversion to triiodomethyl ketone **10**, and consequently, lower yields with secondary alcohols result. Under the optimised conditions for secondary alcohol coupling, this problem is overcome by addition of excess iodine and DBU, the impact of which is twofold. Iodination rates (forward reactions) are increased, resulting in a higher equilibrium concentration of **10** and therefore a higher rate of ester formation, which reduces the relative rates of

side-reactions. In addition, higher concentrations of iodine and DBU ensure that complete conversion to **10** is possible, making up for any loss of these reagents due to side-reactions.

Chapter 5: Experimental

5.1 General Experimental Details

5.1.1 Chemicals

Unless their synthesis is described, chemicals were obtained from commercial sources and were used without further purification, except for tetrabutylammonium hexafluorophosphate ($TBAPF_6$) and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU): $TBAPF_6$ was recrystallised from EtOH; DBU was dried over CaH_2, then distilled and stored in a Straus flask under nitrogen. Anhydrous solvents were only used where explicitly stated. Anhydrous DCM and THF were obtained from the Anhydrous Engineering double alumina drying system located at the University of Bristol and were stored in Straus flasks over activated 3 Å molecular sieves under nitrogen. Anhydrous EtOH was obtained from a commercial source and used without further drying. Anhydrous $CDCl_3$ was obtained by storage of commercially-obtained (non-anhydrous) $CDCl_3$ in a Straus flask over activated 3 Å molecular sieves under nitrogen.

5.1.2 Techniques

Unless stated otherwise, reactions were carried out at room temperature and open to air. Where procedures are described as having been carried out ‘under nitrogen’, standard Schlenk line (using vacuum lines attached to a double manifold, equipped with an oil pump) and glovebox techniques were employed, under an atmosphere of dry nitrogen. Oven-dried glassware was dried overnight in an oven at 180 °C and allowed to cool under vacuum (on a vacuum line, at room temperature and pressures up to ~0.1 mmHg). Molecular sieves were activated by drying overnight in an oven at 180 °C and then with a flame under vacuum (on a vacuum line, at pressures up to ~0.1 mmHg). Solvents were removed under vacuum using a rotary evaporator with water bath temperatures up to 40 °C and pressures up to ~10 mmHg (diaphragm pump), or on a vacuum line at room temperature and pressures up to ~0.1 mmHg (oil pump).

5.1.3 Electrochemical Techniques

Cyclic voltammetry, chronoamperometry and chronopotentiometry experiments were carried out at room temperature using PalmSens4 and MultiPalmSens4 potentiostats and were analysed with the associated PSTrace software.

5.1.4 Chromatography

Thin layer chromatography (TLC) was performed using aluminium-backed silica gel 60 F_{254} plates and reagent grade solvents. Visualisation was achieved by UV fluorescence (254 nm), and/or basic potassium permanganate or phosphomolybdic acid stains. Flash column chromatography (FCC) was performed manually, using silica gel (40-63 μm, 230-400 mesh), or using a Biotage Selekt system with Biotage Sfär Silica (60 μm) or Biotage Sfär Silica HC (20 μm) pre-packed columns. Reagent grade solvents were used in both cases.

5.1.5 Analysis

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded using Bruker Nano400, Jeol ECZ400, Jeol ECS400, Bruker 500 Cryo and Varian 500 spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to residual solvent or tetramethylsilane (TMS) signals (^{1}H and ^{13}C only). Signals are described as singlets (s), doublets (d), triplets (t), quartets (q), quintets (quint), septets (sept) and multiplets (m), or combinations thereof, and are marked as 'apparent' (app) where relevant. Coupling constants (*J*) are quoted to the nearest 0.5 Hz. Spectra of novel compounds were assigned using 2D experiments (COSY, HSQC, HMBC) where required. Mass spectra were recorded by the University of Bristol Mass Spectrometry Service, using Thermo Scientific Q Exactive, Bruker ultrafleXtreme and Waters SYNAPT G2-S spectrometers. Infrared spectra were recorded using a PerkinElmer Spectrum Two spectrometer with an ATR accessory. Specific rotations ($[a]_D^T$) were recorded with a Bellingham & Stanley ADP 220 polarimeter and are quoted in (° mL g^{-1} dm^{-1}). GC-MS analyses were performed with an Agilent 5977E GC/MSD system.

5.2 Electrochemical Haloform Coupling

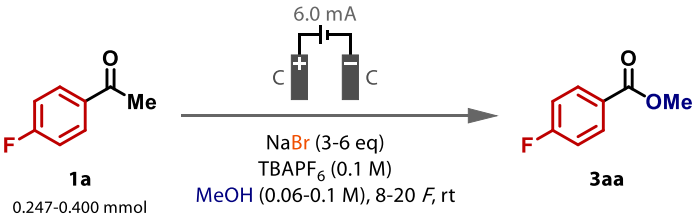
5.2.1 Cyclic Voltammetry

To a small, oven-dried, beaker-type, undivided electrolysis cell, equipped with a small stirrer bar, a glassy carbon or platinum-disc working electrode, a platinum-coil counter electrode and a $Ag/AgNO_3$ reference electrode, was added $TBAPF_6$ (96.9 mg, 0.250 mmol, 0.1 M) and anhydrous solvent (2.5 mL). The resulting solution was degassed by sparging with nitrogen for ~1 min prior to recording a 'blank' cyclic voltammogram (CV; of the electrolyte and solvent). Analyte (0.0125 mmol, 0.005 M) was then added and its CV was recorded. For CVs recorded in the oxidative direction (positive potentials) first, a glassy carbon-disc working electrode was used; for CVs

recorded in the reductive direction (negative potentials) first, a platinum-disc working electrode was used. A scan rate of 0.1 mV s^{-1} was used in both cases.

5.2.2 Bromide Oxidation

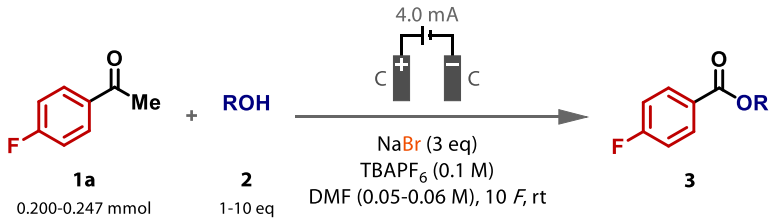
In methanol:



To a small, beaker-type, undivided electrolysis cell, equipped with a small stirrer bar, two graphite-rod electrodes (anode and cathode) and a $Ag/AgNO_3$ reference electrode, connected to a potentiostat, was added 4'-fluoroacetophenone **1a** (1 equiv.), NaBr, $TBAPF_6$ (155 mg, 0.400 mmol, 0.1 M), 4,4'-difluorobiphenyl (internal standard, IS; 0.5 equiv.) and MeOH **2a** (4 mL).[a] A small aliquot (~25 µL) of the resulting solution was taken for ^{19}F NMR analysis. The reaction mixture was then stirred and electrolysed at 6.0 mA until the desired charge had been passed. On completion, an NMR sample was prepared from the undiluted reaction mixture. ^{19}F NMR yields, etc. were calculated by comparison to the **1a**:IS ratio prior to the reaction.

[a] For reaction without $TBAPF_6$ (Table 2.1, entry 5): $TBAPF_6$ was not added.

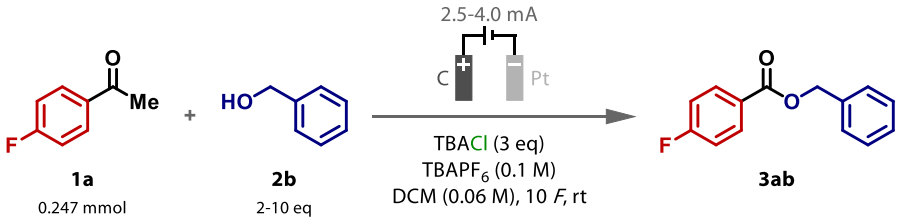
In DMF:



To a small, beaker-type, undivided electrolysis cell, equipped with a small stirrer bar, two graphite-rod electrodes (anode and cathode) and a $Ag/AgNO_3$ reference electrode, connected to a potentiostat, was added 4'-fluoroacetophenone **1a** (1 equiv.), alcohol **2** (if added), NaBr (3 equiv.), $TBAPF_6$ (155 mg, 0.400 mmol, 0.1 M), 4,4'-difluorobiphenyl (IS; 0.5 equiv.) and DMF (4 mL). A small aliquot (~25 µL) of the resulting solution was taken for ^{19}F NMR analysis. The reaction mixture was then stirred and electrolysed at 4.0 mA until 10 *F* had been passed. On completion, an NMR sample was prepared from

the undiluted reaction mixture. ^{19}F NMR yields, etc. were calculated by comparison to the **1a**:IS ratio prior to the reaction.

5.2.3 Chloride Oxidation

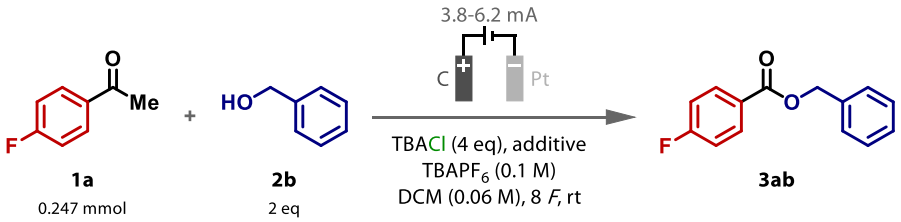


To a small, oven-dried, beaker-type, undivided electrolysis cell, equipped with a small stirrer bar, a graphite-rod anode, a platinum-coil cathode and a Ag/$AgNO_3$ reference electrode, connected to a potentiostat, was added 4'-fluoroacetophenone **1a** (30.0 µL, 0.247 mmol, 1 equiv.), benzyl alcohol **2b**, TBACl (206 mg, 0.741 mmol, 3 equiv.), $TBAPF_6$ (155 mg, 0.400 mmol, 0.1 M), 4,4'-difluorobiphenyl (IS; 23.5 mg, 0.123 mmol, 0.5 equiv.) and anhydrous DCM (4 mL).[a],[b] A small aliquot (~25 µL) of the resulting solution was taken for ^{19}F NMR analysis. The reaction mixture was then stirred and electrolysed at the current required to achieve 1.07 V anodic potential (established prior to the reaction by 30 s chronoamperometry at 1.07 V, i.e. the oxidation potential of chloride) until 10 *F* had been passed. On completion, an NMR sample was prepared by diluting a 100 µL-aliquot of reaction mixture with $CDCl_3$ (400 µL). ^{19}F NMR yields were calculated by comparison to the **1a**:IS ratio prior to the reaction.

[a] For reaction without $TBAPF_6$ (Table 2.3, entry 1): $TBAPF_6$ was not added.

[b] For reaction with TEACl (Table 2.3, entry 4): TEACl (123 mg, 0.741 mmol, 3 equiv.) was added instead of TBACl.

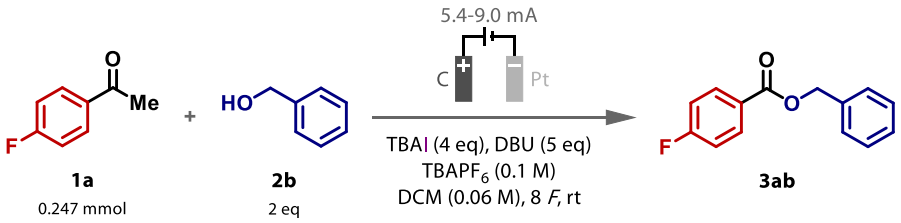
With acid/base additives:



To a small, oven-dried, beaker-type, undivided electrolysis cell, equipped with a small stirrer bar, a graphite-rod anode, platinum-coil cathode and a Ag/$AgNO_3$ reference electrode, connected to a potentiostat, was added 4'-fluoroacetophenone **1a** (30.0 µL,

0.247 mmol, 1 equiv.), benzyl alcohol **2b** (51.1 µL, 0.494 mmol, 2 equiv.), TBACl (274 mg, 0.987 mmol, 4 equiv.), $TBAPF_6$ (155 mg, 0.400 mmol, 0.1 M), acid/base additives and anhydrous DCM (4 mL). The reaction mixture was stirred and electrolysed at the current required to achieve 1.07 V anodic potential (established prior to the reaction by 30 s chronoamperometry at 1.07 V) until 8 *F* had been passed. On completion, an NMR sample was prepared by diluting a 100 µL-aliquot of reaction mixture with $CDCl_3$ (400 µL) and analysed by ^{19}F NMR.

5.2.4 Iodide Oxidation



With IS: To a small, oven-dried, beaker-type, undivided electrolysis cell, equipped with a small stirrer bar, a graphite-rod anode, platinum-coil cathode and a $Ag/AgNO_3$ reference electrode, connected to a potentiostat, was added 4'-fluoroacetophenone **1a** (30.0 µL, 0.247 mmol, 1 equiv.), benzyl alcohol **2b** (51.1 µL, 0.494 mmol, 2 equiv.), TBAI (365 mg, 0.987 mmol, 4 equiv.), DBU (184 µL, 1.23 mmol, 5 equiv.), $TBAPF_6$ (155 mg, 0.400 mmol, 0.1 M), 4,4'-difluorobiphenyl (IS; 23.5 mg, 0.123 mmol, 0.5 equiv.) and anhydrous DCM (4 mL). A small aliquot (~25 µL) of the resulting solution was taken for ^{19}F NMR analysis. The reaction mixture was then stirred and electrolysed at the current required to achieve 0.48 V anodic potential (established prior to the reaction by 30 s chronoamperometry at 0.48 V, i.e. the oxidation potential of iodide) until 8 *F* had been passed. On completion, an NMR sample was prepared by diluting a 100 µL-aliquot of reaction mixture with $CDCl_3$ (400 µL). ^{19}F NMR yields were calculated by comparison to the **1a**:IS ratio prior to the reaction.

Without IS: To a small, oven-dried, beaker-type, undivided electrolysis cell, equipped with a small stirrer bar, a graphite-rod anode, platinum-coil cathode and a $Ag/AgNO_3$ reference electrode, connected to a potentiostat, was added 4'-fluoroacetophenone **1a** (30.0 µL, 0.247 mmol, 1 equiv.), benzyl alcohol **2b** (51.1 µL, 0.494 mmol, 2 equiv.), TBAI (365 mg, 0.987 mmol, 4 equiv.), DBU (184 µL, 1.23 mmol, 5 equiv.), $TBAPF_6$ (155 mg, 0.400 mmol, 0.1 M) and anhydrous DCM (4 mL).[a],[b],[c] The reaction mixture was stirred and electrolysed at the current required to achieve 0.48 V anodic potential (established prior to the reaction by 30 s chronoamperometry at 0.48 V) until 8 *F* had been passed.

On completion, an NMR sample was prepared by diluting a 100 µL-aliquot of reaction mixture with $CDCl_3$ (400 µL) and analysed by ^{19}F NMR.

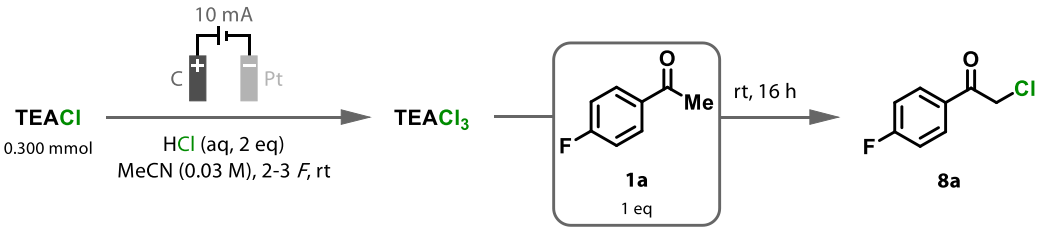
[a] For reaction in divided cell (Table 2.6, entry 2): an oven-dried H-cell with a glass frit separating the two compartments, equipped with two small stirrer bars (one in each compartment), was used. The anodic compartment, equipped with the graphite-rod anode and $Ag/AgNO_3$ reference electrode, was prepared as above. To the cathodic compartment, equipped with the platinum-coil cathode, was added $TBAPF_6$ (155 mg, 0.400 mmol, 0.1 M) and DCM (4 mL).

[b] For ex-cell reaction (Table 2.6, entry 3): 4'-fluoroacetophenone **1a**, benzyl alcohol **2b** and DBU were added to the reaction mixture on completion of the electrolysis. The reaction mixture was then stirred for 24 h before the NMR sample was prepared.

[c] For reaction with $DBU.HBF_4$ (Table 2.6, entry 4): $DBU.HBF_4$ (356 mg, 1.48 mmol, 6 equiv.) was added with the reagents.

5.2.5 Tetraethylammonium Trichloride Synthesis

Undivided cell:



To a 3-neck round-bottom flask,[a] equipped with a stirrer bar, a carbon-felt anode (~1 cm^2 surface area) and a platinum-sheet cathode (~1 cm^2 surface area),[b] connected to a potentiostat, was added TEACl (49.7 mg, 0.300 mmol, 1 equiv.), aqueous HCl (37%; 49.3 µL, 0.600 mmol, 2 equiv.)[c] and MeCN (10 mL). The reaction mixture was then stirred and electrolysed at 10 mA until the desired charge had been passed. On completion, the electrolysis mixture was transferred to a large vial (electrodes and flask rinsed with additional MeCN), to which 4'-fluoroacetophenone **1a** (36.4 µL, 0.300 mmol, 1 equiv.) was added.[d] The reaction mixture was stirred for 16 h, then concentrated under vacuum and an NMR sample was prepared.

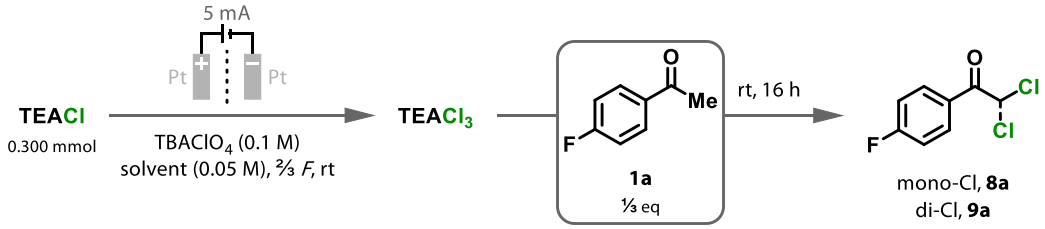
[a] For reactions in round-bottom flask (Table 2.7, entries 4-5): a (single-neck) round-bottom flask was used instead of a 3-neck round-bottom flask.

[b] For reactions with nickel cathode (Table 2.7, entries 3-5): a sheet of nickel foil (~1 cm^2 surface area) was used as the cathode instead of a platinum sheet.

[c] For reaction with $HCl.Et_2O$ (Table 2.7, entry 2): $HCl.Et_2O$ (2.0 M in Et_2O; 300 µL, 0.600 mmol, 2 equiv.) was added instead of aqueous HCl.

[d] For reaction where electrolysis mixture divided three ways (Table 2.7, entry 1): the electrolysis mixture was diluted with additional MeCN (20 mL), then 10 mL-aliquots were transferred to three large vials to which were added (one substrate per vial) 1-dodecyne **11** (15.1 µL, 0.100 mmol, 1 equiv.), 1-octene **12** (15.7µL, 0.100 mmol, 1 equiv.) and 4'-fluoroacetophenone **1a** (12.1 µL, 0.100 mmol, 1 equiv.). 1-Dodecyne **11** and 1-octene **12** reactions were analysed by ^{1}H NMR and chlorination was judged vs literature (1-dodecyne **11**,[141] (*E*)-1,2-dichlorododec-1-ene **13**,[142] 1-octene **12**,[143] 1,2-dichlorooctane **14**[144]). 4'-Fluoroactophenone **1a** reaction was analysed by ^{19}F NMR.

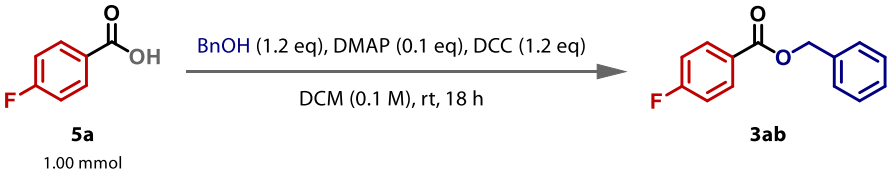
Divided cell:



To each compartment of an oven-dried H-cell with a glass frit separating the two compartments and equipped with two stirrer bars (one in each compartment), which had been evacuated and refilled with nitrogen (×3), was added $TBAClO_4$ (2× 205 mg, 2× 0.600 mmol, 0.1 M). TEACl (49.7 mg, 0.300 mmol, 3 equiv. vs theoretical $TEACl_3$ yield) was added to the anodic compartment, then the cell was evacuated and refilled with nitrogen (×3) again. Under nitrogen, the Suba-seals sealing the compartments were replaced with Suba-seals bearing platinum-coil electrodes, which were positioned as close to the frit as possible, then anhydrous solvent (2× 6 mL) was added to each compartment. The reaction mixture was stirred and electrolysed at 5 mA until ⅔ *F* had been passed. On completion, the anolyte mixture was transferred to a large vial (anode and anodic compartment rinsed with additional solvent) to which 4'-fluoroacetophenone **1a** (12.1 µL, 0.100 mmol, 1 equiv. vs theoretical $TEACl_3$ yield) was added. The reaction mixture was stirred for 16 h, then concentrated under vacuum and a ^{19}F NMR sample was prepared.

5.2.6 Synthesis of Benzyl Ester Sample

Benzyl 4-fluorobenzoate, **3ab**



Synthesised following a literature procedure[145] from 4-fluorobenzoic acid **5a** (140 mg, 1.00 mmol) and isolated by FCC (eluted with 10-20% EtOAc in hexane) as a colourless oil (176 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.07 (m, 2H), 7.47 – 7.32 (m, 5H), 7.14 – 7.07 (m, 2H), 5.36 (s, 2H).

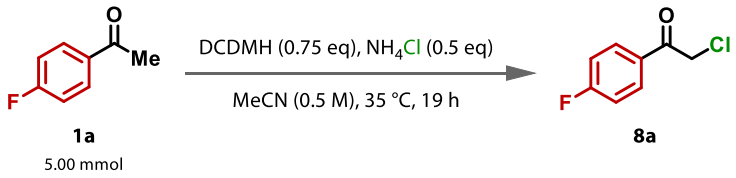
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (d, *J* = 254.0 Hz), 165.6, 136.1, 132.4 (d, *J* = 9.5 Hz), 128.8, 128.5, 128.4, 126.5 (d, *J* = 3.0 Hz), 115.7 (d, *J* = 22.0 Hz), 67.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ −105.55 (tt, *J* = 8.5, 5.5 Hz).

Data are consistent with those previously reported (compound 7f).[146]

5.2.7 Synthesis of Haloacetophenones

2-Chloro-4'-fluoroacetophenone, **8a**



Synthesis based on a literature procedure.[114] To a round-bottom flask was added 4'-fluoroacetophenone **1a** (607 µL, 5.00 mmol, 1 equiv.), NH_4Cl (134 mg, 2.50 mmol, 0.5 equiv.) and MeCN (10 mL). The resulting solution was stirred for 10 min, then 1,3-dichloro-5,5-dimethylhydantoin (DCDMH; 739 mg, 3.75 mmol, 0.75 equiv.) was added in five portions over 50 min. After the final addition, the reaction mixture was stirred for 19 h at 35 °C. On completion, the reaction mixture was concentrated under vacuum, then re-dissolved in EtOAc, washed with deionised water (×2), dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was

purified by FCC (eluted with 20% Et_2O in hexane) to obtain **8a** as a white solid (607 mg, 70%).

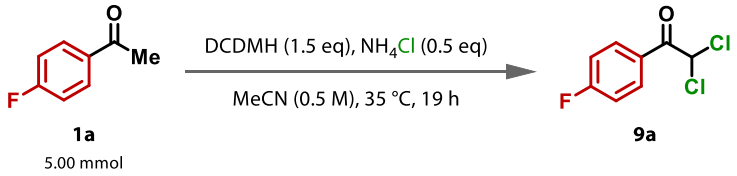
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.96 (m, 2H), 7.22 – 7.14 (m, 2H), 4.67 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8, 166.3 (d, *J* = 256.5 Hz), 131.5 (d, *J* = 9.5 Hz), 130.8, 116.3 (d, *J* = 22.0 Hz), 45.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ −102.93 (tt, *J* = 8.5, 5.5 Hz).

Data are consistent with those previously reported (compound 3g).[147]

2,2-Dichloro-4'-fluoroacetophenone, **9a**



1a
5.00 mmol

9a

Synthesised by a modified literature procedure.[114] To a round-bottom flask was added 4'-fluoroacetophenone **1a** (607 µL, 5.00 mmol, 1 equiv.), NH_4Cl (134 mg, 2.50 mmol, 0.5 equiv.) and MeCN (10 mL). The resulting solution was stirred for 10 min, then DCDMH (1.48 g, 7.5 mmol, 1.5 equiv.) was added in four portions over 35 min. After the final addition, the reaction mixture was stirred for 19 h at 35 °C. On completion, the reaction mixture was concentrated under vacuum, then re-dissolved in EtOAc, washed with deionised water (×2), dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by FCC (eluted with 5-10% Et_2O in hexane) to obtain **9a** as a pale-yellow oil (913 mg, 88%).

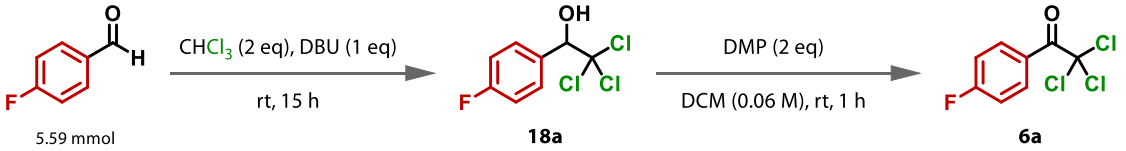
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.10 (m, 2H), 7.21 – 7.14 (m, 2H), 6.63 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 184.7, 166.6 (d, *J* = 258.0 Hz), 132.9 (d, *J* = 9.5 Hz), 127.7 (d, *J* = 3.0 Hz), 116.4 (d, *J* = 22.5 Hz), 68.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ −101.68 (tt, *J* = 8.5, 5.0 Hz).

Data are consistent with those previously reported (compound 2e).[148] *As ^{19}F NMR data have not previously been reported, a copy of the spectrum is included.*

2,2,2-Trichloro-4'-fluoroacetophenone, **6a**



Synthesised by modified literature procedures.[149,150] To a round-bottom flask, which had been evacuated and refilled with nitrogen (×3), was added 4-fluorobenzaldehyde (600 µL, 5.59 mmol, 1 equiv.) and $CHCl_3$ (895 µL, 11.2 mmol, 2 equiv.), followed by dropwise addition of DBU (836 µL, 5.59 mmol, 1 equiv.). The reaction mixture was stirred for 15 h, then diluted with $CHCl_3$ and washed with 2 M aq. HCl. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum to obtain crude 2,2,2-trichloro-1-(4-fluorophenyl)ethanol **18a** as a yellow oil (1.31 g), which was used in the following step without further purification.

To a round-bottom flask containing crude 2,2,2-trichloro-1-(4-fluorophenyl)ethanol **18a** (1.31 g) in DCM (100 mL) was added Dess-Martin periodinane (DMP; 4.74 g, 11.2 mmol, 2 equiv.). The reaction mixture was stirred for 1 h, then the reaction mixture was filtered through Celite and the filtrate was concentrated under vacuum. The crude product was purified by FCC (eluted with 20% EtOAc in hexane) to obtain **6a** as a pale-yellow oil (1.15 g, 85%).

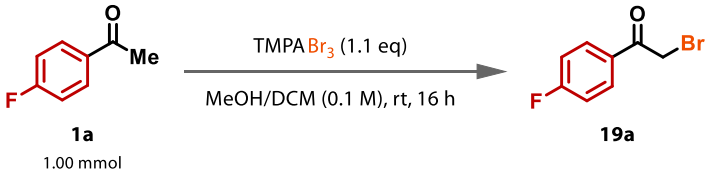
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.28 (m, 2H), 7.21 – 7.13 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9, 166.3 (d, *J* = 258.5 Hz), 134.6 (d, *J* = 9.5 Hz), 125.3 (d, *J* = 3.0 Hz), 115.9 (d, *J* = 22.0 Hz), 95.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ −101.77 (tt, *J* = 8.0, 5.0 Hz).

Data are consistent with those previously reported (compound 4b).[151] *As ^{19}F NMR data have not previously been reported, a copy of the spectrum is included.*

2-Bromo-4'-fluoroacetophenone, **19a**



To a round-bottom flask was added 4'-fluoroacetophenone **1a** (121 µL, 1.00 mmol, 1 equiv.), trimethylphenylammonium tribromide ($TMPABr_3$; 414 mg, 1.10 mmol, 1.1 equiv.), MeOH (2 mL) and DCM (5 mL). The resulting solution was stirred for 16 h, then deionised water was added and the mixture was extracted with DCM (×3), washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product contained a 91:9 mixture of the mono- and dibrominated products and was combined with the crude product from an attempted dibromination (containing a 60:40 mixture of the mono- and dibrominated products). The combined crudes were purified by FCC (eluted with 5% EtOAc in hexane) to obtain **19a** as a white solid (312 mg, yield incalculable).

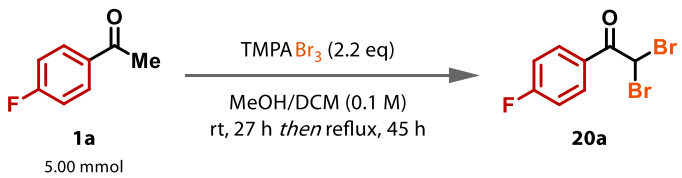
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 2H), 7.21 – 7.14 (m, 2H), 4.41 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0, 166.3 (d, *J* = 256.5 Hz), 131.9 (d, *J* = 9.5 Hz), 130.5 (d, *J* = 3.0 Hz), 116.2 (d, *J* = 22.0 Hz), 30.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ −103.06 (tt, *J* = 8.5, 5.0 Hz).

Data are consistent with those previously reported (compound 2f/s7).[152,153]

2,2-Dibromo-4'-fluoroacetophenone, **20a**



To a round-bottom flask was added 4'-fluoroacetophenone **1a** (607 µL, 5.00 mmol, 1 equiv.), $TMPABr_3$ (4.14 g, 11.0 mmol, 2.2 equiv.), MeOH (15 mL) and DCM (37.5 mL) and the resulting solution was stirred for 27 h. TLC showed complete conversion of **1a**, but predominantly to the monobrominated product, so stirring was continued for a further 45 h under reflux. After this time, despite incomplete dibromination, the reaction was

cooled to room temperature and deionised water was added. The mixture was extracted with DCM (×3), washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by FCC (eluted with 5% EtOAc in hexane) to obtain **20a** as a pale-yellow oil (941 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.12 (m, 2H), 7.23 – 7.15 (m, 2H), 6.61 (s, 1H).

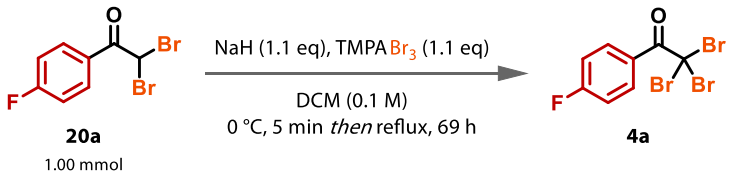
^{13}C NMR (101 MHz, $CDCl_3$) δ 184.7, 166.4 (d, *J* = 258.0 Hz), 132.8 (d, *J* = 9.5 Hz), 127.2 (d, *J* = 3.0 Hz), 116.3 (d, *J* = 22.0 Hz), 39.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ −101.77 (tt, *J* = 8.5, 5.0 Hz).

Data are consistent with those previously reported (compound 3e).[154]

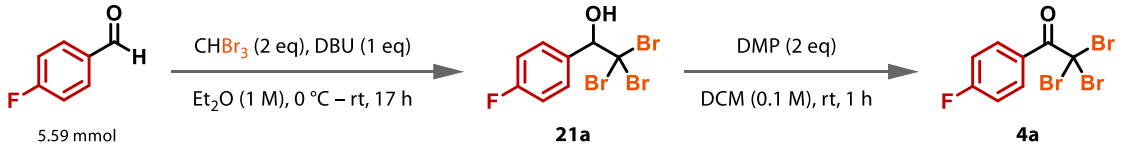
2,2,2-Tribromo-4'-fluoroacetophenone, **4a**

Method 1:



To a round-bottom flask, containing NaH (60% in mineral oil; 44.0 mg, 1.10 mmol, 1.1 equiv.) and DCM (4 mL) at 0 °C (ice-water bath), was added dropwise a solution of 2,2-dibromo-4'-fluoroacetophenone **20a** (296 mg, 1.00 mmol, 1 equiv.) in DCM (6 mL). The reaction mixture was stirred for 5 min at 0 °C, then the reaction was allowed to warm to room temperature. After 30 min, $TMPABr_3$ (414 mg, 1.10 mmol, 1.1 equiv.) was added in one portion and the reaction mixture was stirred for 69 h under reflux. After this time, despite incomplete conversion, the reaction was cooled to room temperature, filtered, and concentrated under vacuum. The crude product was purified by FCC (eluted with 0-1% EtOAc in hexane) to obtain **4a** as a yellow oil (136 mg, 36%).

Method 2:



Synthesis based on literature procedures.[149,150] To a round-bottom flask, which had been evacuated and refilled with nitrogen (×3), was added 4-fluorobenzaldehyde (600 µL, 5.59 mmol, 1 equiv.), $CHBr_3$ (978 µL, 11.2 mmol, 2 equiv.) and Et_2O (6 mL). The resulting solution was cooled to 0 °C (ice-water bath), then DBU (836 µL, 5.59 mmol, 1 equiv.) was added dropwise. The reaction mixture was stirred for 17 h and allowed to warm to room temperature, then diluted with DCM and washed with 2 M aq. HCl. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was partially purified by FCC (eluted with 10% EtOAc in hexane) to remove high R_f impurities, giving crude 2,2,2-tribromo-1-(4-fluorophenyl)ethanol **21a** as a yellow oil (938 mg).

To a round-bottom flask containing crude 2,2,2-tribromo-1-(4-fluorophenyl)ethanol **21a** (912 mg) in DCM (45 mL) was added DMP (2.05 g, 4.84 mmol, 2 equiv.). The reaction mixture was stirred for 1 h, then filtered through Celite and the filtrate was concentrated under vacuum. The crude product was purified by FCC (eluted with 1% Et_2O in hexane) to obtain **4a** as a colourless oil (398 mg, 19%).

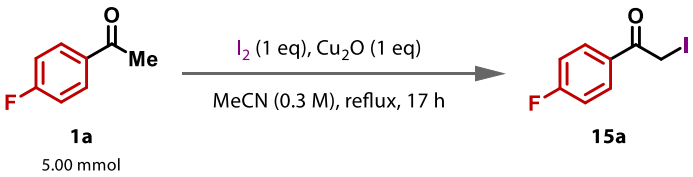
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.37 (m, 2H), 7.19 – 7.12 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 166.1 (d, *J* = 258.0 Hz), 135.0 (d, *J* = 9.5 Hz), 124.5 (d, *J* = 3.5 Hz), 115.7 (d, *J* = 22.0 Hz), 41.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ −102.43 (tt, *J* = 8.0, 5.0 Hz).

Data are consistent with those previously reported (compound 2o).[155] *As ^{19}F NMR data have not previously been reported, a copy of the spectrum is included.*

2-Iodo-4'-fluoroacetophenone, **15a**



Synthesised by a modified literature procedure.[156] To a round-bottom flask was added 4'-fluoroacetophenone **1a** (607 µL, 5.00 mmol, 1 equiv.) and MeOH (20 mL), followed by finely-powdered Cu_2O (398 mg, 5.00 mmol, 1 equiv.) and iodine (1.27 g, 5.00 mmol, 1 equiv.). The reaction mixture was stirred for 17 h under reflux, then allowed to cool to room temperature, filtered, and concentrated under vacuum. The residue was redissolved in sat. aq. $Na_2S_2O_3$, then extracted with EtOAc (×3), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by FCC (eluted with 0-6% EtOAc in pentane) to obtain **15a** as a yellow oil (829 mg, 63%), which became and remained a yellow solid on freezing (at −20 °C). NB: **15a** is light-sensitive, but storage at −20 °C is not believed to be necessary.

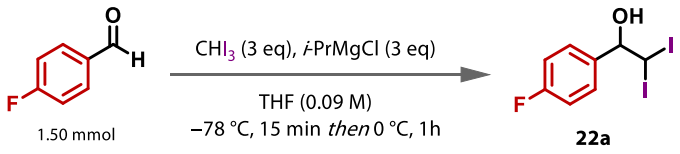
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 2H), 7.19 – 7.11 (m, 2H), 4.33 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 166.2 (d, *J* = 256.5 Hz), 131.9 (d, *J* = 9.5 Hz), 130.0 (d, *J* = 3.0 Hz), 116.2 (d, *J* = 22.0 Hz), 1.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ −103.50 (tt, *J* = 8.5, 5.5 Hz).

Data are consistent with those previously reported (compound 2x).[157]

2,2-Diiodo-1-(4-fluorophenyl)ethanol, ***22a***



Synthesised by a modified literature procedure.[158] To an oven-dried 2-neck round-bottom flask, which had been evacuated and refilled with nitrogen (×3), was added CHI_3 (1.77 g, 4.50 mmol, 3 equiv.) and anhydrous THF (15 mL). The resulting solution was cooled to −78 °C (dry ice-acetone bath), then *i*-PrMgCl (2.0 M in THF; 2.25 mL, 4.50 mmol, 3 equiv.) was added dropwise, followed by dropwise addition of a solution of

4-fluorobenzaldehyde (162 µL, 1.50 mmol, 1 equiv.) in anhydrous THF (1.5 mL), prepared in a separate oven-dried Schlenk tube, which had been evacuated and refilled with nitrogen (×3). The reaction mixture was stirred for 15 min at −78 °C, then allowed to warm to 0 °C (ice-water bath) and stirred for a further 1 h. After confirming complete conversion (by TLC), sat. aq. NH_4Cl was added and the mixture was extracted with DCM (×3). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by FCC (eluted with 0-15% EtOAc in pentane) to obtain **22a** as a yellow oil (378 mg, 64%). NB: **22a** may be light-sensitive.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 2H, Ar-H), 7.10 – 7.02 (m, 2H, Ar-H), 5.28 (d, *J* = 4.5 Hz, 1H, CHI_2), 4.68 (app t, *J* = 4.0 Hz, 1H, C*H*OH), 2.88 (d, *J* = 4.0 Hz, 1H, OH).

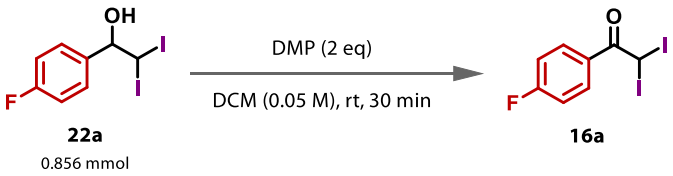
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (d, *J* = 248.0 Hz, Ar), 134.9 (d, *J* = 3.0 Hz, Ar), 128.5 (d, *J* = 8.5 Hz, Ar), 115.6 (d, *J* = 21.5 Hz, Ar), 79.1 (CHOH), −10.8 (d, *J* = 2.0 Hz, CHI_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ −112.46 (tt, *J* = 8.5, 5.0 Hz).

HRMS (EI) m/z: $[M]^+$ Calcd for $C_8H_7OFI_2$ 391.8565; found 391.8565; 0.00 ppm error.

IR (neat) ν_{max} / cm^{-1}: 3443, 1603, 1508, 1227, 1073, 836.

2,2-Diiodo-4'-fluoroacetophenone, **16a**



22a
0.856 mmol

16a

To a round-bottom flask was added 2,2-diiodo-1-(4-fluorophenyl)ethanol **22a** (336 mg, 0.856 mmol, 1 equiv.), DMP (727 mg, 1.71 mmol, 2 equiv.) and DCM (17 mL). The reaction mixture was stirred for 30 min, then filtered through a short plug of silica (washed with DCM) and the filtrate was concentrated under vacuum to obtain **16a** as a yellow oil (254 mg, 76%). NB: **16a** is light-sensitive.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.05 (m, 2H, Ar-H), 7.19 – 7.12 (m, 2H, Ar-H), 6.44 (s, 1H, CHI_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.9 (C=O), 166.3 (d, *J* = 257.5 Hz, Ar), 132.5 (d, *J* = 9.5 Hz, Ar), 125.1 (d, *J* = 3.0 Hz, Ar), 116.4 (d, *J* = 22.0 Hz, Ar), −29.7 (CHI_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ −102.42 (tt, J = 8.0, 5.0 Hz).

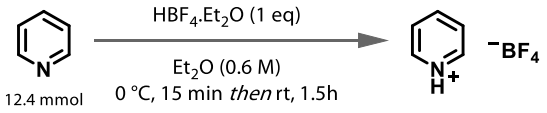
HRMS (EI) m/z: $[M]^+$ Calcd for $C_8H_5OFI_2$ 389.8408; found 389.8406; 0.51 ppm error.

IR (neat) ν_{max} / cm^{-1}: 1677, 1599, 1505, 1253, 1159, 980, 847, 577.

^{13}C NMR data are inconsistent with those in the only previous report (compound 2aa),[159] *so **16a** was fully characterised. Copies of NMR spectra are included.*

5.2.8 Synthesis of Conjugate Acid Salts

Pyridinium tetrafluoroborate (pyr.HBF_4)



To a round-bottom flask was added HBF_4.Et_2O (1.69 mL, 12.4 mmol, 1 equiv.) and Et_2O (20 mL). The resulting solution was cooled to 0 °C (ice-water bath), then pyridine (1.00 mL, 12.4 mmol, 1 equiv.) was added dropwise. After 15 min, the reaction mixture was allowed to warm to room temperature and was stirred for a further 1.5 h. The precipitate that formed was collected by filtration (Büchner, washed with cold Et_2O) and dried under vacuum overnight to obtain pyridinium tetrafluoroborate as a white solid (1.83 g, 88%).

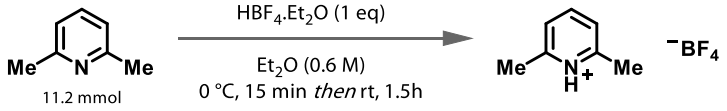
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 – 8.89 (m, 2H), 8.60 (tt, *J* = 8.0, 1.5 Hz, 1H), 8.11 – 8.03 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 146.0, 142.4, 127.1.

^{19}F NMR (376 MHz, DMSO-d_6) δ −148.23 (s, 0.8F), −148.28 (s, 3.2F).

Data are consistent with those previously reported.[160]

2,6-Lutidinium tetrafluoroborate (lut.HBF_4)



To a round-bottom flask was added $HBF_4.Et_2O$ (1.53 mL, 11.2 mmol, 1 equiv.) and Et_2O (20 mL). The resulting solution was cooled to 0 °C (ice-water bath), then 2,6-lutidine (1.30 mL, 11.2 mmol, 1 equiv.) was added dropwise. After 15 min, the reaction mixture was allowed to warm to room temperature and was stirred for a further 1.5 h. The precipitate formed was collected by filtration (Büchner, washed with cold Et_2O) and dried under vacuum overnight to obtain 2,6-lutidinium tetrafluoroborate as a pale pink solid (0.954 g, 44%).

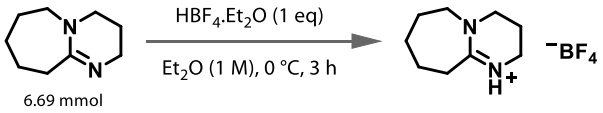
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (t, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 2.68 (s, 6H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 153.0, 145.6, 124.6, 19.2.

^{19}F NMR (376 MHz, DMSO-d_6) δ −148.28 (s, 0.8F), −148.33 (s, 3.2F).

Data are consistent with those previously reported.[160]

1,8-Diazabicyclo[5.4.0]undec-7-enium tetrafluoroborate (DBU.HBF_4)



To a round-bottom flask was added DBU (1.00 mL, 6.69 mmol, 1 equiv.) and Et_2O (6.7 mL). The resulting solution was cooled to 0 °C (ice-water bath), then $HBF_4.Et_2O$ (0.911 mL, 6.69 mmol, 1 equiv.) was added dropwise. After 3 h, the precipitate formed was collected by filtration (Büchner, washed with cold Et_2O) and dried under vacuum overnight to obtain 1,8-diazabicyclo[5.4.0]undec-7-enium tetrafluoroborate as an off-white solid (1.18 g, 74%).

^{1}H NMR (400 MHz, D_2O) δ 3.65 – 3.49 (m, 4H), 3.35 (t, *J* = 6.0 Hz, 2H), 2.69 – 2.62 (m, 2H), 2.05 (app quint, *J* = 6.0 Hz, 2H), 1.84 – 1.65 (m, 6H).

^{13}C NMR (101 MHz, D_2O) δ 166.0, 54.1, 48.2, 38.0, 32.8, 28.4, 25.8, 23.3, 18.9.

^{19}F NMR (376 MHz, D_2O) δ −150.42 (s, 0.8F), −150.47 (s, 3.2F).

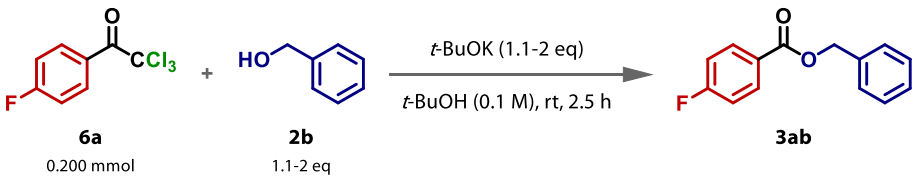
Data are consistent with those previously reported.[161] *NB: Only 8 of the 9 ^{13}C signals were reported, so, based on the otherwise corroborating data, it is believed that the signal at 25.8 ppm was accidentally omitted. As ^{19}F NMR data have not previously been reported, a copy of the spectrum is included.*

5.3 Chemical Haloform Coupling

5.3.1 Preliminary Investigations

5.3.1.1 Trichloroacetophenone Cleavage

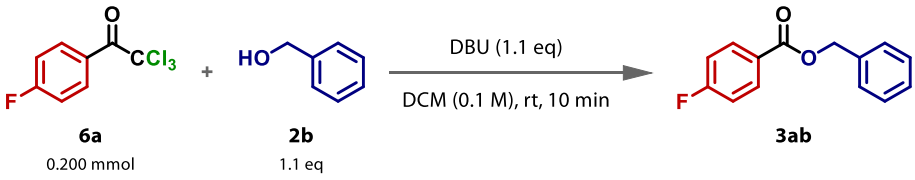
With *t*-BuOK:



6a 0.200 mmol | **2b** 1.1-2 eq | **3ab**

To an oven-dried Schlenk tube, which had been evacuated and refilled with nitrogen (×3) was added benzyl alcohol **2b**, anhydrous *t*-BuOK and anhydrous *t*-BuOH (1.5 mL). A 1 mL-aliquot of this solution was added to a solution of 2,2,2-trichloro-4'-fluoroacetophenone **6a** (48.3 mg, 0.200 mmol, 1 equiv.) in anhydrous *t*-BuOH (1 mL) in a separate oven-dried Schlenk tube, which had also been evacuated and refilled with nitrogen (×3). The reaction was monitored by TLC and when no further changes were detected (after 2.5 h), 4,4'-difluorobiphenyl (IS; 19.0 mg, 0.100 mmol, 0.5 equiv.) was added and an NMR sample was prepared from the undiluted reaction mixture.

With DBU:



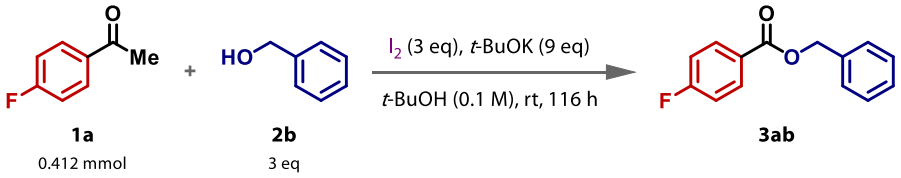
6a 0.200 mmol | **2b** 1.1 eq | **3ab**

To an oven-dried Schlenk tube, which had been evacuated and refilled with nitrogen (×3), was added 2,2,2-trichloro-4'-fluoroacetophenone **6a** (48.3 mg, 0.200 mmol, 1 equiv.), benzyl alcohol **2b** (22.8 µL, 0.220 mmol, 1.1 equiv.) and anhydrous DCM

(2 mL), followed by addition of DBU (32.9 µL, 0.220 mmol, 1.1 equiv.) in one portion. The reaction was monitored by TLC and on completion (within 10 min), the reaction mixture was concentrated under vacuum. 4,4'-Difluorobiphenyl (IS; 19.0 mg, 0.100 mmol, 0.5 equiv.) was added to the residue and an NMR sample was prepared.

5.3.1.2 Haloform Reaction

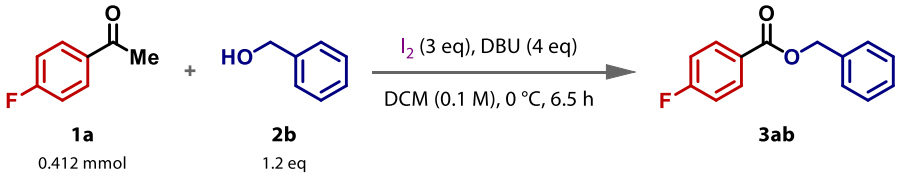
With I_2/*t*-BuOK:



1a 0.412 mmol + **2b** 3 eq → **3ab**

Based on a literature procedure.[35] To an oven-dried Schlenk tube, which had been evacuated and refilled with nitrogen (×3), was added *t*-BuOK (416 mg, 3.71 mmol, 9 equiv.) and *t*-BuOH (3 mL), followed by addition of iodine (314 mg, 1.24 mmol, 3 equiv.). The reaction mixture was stirred for 5 min, then benzyl alcohol **2b** (128 µL, 1.24 mmol, 3 equiv.) was added, followed by dropwise addition of a solution of 4'-fluoroacetophenone **1a** (50.0 µL, 0.412 mmol, 1 equiv.) in anhydrous *t*-BuOH (1.1 mL). The reaction mixture was stirred for 116 h. After this time, despite incomplete conversion, the reaction mixture was concentrated under vacuum and an NMR sample was prepared.

With I_2/DBU:



1a 0.412 mmol + **2b** 1.2 eq → **3ab**

Based on a literature procedure.[66] To an oven-dried Schlenk tube, which had been evacuated and refilled with nitrogen (×3), was added 4'-fluoroacetophenone **1a** (50.0 µL, 0.412 mmol, 1 equiv.), benzyl alcohol **2b** (51.1 µL, 0.494 mmol, 1.2 equiv.), iodine (314 mg, 1.24 mmol, 3 equiv.) and anhydrous DCM (4.1 mL). The resulting mixture was cooled to 0 °C (ice-water bath), then DBU (246 µL, 1.65 mmol, 4 equiv.) was added in one portion and the reaction was monitored by TLC. On completion (after 6.5 h), sat. aq. $Na_2S_2O_3$ was added. The mixture was extracted with EtOAc (×3), washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum.

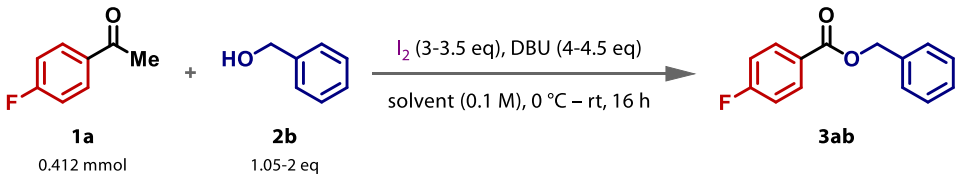
4,4'-Difluorobiphenyl (IS; 39.2 mg, 0.206 mmol, 0.5 equiv.) was added to the residue and an NMR sample was prepared.

2.47 mmol scale reaction: To an oven-dried 2-neck round-bottom flask, which had been evacuated and refilled with nitrogen (×3), was added 4'-fluoroacetophenone **1a** (300 µL, 2.47 mmol, 1 equiv.), benzyl alcohol **2b** (307 µL, 2.97 mmol, 1.2 equiv.), iodine (1.88 g, 7.41 mmol, 3 equiv.) and anhydrous DCM (24.7 mL). The resulting mixture was cooled to 0 °C (ice-water bath), then DBU (1.48 mL, 9.89 mmol, 4 equiv.) was added dropwise. The reaction mixture was stirred for 20 h and allowed to warm to room temperature. Sat. aq. $Na_2S_2O_3$ was added, then the reaction mixture was extracted with EtOAc (×3), washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by FCC (eluted with 1-5% Et_2O in hexane) to obtain benzyl 4-fluorobenzoate **3ab** as a colourless oil (474 mg, 83%).

NMR data were consistent with those previously recorded (see 5.2.6).

5.3.2 Reaction Optimisation

5.3.2.1 Primary Alcohol

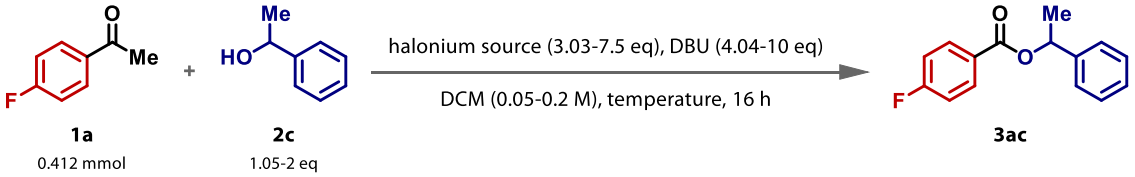


To an oven-dried Schlenk tube, which had been evacuated and refilled with nitrogen (×3), was added 4'-fluoroacetophenone **1a** (50.0 µL, 0.412 mmol, 1 equiv.), benzyl alcohol **2b**, 4,4'-difluorobiphenyl (IS; 23.5 mg, 0.124 mmol, 0.3 equiv.) and solvent (4.1 mL). A small aliquot (~25 µL) of the resulting solution was taken for ^{19}F NMR analysis, then the halonium source was added in one portion. The reaction mixture was cooled to 0 °C (ice-water bath), then DBU was added dropwise. The reaction mixture was stirred for 16 h,[a] with the reaction allowed to warm to room temperature.[b] On completion, an NMR sample was prepared by diluting a 100 µL-aliquot of reaction mixture with $CDCl_3$ (400 µL). ^{19}F NMR yields, etc. were calculated by comparison to the **1a**:IS ratio prior to the reaction.

[a] For reactions stopped after 6 and 8 h (Table 3.1, entries 1 and 10): NMR samples prepared at these times and immediately analysed.

[b] For reaction at 0 °C (Table 3.1, entry 1): reaction maintained at 0 °C, i.e. not allowed to warm to room temperature.

5.3.2.2 Secondary Alcohol



To an oven-dried Schlenk tube, which had been evacuated and refilled with nitrogen (×3), was added 4'-fluoroacetophenone **1a** (50.0 µL, 0.412 mmol, 1 equiv.), 1-(2-fluorophenyl)ethanol **2c**, 4,4'-difluorobiphenyl (IS; 23.5 mg, 0.124 mmol, 0.3 equiv.) and anhydrous DCM.[a],[b],[c],[d] A small aliquot (~25 µL) of the resulting solution was taken for ^{19}F NMR analysis, then the halonium source was added in one portion. The reaction mixture was cooled to the desired temperature in an appropriate cooling bath, then DBU was added dropwise.[e] The reaction mixture was stirred for 16 h, with the reaction allowed to warm to room temperature. On completion, an NMR sample was prepared by diluting a 100 µL-aliquot of reaction mixture with $CDCl_3$ (400 µL). ^{19}F NMR yields were calculated by comparison to the **1a**:IS ratio prior to the reaction.

[a] Stock solutions were used for most reactions, prepared as follows: to an oven-dried Schlenk tube with a Young's tap, which had been evacuated and refilled with nitrogen (×3), was added 4'-fluoroacetophenone **1a** (1.00 mL, 8.24 mmol, 1 equiv.), 1-(2-fluorophenyl)ethanol **2c** (1.09 mL, 8.63 mmol, 1.05 equiv.), 4,4'-difluorobiphenyl (IS; 470 mg, 2.47 mmol, 0.3 equiv.) and anhydrous DCM (17.9 mL). A 1 mL-aliquot of the stock solution (corresponding to 0.412 mmol **1a**, 0.432 mmol **2c**, 0.124 mmol IS) was diluted with anhydrous DCM (3.1 mL) for each reaction with no aliquot taken for pre-reaction ^{19}F NMR analysis (this was carried out on a separate aliquot of the stock solution).

[b] For reaction with controlled addition of **2c** (Table 3.2, entry 6): to an oven-dried Schlenk tube which had been evacuated and refilled with nitrogen (×3), was added 1-(2-fluorophenyl)ethanol **2c** (81.9 µL, 0.649 mmol, 1.58 equiv.) and anhydrous DCM (668 µL). This solution was drawn into a 1 mL-syringe, from which 0.5 mL (corresponding to 0.432 mmol **2c**) was dispensed into the reaction mixture over 2 h, starting immediately after addition of DBU.

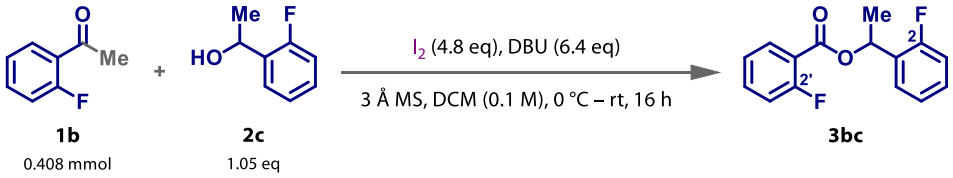
[c] For reactions with controlled addition of **1a** and **2c** (Table 3.3, entries 9-11): to an oven-dried Schlenk tube, which had been evacuated and refilled with nitrogen (×3), was added 4'-fluoroacetophenone **1a** (62.5 µL, 0.515 mmol, 1.25 equiv.), 1-(2-fluorophenyl)ethanol **2c** (68.3 µL, 0.541 mmol, 1.31 equiv.), 4,4'-difluorobiphenyl (IS; 29.4 mg, 0.155 mmol, 0.375 equiv.) and anhydrous DCM (1.12 mL). This solution was drawn into a 1 mL-syringe, from which 1 mL (corresponding to 0.412 mmol **1a**, 0.432 mmol **2c**, 0.124 mmol IS) was dispensed into the mixture of iodine and DBU in DCM (3.1 mL) over the desired time, starting immediately after addition of DBU.

[d] For reactions with molecular sieves (Table 3.4, entries 8-14): 3 Å molecular sieves (410 mg) were activated in the Schlenk tube prior to use.

[e] For reaction with controlled addition of DBU (Table 3.2, entry 7): to an oven-dried Schlenk tube which had been evacuated and refilled with nitrogen (×3), was added DBU (381 µL, 2.50 mmol, 1.58 equiv.). This solution was drawn into a 1 mL-syringe, from which 0.5 mL (corresponding to 1.69 mmol DBU) was dispensed into the reaction mixture over 5 h.

5.3.2.3 Synthesis of Side-Products

*1-(2-Fluorophenyl)ethyl 2-fluorobenzoate, **3bc***



To an oven-dried Schlenk tube containing activated 3 Å molecular sieves (410 mg), which had been evacuated and refilled with nitrogen (×3), was added 2'-fluoroacetophenone **1b** (56.3 mg, 0.408 mmol, 1 equiv.), 1-(2-fluorophenyl)ethanol **2c** (54.0 µL, 0.428 mmol, 1.05 equiv.) and anhydrous DCM (4.1 mL), followed by addition of iodine (496 mg, 1.96 mmol, 4.8 equiv.) in one portion. The reaction mixture was cooled to 0 °C (ice-water bath), then DBU (390 µL, 2.61 mmol, 6.4 equiv.) was added dropwise. The reaction mixture was stirred for 16 h and allowed to warm to room temperature. The reaction mixture was diluted with EtOAc, filtered, then added to sat. aq. $Na_2S_2O_3$. The mixture was separated and the aqueous layer was extracted a further two times with EtOAc. The combined organic fractions were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by FCC (eluted with 5% EtOAc in pentane) to obtain **3bc** as a colourless oil (81.2 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H, Ar-H), 7.76 (ddd, *J* = 9.5, 2.5, 1.5 Hz, 1H, Ar-H), 7.50 – 7.38 (m, 2H, Ar-H), 7.32 – 7.22 (m, 2H, Ar-H), 7.15 (app td, *J* = 7.5, 1.0 Hz, 1H, Ar-H), 7.07 (ddd, *J* = 10.5, 8.0, 1.0 Hz, 1H, Ar-H), 6.37 (q, *J* = 6.5 Hz, 1H, C*H*Me), 1.69 (d, *J* = 6.5 Hz, 3H, Me).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6 (d, *J* = 3.0 Hz, C=O), 162.7 (d, *J* = 247.0 Hz, Ar), 160.0 (d, *J* = 247.5 Hz, Ar), 132.7 (d, *J* = 7.5 Hz, Ar), 130.2 (d, *J* = 8.0 Hz, Ar), 129.7 (d, *J* = 8.5 Hz, Ar), 128.8 (d, *J* = 13.5 Hz, Ar), 127.3 (d, *J* = 4.0 Hz, Ar), 125.6 (d, *J* = 3.0 Hz, Ar), 124.5 (d, *J* = 3.5 Hz, Ar), 120.2 (d, *J* = 21.0 Hz, Ar), 116.7 (d, *J* = 23.0 Hz, Ar), 115.9 (d, *J* = 21.5 Hz, Ar), 68.1 (d, *J* = 3.0 Hz, *C*HMe), 21.4 (d, *J* = 1.0 Hz, Me).

^{19}F NMR (376 MHz, $CDCl_3$) δ −112.35 (ddd, *J* = 9.5, 8.5, 5.5 Hz, 1F, 2'-F), −118.21 (ddd, *J* = 10.5, 7.5, 5.0 Hz, 1F, 2-F).

HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{12}O_2F_2$ 262.0800; found 262.0798; 0.76 ppm error.

IR (neat) ν_{max} / cm^{-1}: 1716, 1613, 1489, 1455, 1294, 1249, 1230, 1124, 1064, 753.

5.3.3 Reaction Scope

5.3.3.1 Robustness Screen

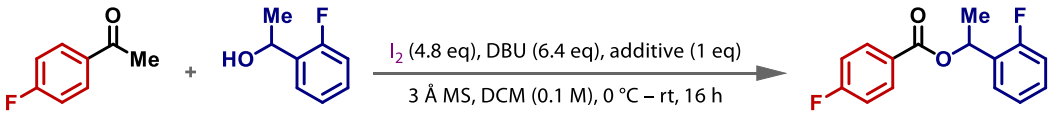
The robustness screen was based on the protocol reported by Glorius and co-workers,[135] and used the 'Group A' functional group additives from their initial report.[134]

Calibration Procedure

The robustness screen results were calculated by GC-MS, using single-point calibrations for each of the additives, as well as the reaction product, 1-(2-fluorophenyl)ethyl 4-fluorobenzoate **3ac**. Based on analyte retention times and incompatibilities, analytes (additives and reaction components) were calibrated in batches: Group 1 (additives): 1-dodecene, decanenitrile, 1-chlorododecane, acetanilide, methyl benzoate, benzonitrile, chlorobenzene, benzaldehyde; Group 2 (additives): 1-decyne, 6-undecanone, 1-nonanol, 2-vinylnaphthalene, 4-octyne, phenol, *N*-methylacetanilide; Group 3 (reaction components): 1-(2-fluorophenyl)ethanol **2c**, 2-iodo-4'-fluoroacetophenone **15a**, 1-(2-fluorophenyl)ethyl 4-fluorobenzoate **3ac**, iodoform; Group 4 (reaction components): 4'-fluoroacetophenone **1a**, 1-(2-fluorophenyl)ethyl 2-fluorobenzoate **3bc**. Dodecylamine and aniline were calibrated individually.

Calibration stock solutions were prepared containing the analytes (0.200 mmol, 1 equiv. of each) and mesitylene (as a standard; 27.8 µL, 0.200 mmol, 1 equiv.) in DCM (20 mL). For each calibration solution, a 30 µL-aliquot was diluted with DCM (1.5 mL) and filtered through silica into a vial for analysis. The dodecylamine solution was prepared by filtering through Celite, to avoid removing the additive. Additional Group 1 and Group 2 samples were prepared by filtering through Celite, to avoid removing acetanilide and *N*-methylacetanilide, respectively.

Reaction Procedure



A stock solution was used, prepared as follows: to an oven-dried Schlenk tube with a Young's tap, which had been evacuated and refilled with nitrogen (×3), was added 4'-fluoroacetophenone **1a** (510 µL, 4.20 mmol, 1 equiv.), 1-(2-fluorophenyl)ethanol **2c** (557 µL, 4.41 mmol, 1.05 equiv.) and anhydrous DCM (19.9 mL). A fresh stock solution was prepared for running repeat reactions to check reproducibility.

To an oven-dried Schlenk tube containing activated 3 Å molecular sieves (200 mg), which had been evacuated and refilled with nitrogen (×3), was added a 1 mL-aliquot of the stock solution (corresponding to 0.200 mmol **1a** and 0.210 mmol **2c**), an additive (0.200 mmol, 1 equiv.) and anhydrous DCM (1 mL), followed by addition of iodine (243 mg, 0.960 mmol, 4.8 equiv.) in one portion. The reaction mixture was cooled to 0 °C (ice-water bath), then DBU (191 µL, 1.28 mmol, 6.4 equiv.) was added dropwise. The reaction mixture was stirred for 16 h and allowed to warm to room temperature. On completion, sat. aq. $Na_2S_2O_3$ (1 mL) was added to the reaction mixture and stirred vigorously to quench any unreacted iodine. Mesitylene (GC-MS standard; 27.8 µL, 0.200 mmol, 1 equiv.) was then added to the stirring mixture. The biphasic mixture was allowed to partition, then a 100 µL-aliquot of the DCM layer was diluted with DCM (900 µL). A 30 µL-aliquot of this solution was then further diluted with DCM (1.5 mL) and filtered through silica into a vial for analysis by the same GC-MS method as used for calibration. Solutions from reactions with dodecylamine, acetanilide and *N*-methylacetanilide as additives were filtered through Celite, to avoid removing the additives.

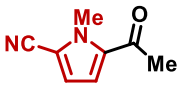
Complete Results

Additive	**3ac** Yield[a] (Repeat)[b] / %	Additive Recovery[a] (Repeat)[b] / %	Side-Products Identified[c]
None (control)	79 (74)	N/A	N/A
1-Dodecene	79	99	None
1-Decyne	64	5	Iododecyne
Decanenitrile	72 (77)	103 (101)	None
1-Chlorododecane	77	107	None
Dodecylamine[d]	20 (19)	– (–)	Dodecanenitrile, dodecyl amide
6-Undecanone	55 (61)	52 (66)	None
1-Nonanol	13	5	Nonyl ester
Acetanilide[e]	96 (87)	250 (235)	None
Methyl benzoate	81 (83)	95 (96)	None
2-Vinylnaphthalene	46	11	None
4-Octyne	67	94	None
Benzonitrile	82	100	None
Chlorobenzene	72	97	None
Aniline	47	0	Iodoaniline, azobenzene, iodoazobenzene
Benzaldehyde	61	79	None
Phenol	11	0	Triiodophenol
N-Methylacetanilide[e]	87 (69)	303 (359)	None

[a] Ester yields and additive recoveries calculated by comparison of analyte:mesitylene ratios in reaction mixtures and calibration solutions. [b] Some reactions were repeated to verify reproducibility. [c] Side-products identified by comparison of mass spectra of peaks in chromatogram to NERC database. [d] Additive recovery could not be quantified, due to co-elution with DBU (which was not removed by filtering through Celite). [e] Additive recoveries were reproducibly >>100%. Issue appeared to be calibration-related, but individual re-calibration of these additives did not resolve it. These results were therefore not included in the summarised results (Scheme 3.6).

5.3.3.2 Substrate Synthesis

5-Acetyl-1-methyl-1H-pyrrole-2-carbonitrile, ***1m***



This substrate was provided by Luke Elliot (University of Bristol).

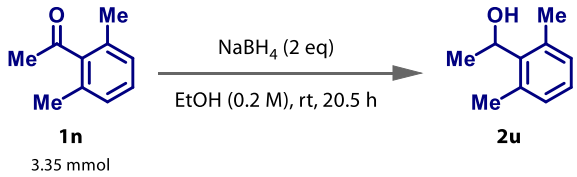
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.17 (d, *J* = 2.0 Hz, 1H, Ar-H), 3.82 (s, 3H, NMe), 2.40 (s, 3H, COMe).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1 (C=O), 130.5 (Ar), 126.2 (Ar), 120.2 (Ar), 112.5 (CN), 106.5 (Ar), 36.1 (NMe), 27.4 (CO*Me*).

HRMS (EI) m/z: $[M]^+$ Calcd for $C_8H_8N_2O$ 148.0631; found 148.0628; 2.03 ppm error.

IR (neat) ν_{max} / cm^{-1}: 3115, 2217, 1667, 1542, 1240, 1195, 861, 649.

1-(2,6-Dimethylphenyl)ethanol, **2u**



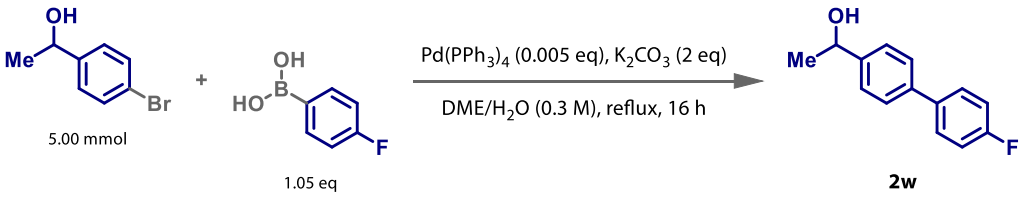
To an oven-dried round-bottom flask, which had been evacuated and refilled with nitrogen (×3), was added $NaBH_4$ (254 mg, 6.71 mmol, 2 equiv.) and anhydrous EtOH (16.8 mL), followed by addition of 2,6-dimethylacetophenone **1n** (497 mg, 3.35 mmol). The reaction mixture was stirred for 20.5 h, then concentrated under vacuum, dissolved in deionised water and extracted with DCM (×3). The combined organic fractions were concentrated under vacuum and the crude product was purified by FCC (eluted with 0-20% EtOAc in pentane) to obtain **2u** as a white solid (250 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 8.5, 6.0 Hz, 1H), 7.02 – 6.97 (m, 2H), 5.40 (qd, *J* = 7.0, 3.0 Hz, 1H), 2.45 (s, 6H), 1.74 (d, *J* = 3.0 Hz, 1H), 1.54 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7, 135.8, 129.6, 127.1, 67.8, 21.6, 20.8.

Data are consistent with those previously reported (compound 16h).[162]

1-(4'-Fluoro-[1,1'-biphenyl]-4-yl)ethanol, **2w**



Synthesised by Alex Atkins. To a round-bottom flask was added 1-(4-bromophenyl)ethanol (685 µL, 5.00 mmol, 1 equiv.), (4-fluorophenyl)boronic acid (735 mg, 5.25 mmol, 1.05 equiv.), $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol, 0.005 equiv.), DME (12.5 mL) and 2 M aq. K_2CO_3 (5 mL). The reaction mixture was stirred for 16 h under reflux, then allowed to cool to room temperature. Sat. aq. NH_4Cl was added, then the mixture was separated and the aqueous layer was extracted a further two times with DCM. The combined organic fractions were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by FCC (eluted with 25% EtOAc in pentane) to obtain **2w** as an off-white solid (777 mg, 72%).

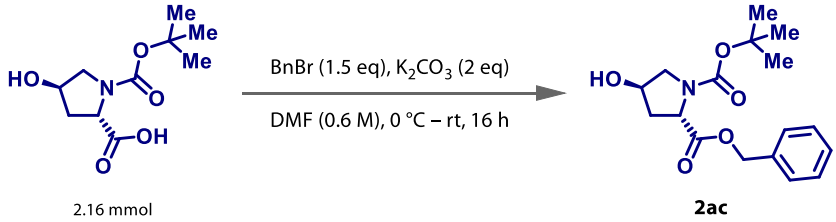
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 4H), 7.47 – 7.43 (m, 2H), 7.16 – 7.09 (m, 2H), 4.96 (q, *J* = 6.5 Hz, 1H), 1.54 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.6 (d, *J* = 246.5 Hz), 145.0, 139.6, 137.1 (d, *J* = 3.0 Hz), 128.8 (d, *J* = 8.0 Hz), 127.3, 126.1, 115.8 (d, *J* = 21.5 Hz), 70.3, 25.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ −115.67 (tt, *J* = 8.5, 5.5 Hz).

Data are consistent with those previously reported (compound 5e).[163] *As ^{19}F NMR data have not previously been reported, a copy of the spectrum is included.*

2-Benzyl 1-(*tert*-butyl) (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate, **2ac**



2.16 mmol

2ac

Synthesised by David Heard. Synthesised following a literature procedure[164] from (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (500 mg, 2.16 mmol) and isolated by FCC (eluted with 0-56% EtOAc in pentane) as a pale-yellow oil (641 mg, 92%, 2:1 mixture of rotamers *A*:*B*).

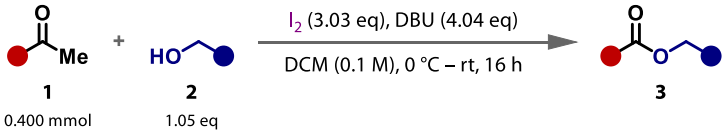
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.28 (m, 5H, *A*+*B*), 5.28 – 5.05 (m, 2H, *A*+*B*), 4.53 – 4.39 (m, 2H, *A*+*B*), 3.63 (d, *J* = 4.5 Hz, 0.33H, *B*), 3.60 (d, *J* = 4.5 Hz, 0.67H, *A*), 3.54 (d, *J* = 11.5 Hz, 0.67H, *A*), 3.44 (d, *J* = 11.5 Hz, 0.33H, *B*), 2.52 – 2.15 (m, 2H, *A*+*B*), 2.05 (app ddd, *J* = 13.0, 8.0, 5.0 Hz, 1H, *A*+*B*), 1.45 (s, 3H, *B*), 1.33 (s, 6H, *A*).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.1 (*A*), 172.8 (*B*), 154.7 (*B*), 154.1 (*A*), 135.8 (*B*), 135.6 (*A*), 128.7 (*A*), 128.6 (*B*), 128.6 (*B*), 128.5 (*A*), 128.3 (*B*), 128.2 (*A*), 80.6 (*A*), 80.4 (*B*), 70.2 (*B*), 69.5 (*A*), 66.9 (*A*+*B*), 58.1 (*A*), 57.8 (*B*), 54.8 (*A*), 53.5 (*B*), 39.3 (*A*), 38.5 (*B*), 28.5 (*B*), 28.3 (*A*).

Data are consistent with those previously reported (compound P-2).[164]

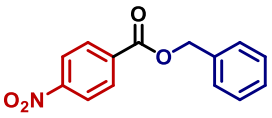
5.3.3.3 Synthesis of Esters with Primary Alcohols

Procedure A:



To an oven-dried Schlenk tube, which had been evacuated and refilled with nitrogen (×3), was added methyl ketone **1** (0.400 mmol, 1 equiv.), alcohol **2** (0.420 mmol, 1.05 equiv.) and anhydrous DCM (4 mL), followed by addition of iodine (308 mg, 1.21 mmol, 3.03 equiv.) in one portion. The reaction mixture was cooled to 0 °C (ice-water bath), then DBU (241 µL, 1.62 mmol, 4.04 equiv.) was added dropwise. The reaction mixture was stirred for 16 h and allowed to warm to room temperature. The reaction mixture was diluted with EtOAc, filtered, then added to sat. aq. $Na_2S_2O_3$. The mixture was separated and the aqueous layer was extracted a further two times with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by FCC (eluted with EtOAc in pentane).

Benzyl 4-nitrobenzoate, **3cb**



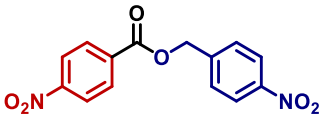
Ester **3cb** was synthesised following Procedure A from 4'-nitroacetophenone **1c** and benzyl alcohol **2b**, and was isolated as a white solid (95.9 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.21 (m, 4H), 7.49 – 7.35 (m, 5H), 5.41 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 150.7, 135.6, 135.4, 131.0, 128.9, 128.8, 128.6, 123.7, 67.8.

Data are consistent with those previously reported (compound 2h).[165]

4-Nitrobenzyl 4-nitrobenzoate, **3cd**



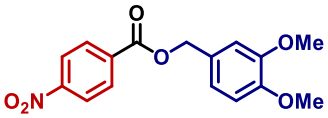
Ester **3cd** was synthesised following Procedure A from 4'-nitroacetophenone **1c** and 4-nitrobenzyl alcohol **2d**, and was isolated as a white solid (95.1 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.22 (m, 6H), 7.64 – 7.60 (m, 2H), 5.50 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 151.0, 148.1, 142.5, 135.0, 131.0, 128.8, 124.1, 123.9, 66.2.

Data are consistent with those previously reported (compound 4hh).[166]

3,4-Dimethoxybenzyl 4-nitrobenzoate, **3ce**



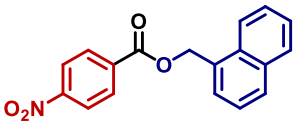
Synthesised by David Heard. Ester **3ce** was synthesised following Procedure A from 4'-nitroacetophenone **1c** and 3,4-dimethoxybenzyl alcohol **2e**, and was isolated as a yellow solid (77.0 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 9.0 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 2H), 7.02 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 5.32 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 150.6, 149.5, 149.1, 135.6, 130.8, 127.7, 123.6, 121.7, 112.0, 111.1, 67.9, 56.0, 56.0.

Data are consistent with those previously reported (compound 3al).[167]

Naphthalen-1-ylmethyl 4-nitrobenzoate, **3cf**



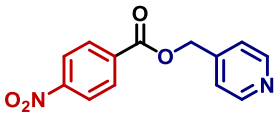
Synthesised by David Heard. Ester **3cf** was synthesised following Procedure A from 4'-nitroacetophenone **1c** and naphthalen-1-ylmethanol **2f**, and was isolated as a white solid (104 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.16 (m, 4H), 8.11 (d, *J* = 9.0 Hz, 1H), 7.94 – 7.88 (m, 2H), 7.67 – 7.46 (m, 4H), 5.86 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 150.6, 135.5, 133.9, 131.8, 130.9, 130.8, 129.9, 129.0, 128.1, 126.9, 126.2, 125.4, 123.6, 123.5, 66.1.

Data are consistent with those previously reported (compound 2k).[168]

Pyridin-4-ylmethyl 4-nitrobenzoate, **3cg**



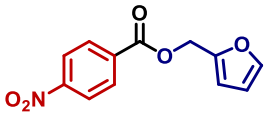
Synthesised by David Heard. Ester **3cg** was synthesised following Procedure A from 4'-nitroacetophenone **1c** and pyridin-4-ylmethanol **2g**, and was isolated as a pink solid (78.5 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 – 8.60 (m, 2H), 8.31 – 8.27 (m, 2H), 8.26 – 8.22 (m, 2H), 7.34 – 7.30 (m, 2H), 5.40 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 150.8, 150.3, 144.2, 134.9, 131.0, 123.8, 122.1, 65.6.

Data are consistent with those previously reported (compound 4g).[169]

Furan-2-ylmethyl 4-nitrobenzoate, **3ch**



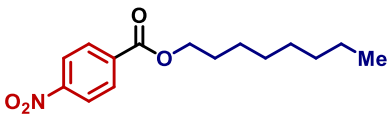
Synthesised by David Heard. Ester **3ch** was synthesised following Procedure A from 4'-nitroacetophenone **1c** and furan-2-ylmethanol **2h**, and was isolated as a yellow oil (19.2 mg, 19%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.25 (m, 2H), 8.24 – 8.19 (m, 2H), 7.47 (dd, *J* = 2.0, 1.0 Hz, 1H), 6.52 (d, *J* = 3.5 Hz, 1H), 6.41 (dd, *J* = 3.5, 2.0 Hz, 1H), 5.35 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 150.7, 148.9, 143.8, 135.4, 131.0, 123.7, 111.6, 110.9, 59.4.

Data are consistent with those previously reported (compound 3at).[167]

Octyl 4-nitrobenzoate, **3ci**



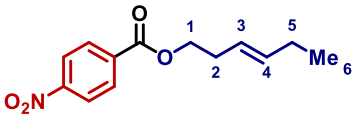
Ester **3ci** was synthesised following Procedure A from 4'-nitroacetophenone **1c** and 1-octanol **2i**, and was isolated as a colourless oil (71.0 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.26 (m, 2H), 8.23 – 8.18 (m, 2H), 4.37 (t, *J* = 6.5 Hz, 2H), 1.79 (app quint, *J* = 7.0 Hz, 2H), 1.49 – 1.22 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 150.6, 136.1, 130.8, 123.7, 66.3, 31.9, 29.4, 29.3, 28.8, 26.1, 22.8, 14.2.

Data are consistent with those previously reported (compound 3au).[170]

(E)-Hex-3-en-1-yl 4-nitrobenzoate, ***3cj***



Synthesised by David Heard. Ester **3cj** was synthesised following Procedure A from 4'-nitroacetophenone **1c** and (*E*)-hex-3-en-1-ol **2j**, and was isolated as a yellow oil (35.8 mg, 36%).

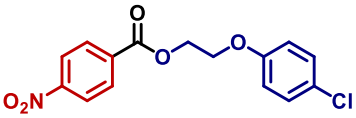
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.26 (m, 2H, Ar-H), 8.22 – 8.17 (m, 2H, Ar-H), 5.62 (dtt, *J* = 15.5, 6.5, 1.5 Hz, 1H, 3-H), 5.43 (dtt, *J* = 15.0, 7.0, 1.5 Hz, 1H, 4-H), 4.37 (t, *J* = 7.0 Hz, 2H, 1-H_2), 2.47 (qd, *J* = 7.0, 1.0 Hz, 2H, 5-H_2), 2.06 – 1.97 (m, 2H, 2-H_2), 0.95 (t, *J* = 7.5 Hz, 3H, 6-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (C=O), 150.6 (Ar), 136.0 (C3), 135.8 (Ar), 130.8 (Ar), 123.8 (C4), 123.6 (Ar), 65.6 (C1), 32.1 (C5), 25.8 (C2), 13.9 (C6).

HRMS (EI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}NO_4$ 250.1074; found 250.1070; 1.60 ppm error.

IR (neat) ν_{max} / cm^{-1}: 3668, 2966, 2901, 1722, 1528, 1274, 1103, 908, 731.

2-(4-Chlorophenoxy)ethyl 4-nitrobenzoate, ***3ck***



Synthesised by David Heard. Ester **3ck** was synthesised following Procedure A from 4'-nitroacetophenone **1c** and 2-(4-chlorophenoxy)ethan-1-ol **2k**, and was isolated as a colourless oil (86.8 mg, 67%).

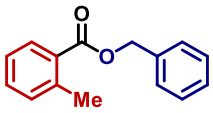
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.24 (m, 2H, Ar-H), 8.22 – 8.18 (m, 2H, Ar-H), 7.26 – 7.21 (m, 2H, Ar-H), 6.89 – 6.84 (m, 2H, Ar-H), 4.71 (t, *J* = 4.5 Hz, 2H, CH_2), 4.30 (t, *J* = 4.5 Hz, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7 (C=O), 157.1 (Ar), 150.7 (Ar), 135.2 (Ar), 131.0 (Ar), 129.6 (Ar), 126.4 (Ar), 123.7 (Ar), 116.0 (Ar), 66.1 (CH_2), 64.2 (CH_2).

HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{12}NO_5Cl$ 321.0399; found 321.0397; 0.62 ppm error.

IR (neat) ν_{max} / cm^{-1}: 2989, 2968, 1728, 1525, 1492, 1349, 1271, 1244, 1102, 1058, 910, 718.

Benzyl 2-methylbenzoate, **3db**



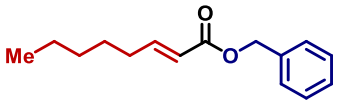
Ester **3db** was synthesised following Procedure A from 2-methylacetophenone **1d** and benzyl alcohol **2b**, and was isolated as a colourless oil (36.5 mg, 40%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.32 (m, 6H), 7.28 – 7.20 (m, 2H), 5.36 (s, 2H), 2.62 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 167.5, 140.5, 136.3, 132.2, 131.8, 130.8, 129.6, 128.7, 128.3, 125.9, 66.6, 22.0.

Data are consistent with those previously reported (compound 3).[171]

Benzyl (*E*)-oct-2-enoate, **3eb**



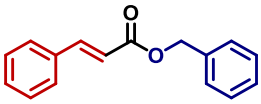
Ester **3eb** was synthesised following Procedure A from (*E*)-non-3-en-2-one **1e** and benzyl alcohol **2b**, and was isolated as a colourless oil (71.2 mg, 77%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.30 (m, 5H), 7.03 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.87 (dt, *J* = 15.5, 1.5 Hz, 1H), 5.18 (s, 2H), 2.20 (app qd, *J* = 7.0, 1.5 Hz, 2H), 1.51 – 1.41 (m, 2H), 1.35 – 1.25 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 166.7, 150.4, 136.3, 128.7, 128.3, 128.3, 121.0, 66.1, 32.4, 31.4, 27.8, 22.5, 14.1.

Data are consistent with those previously reported (compound 3aa).[172]

Benzyl cinnamate, **3fb**



Ester **3fb** was synthesised following Procedure A from (*E*)-4-phenylbut-3-en-2-one **1f** and benzyl alcohol **2b**, and was isolated as a colourless oil (76.4 mg, 80%).

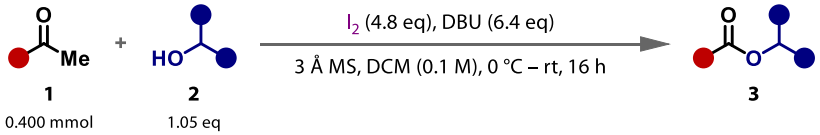
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 16.0 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.46 – 7.33 (m, 8H), 6.51 (d, *J* = 16.0 Hz, 1H), 5.27 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 145.3, 136.2, 134.5, 130.5, 129.0, 128.7, 128.4, 128.4, 128.2, 118.0, 66.5.

Data are consistent with those previously reported (compound 1g).[173]

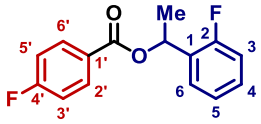
5.3.3.4 Synthesis of Esters with Secondary Alcohols

Procedure B:



To an oven-dried Schlenk tube containing activated 3 Å molecular sieves (400 mg), which had been evacuated and refilled with nitrogen (×3), was added methyl ketone **1** (0.400 mmol, 1 equiv.), alcohol **2** (0.420 mmol, 1.05 equiv.) and anhydrous DCM (4 mL), followed by addition of iodine (487 mg, 1.92 mmol, 4.8 equiv.) in one portion. The reaction mixture was cooled to 0 °C (ice-water bath), then DBU (382 µL, 2.56 mmol, 6.4 equiv.) was added dropwise. The reaction mixture was stirred for 16 h and allowed to warm to room temperature. The reaction mixture was diluted with EtOAc, filtered, then added to sat. aq. $Na_2S_2O_3$. The mixture was separated and the aqueous layer was extracted a further two times with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by FCC (eluted with EtOAc in pentane).

1-(2-Fluorophenyl)ethyl 4-fluorobenzoate, ***3ac***



Ester **3ac** was synthesised following Procedure B from 4'-fluoroacetophenone **1a** and 1-(2-fluorophenyl)ethanol **2c**, and was isolated as a colourless oil (82.5 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.08 (m, 2H, 2'-H, 6'-H), 7.47 (app td, *J* = 7.5, 2.0 Hz, 1H, 6-H), 7.32 – 7.25 (m, 1H, 4-H), 7.18 – 7.04 (m, 4H, 3-H, 5-H, 3'-H, 5'-H), 6.37 (q, *J* = 6.5 Hz, 1H, C*H*Me), 1.69 (d, *J* = 6.5 Hz, 3H, Me).

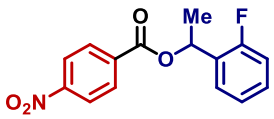
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (d, *J* = 254.0 Hz, C4'), 164.7 (C=O), 160.0 (d, *J* = 247.5 Hz, C2), 132.3 (d, *J* = 9.0 Hz, C2', C6'), 129.6 (d, *J* = 8.5 Hz, C4), 129.0 (d, *J* = 13.5 Hz, C1), 127.3 (d, *J* = 4.0 Hz, C6), 126.7 (d, *J* = 3.0 Hz, C1'), 124.4 (d, *J* = 3.5 Hz, C5), 115.8 (d, *J* = 21.5 Hz, C3), 115.7 (d, *J* = 22.0 Hz, C3', C5'), 67.9 (d, *J* = 3.0 Hz, *C*HMe), 21.5 (Me).

^{19}F NMR (376 MHz, $CDCl_3$) δ −105.59 (tt, *J* = 8.5, 5.5 Hz, 1F, 4'-F), −118.21 (ddd, *J* = 10.5, 7.5, 5.0 Hz, 1F, 2-F).

HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{12}O_2F_2$ 262.0800; found 262.0801; 0.38 ppm error.

IR (neat) ν_{max} / cm^{-1}: 2985, 1717, 1605, 1507, 1492, 1265, 1231, 1153, 1108, 1090, 1063, 853, 756.

1-(2-Fluorophenyl)ethyl 4-nitrobenzoate, ***3cc***



Ester **3cc** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and 1-(2-fluorophenyl)ethanol **2c**, and was isolated as a pale-yellow solid (105 mg, 91%).

1 mmol scale reaction: To an oven-dried 2-neck round-bottom flask containing activated 3 Å molecular sieves (1.00 g), which had been evacuated and refilled with nitrogen (×3), was added 4'-nitroacetophenone **1c** (165 mg, 1.00 mmol, 1 equiv.), 1-(2-fluorophenyl)ethanol **2c** (133 µL, 1.05 mmol, 1.05 equiv.) and anhydrous DCM

(10 mL), followed by addition of iodine (1.22 g, 4.80 mmol, 4.8 equiv.) in one portion. The reaction mixture was cooled to 0 °C (ice-water bath), then DBU (956 µL, 6.40 mmol, 6.4 equiv.) was added dropwise. The reaction mixture was stirred for 16 h and allowed to warm to room temperature. Work-up and purification were carried out following Procedure A to obtain **3cc** as a pale-yellow solid (238 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.22 (m, 4H, Ar-H), 7.48 (app td, *J* = 7.5, 2.0 Hz, 1H, Ar-H), 7.34 – 7.27 (m, 1H, Ar-H), 7.17 (app td, *J* = 7.5, 1.0 Hz, 1H, Ar-H), 7.08 (ddd, *J* = 10.5, 8.5, 1.5 Hz, 1H, Ar-H), 6.40 (q, *J* = 6.5 Hz, 1H, C*H*Me), 1.73 (d, *J* = 6.5 Hz, 3H, Me).

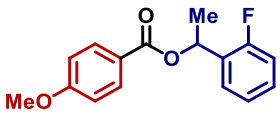
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8 (C=O), 160.0 (d, *J* = 247.5 Hz, Ar), 150.7 (Ar), 135.8 (Ar), 130.9 (Ar), 129.9 (d, *J* = 8.5 Hz, Ar), 128.3 (d, *J* = 13.5 Hz, Ar), 127.3 (d, *J* = 4.0 Hz, Ar), 124.5 (d, *J* = 3.5 Hz, Ar), 123.6 (Ar), 115.9 (d, *J* = 21.5 Hz, Ar), 68.9 (d, *J* = 3.0 Hz, *C*HMe), 21.2 (Me).

^{19}F NMR (376 MHz, $CDCl_3$) δ −117.92 (app dt, *J* = 11.0, 6.0 Hz).

HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{12}NO_4F$ 289.0745; found 289.0745; 0.00 ppm error.

IR (neat) ν_{max} / cm^{-1}: 3112, 3076, 2987, 1723, 1523, 1276, 1232, 1106, 760, 720.

1-(2-Fluorophenyl)ethyl 4-methoxybenzoate, ***3jc***



Ester **3jc** was synthesised following Procedure B from 4'-methoxyacetophenone **1j** and 1-(2-fluorophenyl)ethanol **2c**, and was isolated as a colourless oil (52.3 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.02 (m, 2H, Ar-H), 7.48 (app td, *J* = 7.5, 2.0 Hz, 1H, Ar-H), 7.30 – 7.23 (m, 1H, Ar-H), 7.14 (app td, *J* = 7.5, 1.0 Hz, 1H, Ar-H), 7.06 (ddd, *J* = 10.5, 8.0, 1.0 Hz, 1H, Ar-H), 6.96 – 6.90 (m, 2H, Ar-H), 6.36 (q, *J* = 6.5 Hz, 1H, C*H*Me), 3.86 (s, 3H, OMe), 1.67 (d, *J* = 6.5 Hz, 3H, CH*Me*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4 (C=O), 163.6 (Ar), 159.9 (d, *J* = 247.0 Hz, Ar), 131.8 (Ar), 129.5 (Ar), 129.4 (d, *J* = 8.0 Hz, Ar), 127.3 (d, *J* = 4.0 Hz, Ar), 124.4 (d, *J* = 3.5 Hz,

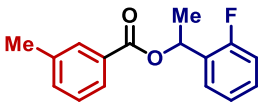
Ar), 122.9 (Ar), 115.7 (d, *J* = 21.5 Hz, Ar), 113.8 (Ar), 67.3 (d, *J* = 3.0 Hz, *C*HMe), 55.6 (OMe), 21.6 (CH*Me*).

^{19}F NMR (376 MHz, $CDCl_3$) δ −118.32 (ddd, *J* = 10.5, 7.5, 5.5 Hz).

HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{15}O_3F$ 274.1000; found 274.0998; 0.73 ppm error.

IR (neat) ν_{max} / cm^{-1}: 2982, 2935, 1709, 1605, 1511, 1251, 1230, 1166, 1098, 1062, 1028, 846, 755.

1-(2-Fluorophenyl)ethyl 3-methylbenzoate, ***3kc***



Ester **3kc** was synthesised following Procedure B from 3'-methylacetophenone **1k** and 1-(2-fluorophenyl)ethanol **2c**, and was isolated as a colourless oil (43.0 mg, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.88 (m, 2H, Ar-H), 7.49 (app td, *J* = 7.5, 2.0 Hz, 1H, Ar-H), 7.40 – 7.24 (m, 3H, Ar-H), 7.15 (app td, *J* = 7.5, 1.0 Hz, 1H, Ar-H), 7.07 (ddd, *J* = 10.5, 8.0, 1.0 Hz, 1H, Ar-H), 6.39 (q, *J* = 6.5 Hz, 1H, C*H*Me), 2.41 (s, 3H, Ar-Me), 1.69 (d, *J* = 6.5 Hz, 3H, CH*Me*).

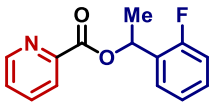
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9 (C=O), 159.9 (d, *J* = 247.5 Hz, Ar), 138.3 (Ar), 133.9 (Ar), 130.4 (Ar), 130.3 (Ar), 129.5 (d, *J* = 8.0 Hz, Ar), 129.2 (d, *J* = 13.5 Hz, Ar), 128.4 (Ar), 127.3 (d, *J* = 4.0 Hz, Ar), 126.9 (Ar), 124.4 (d, *J* = 3.5 Hz, Ar), 115.8 (d, *J* = 21.5 Hz, Ar), 67.5 (d, *J* = 3.0 Hz, *C*HMe), 21.6 (Ar-*Me*), 21.4 (CH*Me*).

^{19}F NMR (376 MHz, $CDCl_3$) δ −118.17 (app dt, *J* = 11.0, 6.0 Hz).

HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{15}O_2F$ 258.1051; found 258.1051; 0.00 ppm error.

IR (neat) ν_{max} / cm^{-1}: 2984, 1717, 1492, 1271, 1232, 1195, 1106, 1064, 757, 742.

1-(2-Fluorophenyl)ethyl picolinate, ***3lc***



Ester **3lc** was synthesised following Procedure B from 2-acetylpyridine **1l** and 1-(2-fluorophenyl)ethanol **2c**, and was isolated as a yellow oil (88.2 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (ddd, *J* = 4.5, 2.0, 1.0 Hz, 1H, Ar-H), 8.12 (app dt, *J* = 8.0, 1.0 Hz, 1H, Ar-H), 7.81 (app td, *J* = 8.0, 2.0 Hz, 1H, Ar-H), 7.53 (app td, *J* = 7.5, 2.0 Hz, 1H, Ar-H), 7.45 (ddd, *J* = 7.5, 4.5, 1.0 Hz, 1H, Ar-H), 7.29 – 7.22 (m, 1H, Ar-H), 7.12 (app td, *J* = 7.5, 1.0 Hz, 1H, Ar-H), 7.04 (ddd, *J* = 10.5, 8.0, 1.0 Hz, 1H, Ar-H), 6.45 (q, *J* = 6.5 Hz, 1H, C*H*Me), 1.73 (d, *J* = 6.5 Hz, 3H, Me).

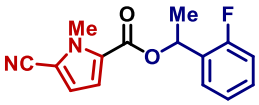
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3 (C=O), 159.9 (d, *J* = 247.5 Hz, Ar), 150.1 (Ar), 148.2 (Ar), 137.0 (Ar), 129.6 (d, *J* = 8.5 Hz, Ar), 128.7 (d, *J* = 13.5 Hz, Ar), 127.3 (d, *J* = 4.0 Hz, Ar), 127.0 (Ar), 125.4 (Ar), 124.4 (d, *J* = 3.5 Hz, Ar), 115.7 (d, *J* = 21.5 Hz, Ar), 68.3 (d, *J* = 3.0 Hz, *C*HMe), 21.3 (Me).

^{19}F NMR (376 MHz, $CDCl_3$) δ −118.07 (app dt, *J* = 11.0, 6.0 Hz).

HRMS (EI) m/z: $[M]^+$ Calcd for $C_{14}H_{12}NO_2F$ 245.0847; found 245.0846; 0.41 ppm error.

IR (neat) ν_{max} / cm^{-1}: 3058, 2986, 1717, 1492, 1302, 1278, 1244, 1230, 1131, 1063, 994, 745, 705.

1-(2-Fluorophenyl)ethyl 5-cyano-1-methyl-1H-pyrrole-2-carboxylate, ***3mc***



Synthesised by David Heard. Ester **3mc** was synthesised following Procedure B from 5-acetyl-1-methyl-1*H*-pyrrole-2-carbonitrile **1m** and 1-(2-fluorophenyl)ethanol **2c**, and was isolated as a white solid (50.9 mg, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H, Ar-H), 7.30 – 7.22 (m, 2H, Ar-H), 7.13 (app td, *J* = 7.5, 1.0 Hz, 1H, Ar-H), 7.04 (ddd, *J* = 10.5, 8.0, 1.0 Hz, 1H, Ar-H), 6.28 (q, *J* = 6.5 Hz, 1H, C*H*Me), 3.80 (s, 3H, NMe), 1.62 (d, *J* = 6.5 Hz, 3H, CH*Me*).

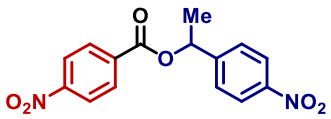
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9 (C=O), 159.9 (d, *J* = 247.5 Hz, Ar), 131.3 (Ar), 129.5 (d, *J* = 8.0 Hz, Ar), 129.0 (d, *J* = 13.5 Hz, Ar), 127.2 (d, *J* = 4.0 Hz, Ar), 124.4 (d, *J* = 3.5 Hz, Ar), 121.2 (Ar), 117.2 (Ar), 115.8 (d, *J* = 21.5 Hz, Ar), 112.5 (CN), 106.1 (Ar), 67.0 (d, *J* = 3.0 Hz, *C*HMe), 36.0 (NMe), 21.4 (CH*Me*).

^{19}F NMR (376 MHz, $CDCl_3$) δ −118.17 (app dt, *J* = 11.0, 6.0 Hz).

HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{13}N_2O_2F$ 272.0956; found 272.0955; 0.37 ppm error.

IR (neat) ν_{max} / cm^{-1}: 2961, 2901, 2224, 1711, 1551, 1492, 1223, 1192, 1065, 981, 909, 760, 731.

1-(4-Nitrophenyl)ethyl 4-nitrobenzoate, ***3cr***



Ester **3cr** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and 1-(4-nitrophenyl)ethanol **2r**, and was isolated as a white solid (111 mg, 88%).

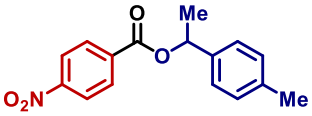
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.27 (m, 2H, Ar-H), 8.26 – 8.21 (m, 4H, Ar-H), 7.64 – 7.58 (m, 2H, Ar-H), 6.20 (q, *J* = 6.5 Hz, 1H, C*H*Me), 1.74 (d, *J* = 6.5 Hz, 3H, Me).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9 (C=O), 150.9 (Ar), 148.3 (Ar), 147.8 (Ar), 135.3 (Ar), 130.9 (Ar), 127.0 (Ar), 124.2 (Ar), 123.8 (Ar), 73.1 (*C*HMe), 22.3 (Me).

HRMS (MALDI) m/z: $[M]^-$ Calcd for $C_{15}H_{12}N_2O_6$ 316.0701; found 316.0705; 1.27 ppm error.

IR (neat) ν_{max} / cm^{-1}: 3112, 2986, 1722, 1519, 1344, 1264, 1101, 1060, 1013, 854, 841, 718, 697.

1-(4-Methylphenyl)ethyl 4-nitrobenzoate, **3cs**



Ester **3cs** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and 1-(4-methylphenyl)ethanol **2s**, and was isolated as a white solid (71.7 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.0 Hz, 2H, Ar-H), 8.23 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.20 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.13 (q, *J* = 6.5 Hz, 1H, C*H*Me), 2.36 (s, 3H, Ar-Me), 1.70 (d, *J* = 6.5 Hz, 3H, CH*Me*).

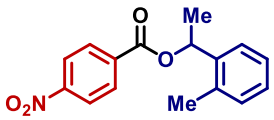
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1 (C=O), 150.6 (Ar), 138.3 (Ar), 138.1 (Ar), 136.1 (Ar), 130.9 (Ar), 129.5 (Ar), 126.3 (Ar), 123.6 (Ar), 74.3 (*C*HMe), 22.2 (CH*Me*), 21.3 (Ar-*Me*).

HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{15}NO_4$ 285.0996; found 285.0995; 0.35 ppm error.

IR (neat) ν_{max} / cm^{-1}: 2982, 1719, 1525, 1266, 1115, 1101, 1056, 1014, 815, 717.

*Only 11 of the 12 ^{13}C signals were reported in the only previous report and ^{1}H signal integrals were not reported (compound 1),[174] so **3cs** was fully characterised. Copies of NMR spectra are included.*

*1-(2-Methylphenyl)ethyl 4-nitrobenzoate, **3ct***



Ester **3ct** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and 1-(2-methylphenyl)ethanol **2t**, and was isolated as a white solid (96.1 mg, 84%).

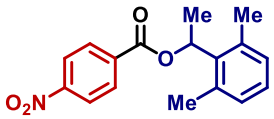
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.27 (m, 2H, Ar-H), 8.26 – 8.22 (m, 2H, Ar-H), 7.52 – 7.46 (m, 1H, Ar-H), 7.28 – 7.17 (m, 3H, Ar-H), 6.36 (q, *J* = 6.5 Hz, 1H, C*H*Me), 2.46 (s, 3H, Ar-Me), 1.69 (d, *J* = 6.5 Hz, 3H, CH*Me*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1 (C=O), 150.7 (Ar), 139.5 (Ar), 136.0 (Ar), 134.9 (Ar), 130.8 (Ar), 130.7 (Ar), 128.1 (Ar), 126.6 (Ar), 125.4 (Ar), 123.7 (Ar), 71.3 (*C*HMe), 21.6 (CH*Me*), 19.2 (Ar-*Me*).

HRMS (MALDI) m/z: $[M]^-$ Calcd for $C_{16}H_{15}NO_4$ 285.1007; found 285.1004; 1.05 ppm error.

IR (neat) ν_{max} / cm^{-1}: 2981, 1719, 1524, 1268, 1115, 1101, 1062, 1049, 872, 841, 760, 717.

1-(2,6-Dimethylphenyl)ethyl 4-nitrobenzoate, ***3cu***



Ester **3cu** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and 1-(2,6-dimethylphenyl)ethanol **2u**, and was isolated as a white solid (34.4 mg, 29%).

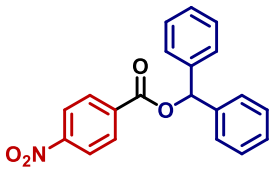
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.27 (m, 2H, Ar-H), 8.25 – 8.20 (m, 2H, Ar-H), 7.09 (dd, *J* = 8.5, 6.5 Hz, 1H, Ar-H), 7.03 (d, *J* = 7.5 Hz, 2H, Ar-H), 6.58 (q, *J* = 7.0 Hz, 1H, C*H*Me), 2.55 (s, 6H, Ar-Me), 1.75 (d, *J* = 7.0 Hz, 3H, CH*Me*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1 (C=O), 150.6 (Ar), 136.7 (Ar), 136.0 (Ar), 136.0 (Ar), 130.8 (Ar), 129.5 (Ar), 127.9 (Ar), 123.7 (Ar), 71.7 (*C*HMe), 20.8 (Ar-*Me*), 19.7 (CH*Me*).

HRMS (MALDI) m/z: $[M]^-$ Calcd for $C_{17}H_{17}NO_4$ 299.1163; found 299.1169; 2.01 ppm error.

IR (neat) ν_{max} / cm^{-1}: 2977, 1718, 1524, 1347, 1271, 1101, 1057, 1014, 872, 841, 772, 718.

Benzhydryl 4-nitrobenzoate, **3cv**



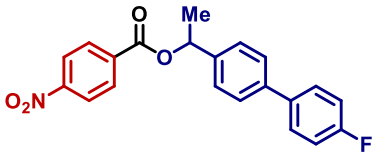
Synthesised by David Heard. Ester **3cv** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and benzhydrol **2v**, and was isolated as a white solid (77.7 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (app s, 4H), 7.48 – 7.43 (m, 4H), 7.42 – 7.37 (m, 4H), 7.37 – 7.31 (m, 2H), 7.17 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 150.7, 139.6, 135.7, 131.0, 128.8, 128.4, 127.2, 123.7, 78.6.

Data are consistent with those previously reported (compound 5g).[175]

1-(4'-Fluoro-[1,1'-biphenyl]-4-yl)ethyl 4-nitrobenzoate, ***3cw***



Synthesised by David Heard. Ester **3cw** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and 1-(4'-fluoro-[1,1'-biphenyl]-4-yl)ethanol **2w**, and was isolated as a white solid (92.4 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.23 (m, 4H, Ar-H), 7.59 – 7.50 (m, 6H, Ar-H), 7.16 – 7.09 (m, 2H, Ar-H), 6.21 (q, *J* = 6.5 Hz, 1H, C*H*Me), 1.76 (d, *J* = 6.5 Hz, 3H, Me).

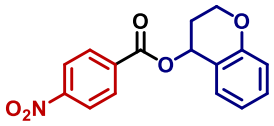
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1 (C=O), 162.6 (d, *J* = 247.0 Hz, Ar), 150.6 (Ar), 140.4 (Ar), 140.1 (Ar), 136.8 (d, *J* = 3.5 Hz, Ar), 135.9 (Ar), 130.9 (Ar), 128.8 (d, *J* = 8.0 Hz, Ar), 127.4 (Ar), 126.8 (Ar), 123.6 (Ar), 115.8 (d, *J* = 21.5 Hz, Ar), 74.0 (*C*HMe), 22.2 (Me).

^{19}F NMR (376 MHz, $CDCl_3$) δ −115.15 (tt, *J* = 8.5, 5.5 Hz).

HRMS (MALDI) m/z: $[M]^-$ Calcd for $C_{21}H_{16}NO_4F$ 365.1063; found 365.1068; 1.37 ppm error.

IR (neat) ν_{max} / cm^{-1}: 2984, 1721, 1527, 1498, 1271, 1103, 908, 823, 732.

Chroman-4-yl 4-nitrobenzoate, ***3cx***



Synthesised by David Heard. Ester **3cx** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and chroman-4-ol **2x**, and was isolated as a white solid (59.6 mg, 50%).

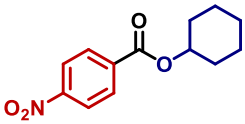
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.24 (m, 2H, Ar-H), 8.23 – 8.19 (m, 2H, Ar-H), 7.36 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-H), 7.27 (ddd, *J* = 9.0, 7.5, 2.0 Hz, 1H, Ar-H), 6.97 – 6.88 (m, 2H, Ar-H), 6.23 (app t, *J* = 4.0 Hz, 1H, C*H*CH_2), 4.44 – 4.31 (m, 2H, CH_2O), 2.37 (app ddt, *J* = 15.5, 11.0, 4.5 Hz, 1H, CHC*H*H), 2.26 (app dq, *J* = 14.5, 3.5 Hz, 1H, CHCH*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2 (C=O), 155.5 (Ar), 150.7 (Ar), 135.7 (Ar), 130.9 (Ar), 130.9 (Ar), 130.7 (Ar), 123.7 (Ar), 120.8 (Ar), 119.6 (Ar), 117.4 (Ar), 67.2 (*C*HCH_2), 62.2 (CH_2O), 28.5 (CH*C*H_2).

HRMS (MALDI) m/z: $[M]^-$ Calcd for $C_{16}H_{13}NO_5$ 299.0794; found 299.0798; 1.34 ppm error.

IR (neat) ν_{max} / cm^{-1}: 2970, 1715, 1608, 1523, 1487, 1345, 1263, 1228, 1103, 1057, 865, 758, 719.

Cyclohexyl 4-nitrobenzoate, **3cy**



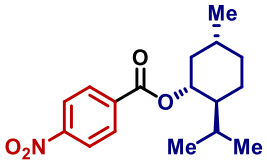
Ester **3cy** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and cyclohexanol **2y**, and was isolated as a pale-yellow oil (83.0 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.25 (m, 2H), 8.23 – 8.18 (m, 2H), 5.06 (tt, *J* = 9.0, 4.0 Hz, 1H), 2.02 – 1.92 (m, 2H), 1.85 – 1.75 (m, 2H), 1.66 – 1.55 (m, 3H), 1.52 – 1.41 (m, 2H), 1.41 – 1.30 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 150.6, 136.5, 130.8, 123.6, 74.5, 31.7, 25.5, 23.8.

Data are consistent with those previously reported (compound 6).[176]

(−)-Menthyl 4-nitrobenzoate, **3cz**



Synthesised by David Heard. Ester **3cz** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and (−)-menthol **2z**, and was isolated as a yellow solid (66.3 mg, 54%).

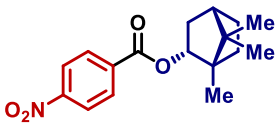
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.25 (m, 2H), 8.22 – 8.17 (m, 2H), 4.96 (app td, *J* = 11.0, 4.5 Hz, 1H), 2.16 – 2.08 (m, 1H), 1.91 (app septd, *J* = 7.0, 3.0 Hz, 1H), 1.78 – 1.69 (m, 2H), 1.62 – 1.51 (m, 2H), 1.20 – 1.06 (m, 2H), 0.99 – 0.87 (m, 7H), 0.79 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 150.5, 136.3, 130.8, 123.6, 76.2, 47.3, 40.9, 34.3, 31.6, 26.7, 23.7, 22.1, 20.8, 16.6.

Optical Rotation: $[\alpha]_D^{22}$ −34 (*c* 1.0, $CHCl_3$).

Data are consistent with those previously reported (compound 4).[177]

(−)-Bornyl 4-nitrobenzoate, **3caa**



Synthesised by David Heard. Ester **3caa** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and (−)-borneol **2aa**, and was isolated as a white solid (23.6 mg, 19%).

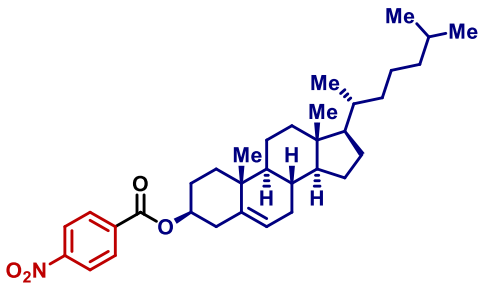
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.27 (m, 2H), 8.24 – 8.19 (m, 2H), 5.15 (ddd, *J* = 10.0, 3.5, 2.0 Hz, 1H), 2.55 – 2.45 (m, 1H), 2.08 (ddd, *J* = 13.5, 9.5, 4.5 Hz, 1H), 1.88 – 1.78 (m, 1H), 1.77 (app t, *J* = 4.5 Hz, 1H), 1.49 – 1.39 (m, 1H), 1.32 (ddd, *J* = 12.0, 9.5, 4.5 Hz, 1H), 1.13 (dd, *J* = 14.0, 3.5 Hz, 1H), 0.97 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 150.6, 136.4, 130.7, 123.7, 82.0, 49.3, 48.1, 45.0, 37.0, 28.2, 27.5, 19.8, 19.0, 13.8.

Optical Rotation: $[\alpha]_D^{22}$ −16 (*c* 0.5, $CHCl_3$).

Data are consistent with those previously reported (compound 11e).[178]

Cholesteryl 4-nitrobenzoate, **3cab**



Synthesised by David Heard. Ester **3cab** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and cholesterol **2ab**, and was isolated as a white solid (93.2 mg, 44%).

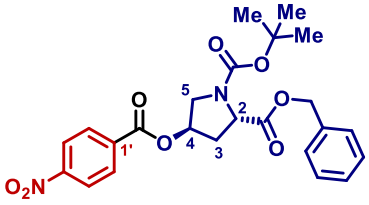
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.25 (m, 2H), 8.22 – 8.18 (m, 2H), 5.43 (app d, *J* = 4.5 Hz, 1H), 4.94 – 4.83 (m, 1H), 2.51 – 2.44 (m, 2H), 2.06 – 1.70 (m, 6H), 1.65 – 0.95 (m, 23H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 2.0 Hz, 3H), 0.85 (d, *J* = 2.0 Hz, 3H), 0.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 150.5, 139.4, 136.3, 130.8, 123.6, 123.3, 75.9, 56.8, 56.2, 50.1, 42.4, 39.8, 39.6, 38.2, 37.1, 36.7, 36.2, 35.9, 32.0, 32.0, 28.4, 28.1, 27.9, 24.4, 24.0, 23.0, 22.7, 21.2, 19.5, 18.8, 12.0.

Optical Rotation: $[\alpha]_D^{22}$ +5 (*c* 0.2, $CHCl_3$).

Data are consistent with those previously reported (compound 3m).[179]

2-Benzyl 1-(tert-butyl) (2S,4R)-4-((4-nitrobenzoyl)oxy)pyrrolidine-1,2-dicarboxylate, ***3cac***



Synthesised by David Heard. Ester **3cac** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and 2-benzyl 1-(*tert*-butyl) (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate **2ac**, and was isolated as a white solid (143 mg, 76%, 3:2 mixture of rotamers *A*:*B*- calculated from C2-H signals, as these were clearly resolved).

^{1}H NMR (400 MHz, $CDCl_3$): *cf.* diastereomer[180]; δ 8.29 (d, *J* = 9.0 Hz, 2H, Ar-H, *A*+*B*), 8.17 (d, *J* = 9.0 Hz, 2H, Ar-H, *A*+*B*), 7.41 – 7.30 (m, 5H, Ar-H, *A*+*B*), 5.58 – 5.52 (m, 1H, 4-H, *A*+*B*), 5.32 – 5.10 (m, 2H, C*H*$_2$Ph, *A*+*B*), 4.59 (app t, *J* = 8.0 Hz, 0.4H, 2-H, *B*), 4.48 (app t, *J* = 8.0 Hz, 0.6H, 2-H, *A*), 3.91 – 3.81 (m, 1.2H, 5-H, *A*), 3.71 (app d, *J* = 12.5 Hz, 0.8H, 5-H, *B*), 2.63 – 2.50 (m, 1H, 3-H, *A*+*B*), 2.41 – 2.28 (m, 1H, 3-H, *A*+*B*), 1.46 (s, 3.6H, Me, *B*), 1.37 (s, 5.4H, Me, *A*).

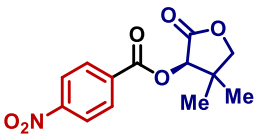
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3 (2-C=O, *A*), 171.9 (2-C=O, *B*), 164.1 (1'-C=O, *B*), 164.0 (1'-C=O, *A*), 154.2 (N-C=O, *B*), 153.7 (N-C=O, *A*), 150.8 (Ar, *B*), 150.7 (Ar, *A*), 135.5 (Ar, *B*), 135.3 (Ar, *A*), 135.0 (Ar, *A*), 134.9 (Ar, *B*), 130.9 (Ar, *A*+*B*), 128.7 (Ar, *A*), 128.6 (Ar, *B*), 128.6 (Ar, *B*), 128.5 (Ar, *A*), 128.4 (Ar, *B*), 128.2 (Ar, *A*), 123.7 (Ar, *B*), 123.6 (Ar, *A*), 80.9 (*C*Me$_3$, *A*), 80.8 (*C*Me$_3$, *B*), 74.4 (C4, *B*), 73.7 (C4, *A*), 67.1 (*C*H$_2$Ph, *A*+*B*), 58.0 (C2, *A*), 57.7 (C2, *B*), 52.3 (C5, *B*), 52.0 (C5, *A*), 36.6 (C3, *A*), 35.6 (C3, *B*), 28.4 (Me, *B*), 28.2 (Me, *A*).

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{27}N_2O_8$ 471.1767; found 471.1765; 0.42 ppm error.

IR (neat) ν_{max} / cm^{-1}: 2976, 2901, 1726, 1698, 1528, 1398, 1270, 1157, 1115, 1102, 732, 720.

Optical Rotation: $[\alpha]_D^{22}$ −13 (*c* 1.0, $CHCl_3$).

O-(4-Nitrobenzoyl)-D-pantolactone, ***3cad***



Synthesised by David Heard. Ester **3cad** was synthesised following Procedure B from 4'-nitroacetophenone **1c** and D-pantolactone **2ad**, and was isolated as a white solid (79.7 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 – 8.28 (m, 2H, Ar-H), 8.27 – 8.22 (m, 2H, Ar-H), 5.63 (s, 1H, CH), 4.14 (app s, 2H, CH_2), 1.29 (s, 3H, Me), 1.23 (s, 3H, Me).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9 (CH*C*=O), 163.7 (Ar*C*=O), 151.0 (Ar), 134.2 (Ar), 131.3 (Ar), 123.8 (Ar), 76.4 (CH), 76.3 (CH_2), 40.6 (*C*Me_2), 23.1 (Me), 20.1 (Me).

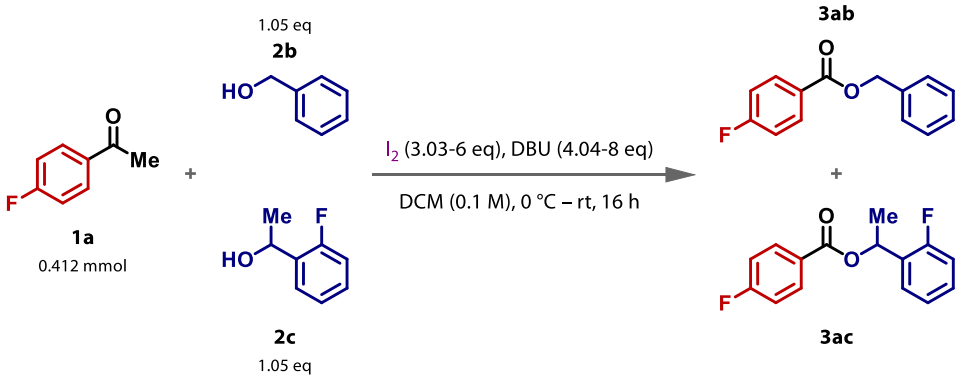
HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{13}H_{13}NO_6$ 279.0743; found 279.0750; 2.51 ppm error.

IR (neat) ν_{max} / cm^{-1}: 2970, 1789, 1735, 1527, 1266, 1120, 1105, 717.

Optical Rotation: $[\alpha]_D^{22}$ +2 (*c* 1.0, $CHCl_3$).

5.3.4 Mechanistic Experiments

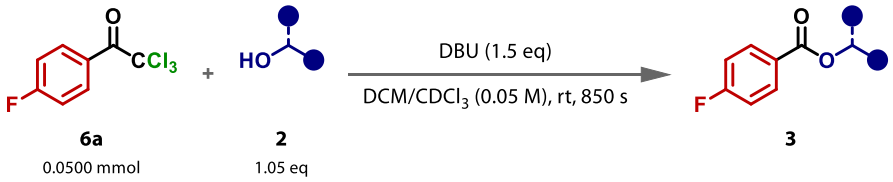
5.3.4.1 Competition Experiments



To an oven-dried Schlenk tube, which had been evacuated and refilled with nitrogen (×3), was added 4'-fluoroacetophenone **1a** (50.0 µL, 0.412 mmol, 1 equiv.), benzyl alcohol **2b** (44.8 µL, 0.432 mmol, 1.05 equiv.), 1-(2-fluorophenyl)ethanol **2c** (54.6 µL, 0.432 mmol, 1.05 equiv.), 4,4'-difluorobiphenyl (IS; 23.5 mg, 0.124 mmol, 0.3 equiv.) and anhydrous DCM (4.1 mL). A small aliquot (~25 µL) of the resulting solution was

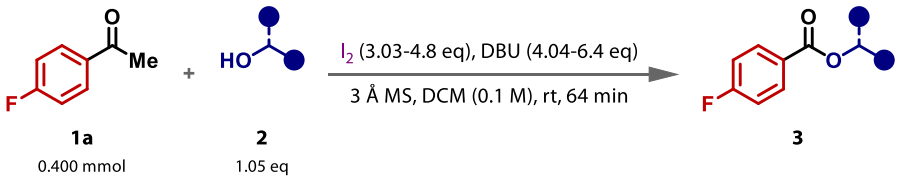
taken for ^{19}F NMR analysis, then iodine was added in one portion. The reaction mixture was cooled to 0 °C (ice-water bath) and DBU was added dropwise. The reaction mixture was stirred for 16 h and allowed to warm to room temperature. On completion, an NMR sample was prepared by diluting a 100 µL-aliquot of reaction mixture with $CDCl_3$ (400 µL). ^{19}F NMR yields were calculated by comparison to the **1a**:IS ratio prior to the reaction.

5.3.4.2 Monitored Trichloroacetophenone Cleavage



To an oven-dried Schlenk tube containing activated 3 Å molecular sieves (300 mg), which had been evacuated and refilled with nitrogen (×3), was added 2,2,2-trichloro-4'-fluoroacetophenone **6a** (36.2 mg, 0.150 mmol, 3 equiv.), alcohol **2** (0.158 mmol, 3.15 equiv.), 4,4'-difluorobiphenyl (IS; 14.3 mg, 0.0750 mmol, 1.5 equiv.), anhydrous DCM (1.2 mL) and anhydrous $CDCl_3$ (1.8 mL). A 1 mL-aliquot of the resulting solution (corresponding to 0.0500 mmol **6a**, 0.0525 mmol **2** and 0.0250 mmol IS) was transferred to an NMR tube under nitrogen and analysed by ^{19}F NMR to determine the **6a**:IS ratio prior to reaction. DBU (11.2 µL, 0.0750 mmol, 1.5 equiv.) was added to the NMR tube in one portion (open to air), which was shaken to mix and then monitored by ^{19}F NMR (spectra acquired at 10 s intervals).

5.3.4.3 Monitored Haloform Couplings

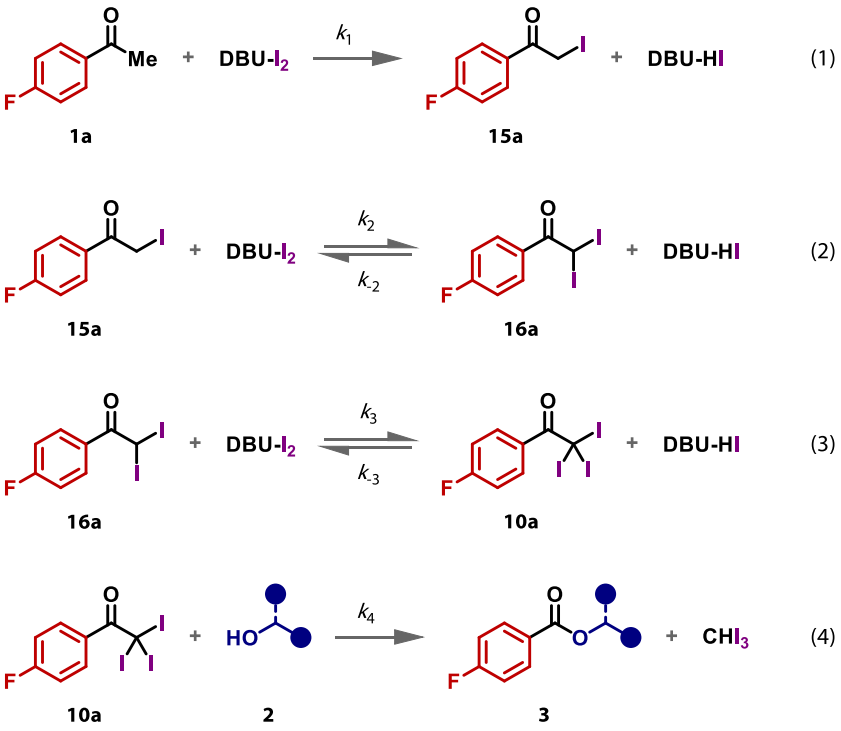


To an oven-dried Schlenk tube containing activated 3 Å molecular sieves (400 mg), which had been evacuated and refilled with nitrogen (×3), was added 4'-fluoroacetophenone **1a** (48.6 µL, 0.400 mmol, 1 equiv.), alcohol **2** (if added; 0.420 mmol, 1.05 equiv.), 4,4'-difluorobiphenyl (IS; 23.5 mg, 0.124 mmol, 0.3 equiv.), additive (if any, i.e. iodoform) and anhydrous DCM (4 mL). A small aliquot (~25 µL) of the resulting solution was taken for ^{19}F NMR analysis, then iodine was added in one portion. DBU was then added in one portion and ~250 µL-aliquots of the reaction mixture were taken after 1, 2, 4, 8, 16, 32 and 64 min. Aliquots were immediately quenched with

sat. aq. NH_4Cl (~0.7 mL) and NMR samples were prepared by diluting a 100 µL-aliquot of the quenched reaction mixture with $CDCl_3$ (400 µL). ^{19}F NMR yields were calculated by comparison to the **1a**:IS ratio prior to reaction. NB: NMR samples were protected from exposure to light, due to the light sensitivity of reaction intermediates.

5.3.4.4 COPASI Modelling

A model of the haloform coupling was constructed using COPASI,[136] based on four elementary reactions:



Initial concentrations (in mmol mL^{-1}) of reaction species were set as:

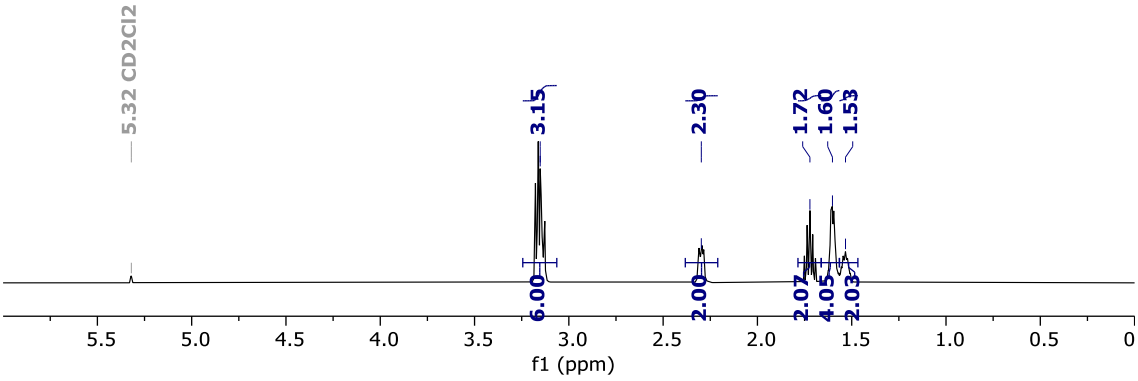
Species	Without alcohol	With primary alcohol **2b**	With secondary alcohol **2c**	With secondary alcohol **2c** (4.8 eq I_2, 6.4 eq DBU)
1a	0.100	0.100	0.100	0.100
DBU-I_2	0.303	0.303	0.303	0.480
15a	0	0	0	0
DBU-HI	0	0	0	0
16a	0	0	0	0
10a	0	0	0	0
2	0	0.105	0.105	0.105
3	0	0	0	0
CHI_3	0	0	0	0

Rate constant k_1 was calculated by the method of initial rates from the concentration of acetophenone **1a** over the first 4 min of the monitored alcohol-free reaction.

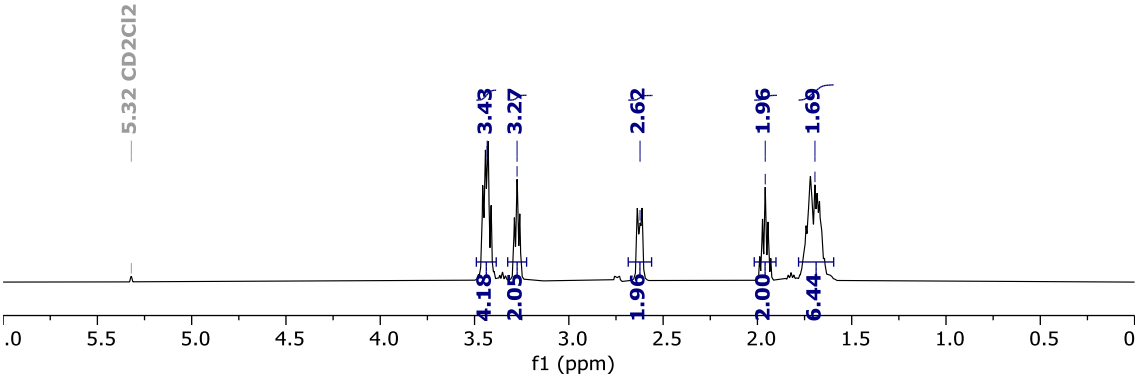
Rate constants k_2, k_{-2}, k_3 and k_{-3} were calculated using the 'parameter estimation' tool in COPASI. The concentrations of **1a**, iodoacetophenone **15a**, diiodoacetophenone **16a** and triiodoacetophenone **10a** over 64 min in the monitored alcohol-free reaction were imported and matched to their corresponding terms in the elementary reactions. *k* values were determined using the 'genetic algorithm' method, with their lower and upper bounds set to 0.000001 and 1,000,000 mL mmol^{-1} s^{-1}, respectively and with k_1 fixed at its previously calculated value.

The values of k_4 with primary **2b** and secondary alcohol **2c** were (separately) calculated in the same manner using experimental data from the monitored reactions with **2b** and **2c** (primary alcohol coupling conditions), respectively, and with the values of k_1, k_2, k_{-2}, k_3 and k_{-3} fixed at their previously calculated values.

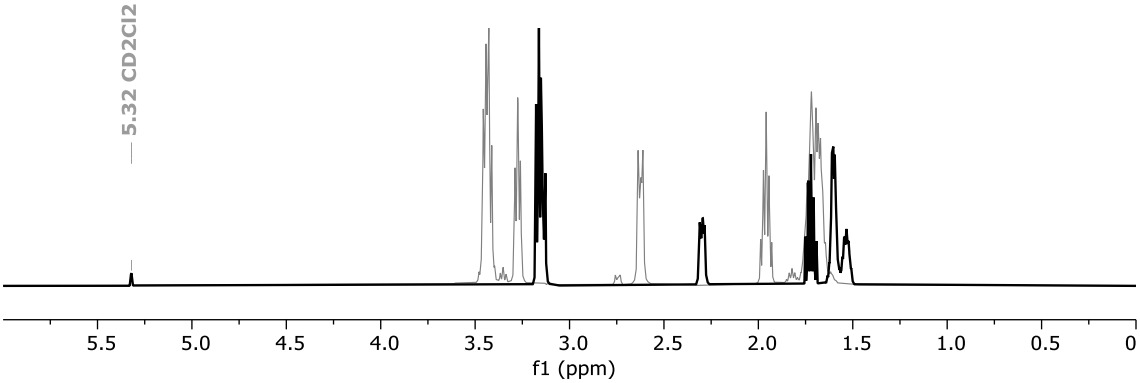
Observation of DBU-iodine complex: Solutions of DBU (0.400 mmol in 1 mL CD_2Cl_2), and iodine and DBU (0.300 mmol iodine and 0.400 mmol DBU in 1 mL CD_2Cl_2) were analysed by ^{1}H NMR.



^{1}H NMR spectrum of DBU in CD_2Cl_2.



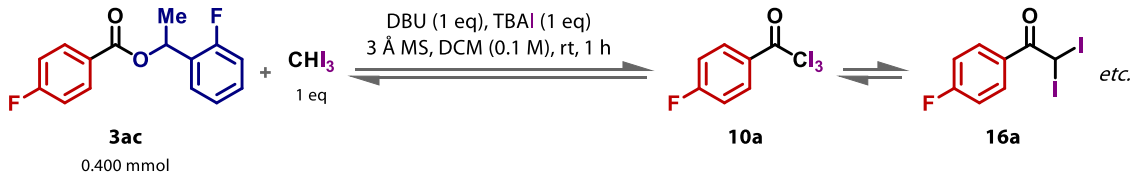
^{1}H NMR spectrum of a 3:4 mixture of iodine and DBU in CD_2Cl_2.



Superimposed ^{1}H NMR spectra of DBU (foreground) and a 3:4 mixture of iodine and DBU (background).

The downfield shift of the DBU signals on addition of iodine strongly suggests that there is an interaction between DBU and iodine in solution, i.e. formation of a DBU-iodine 'complex'. Furthermore, reaction mixtures containing iodine were observed to rapidly turn from purple to brown on addition of DBU, also suggesting a loss of 'free' iodine in solution.

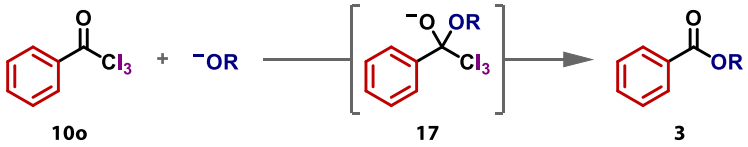
5.3.4.5 Reversibility of Ester Formation Experiment



To an oven-dried Schlenk tube containing activated 3 Å molecular sieves (400 mg), which had been evacuated and refilled with nitrogen (×3), was added 1-(2-fluorophenyl)ethyl 4-fluorobenzoate **3ac** (105 mg, 0.400 mmol, 1 equiv.), iodoform (157 mg, 0.400 mmol, 1 equiv.), TBAI (148 mg, 0.400 mmol, 1 equiv.), 4,4'-difluorobiphenyl (IS; 22.8 mg, 0.120 mmol, 0.3 equiv.) and anhydrous DCM (4 mL). The resulting solution was stirred for 1.5 h, then a small aliquot (~25 µL) was taken for ^{19}F NMR analysis. DBU (59.8 µL, 0.400 mmol, 1 equiv.) was added to the reaction mixture in one portion, then after 1 h, a ~250 µL-aliquot of the reaction mixture was taken and immediately quenched with sat. aq. NH_4Cl (~0.7 mL). An NMR sample was prepared by diluting a 100 µL-aliquot of the quenched reaction mixture with $CDCl_3$ (400 µL). ^{19}F NMR yield was calculated by comparison to the **3ac**:IS ratio prior to the reaction.

5.3.4.6 DFT Modelling

Calculations performed by Stephen Sweeting.



Geometries in the reactions between 2,2,2-triiodo-1-phenylethanone **10o** and alkoxides were optimised to the ground state using DFT, using the hybrid metafunctional M06-2X[181] and the def2-QZVPPD Karlsruhe basis set.[182–185] Calculations were performed in Gaussian 16[186] and structures were visualised using GaussView 6.1.[187]

Solvent effects were modelled using the polarisable continuum model and the self-consistent reaction field approach, as implemented in Gaussian 16.[188] Thermal corrections to Gibbs free energies were calculated from zero-point vibrational energies, assuming ideal gas behaviour for the correction calculations.

5.3.4.7 Light Sensitivity Experiments

2-Iodo-4'-fluoroacetophenone **15a** (19.8 mg, 0.0750 mmol, 1 equiv.) and 4,4'-difluorobiphenyl (IS; 7.13 mg, 0.0375 mmol, 0.5 equiv.) were dissolved in $CDCl_3$ (1.5 mL). Two 0.6 mL-aliquots of this solution were transferred to NMR tubes (samples A and B), which were analysed by ^{19}F NMR. Sample A was irradiated with a compact fluorescent lamp (CFL; 700 lm, 10 W) for 17 h, while sample B was protected from exposure to light. The samples were then re-analysed by ^{19}F NMR.

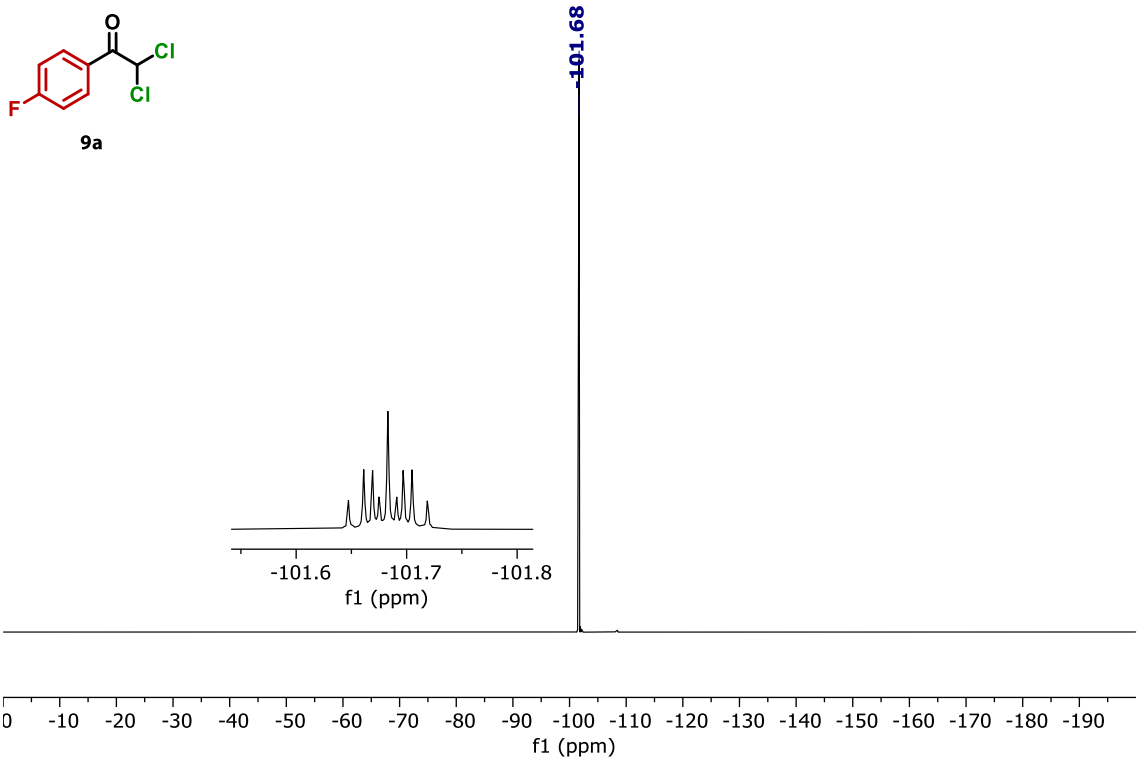
2,2-Diiodo-4'-fluoroacetophenone **16a** (33.0 mg, 0.125 mmol, 1 equiv.) and 4,4'-difluorobiphenyl (IS; 11.9 mg, 0.0625 mmol, 0.5 equiv.) were dissolved in a mixture of DCM (0.5 mL) and $CDCl_3$ (2 mL). Three 0.6 mL-aliquots of this solution were transferred to NMR tubes (samples A, B and C), which were analysed by ^{19}F NMR. Sample A was irradiated with a CFL (700 lm, 10 W) for 17 h, while sample B was stored under ambient lighting in a fumehood and sample C was protected from exposure to light. The samples were then re-analysed by ^{19}F NMR.

5.4 NMR Spectra of Novel Compounds

Spectra are also included for known compounds where ^{19}F NMR data have not previously been reported (^{19}F NMR spectra only included) and for compounds where the NMR data reported here are not fully consistent with those in the only previous report. See characterisation data for further details.

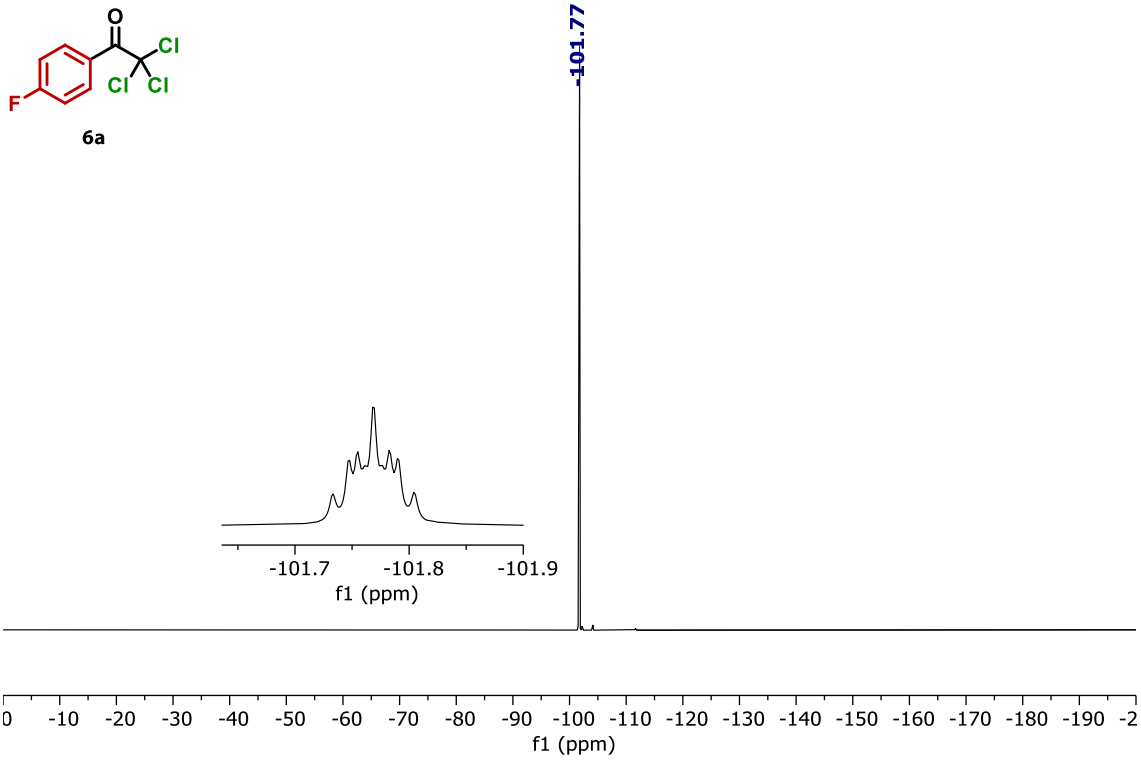
2,2-Dichloro-4'-fluoroacetophenone, **9a**

^{19}F NMR (376 MHz, $CDCl_3$)



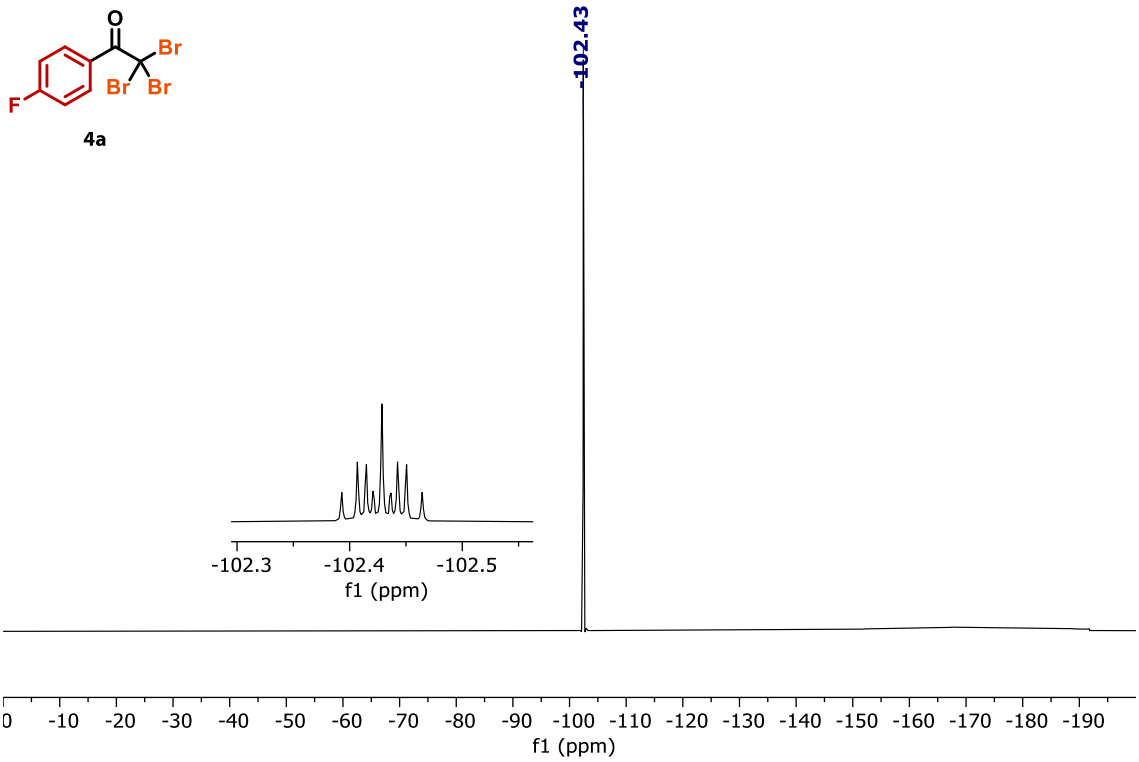
2,2,2-Trichloro-4'-fluoroacetophenone, **6a**

^{19}F NMR (376 MHz, $CDCl_3$)



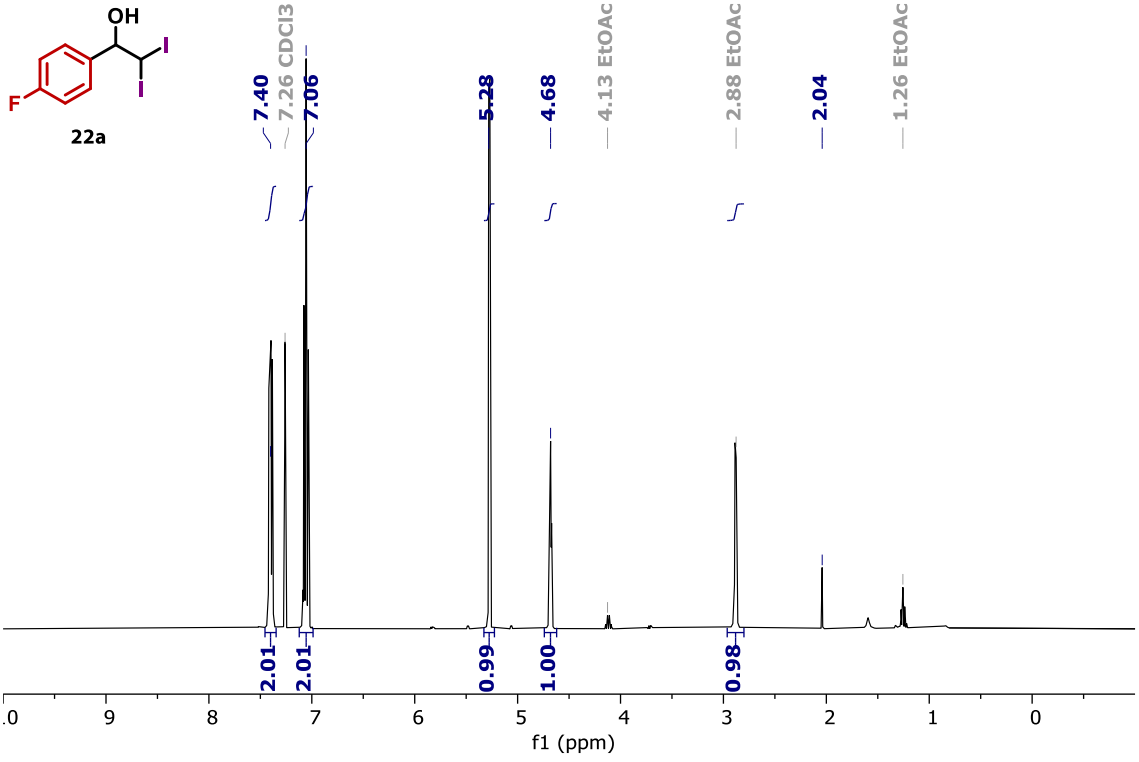
2,2,2-Tribromo-4’-fluoroacetophenone, **4a**

^{19}F NMR (376 MHz, $CDCl_3$)

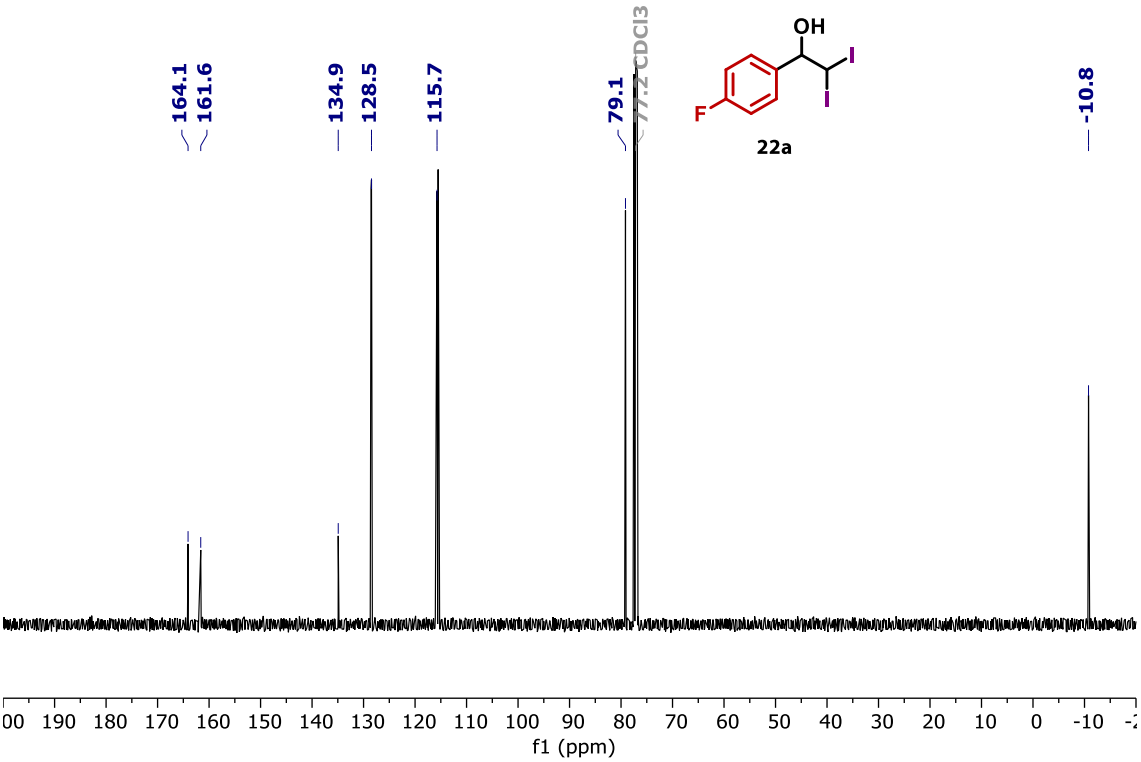


2,2-Diiodo-1-(4-fluorophenyl)ethanol, ***22a***

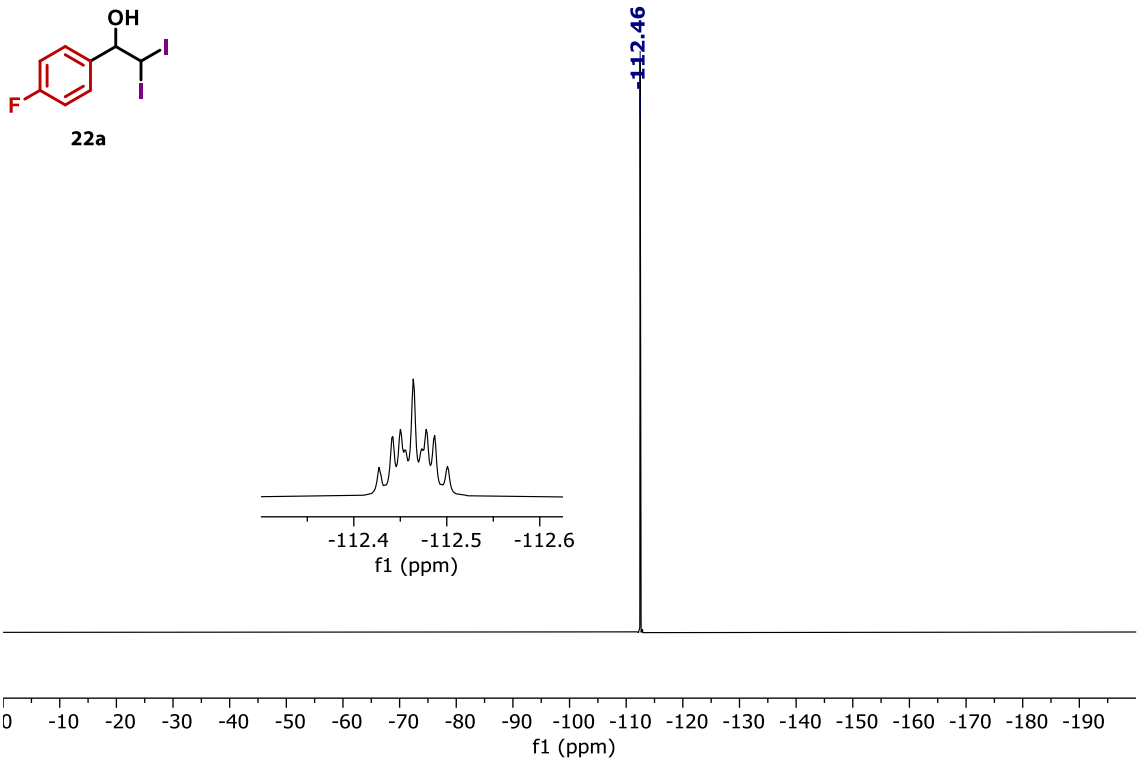
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

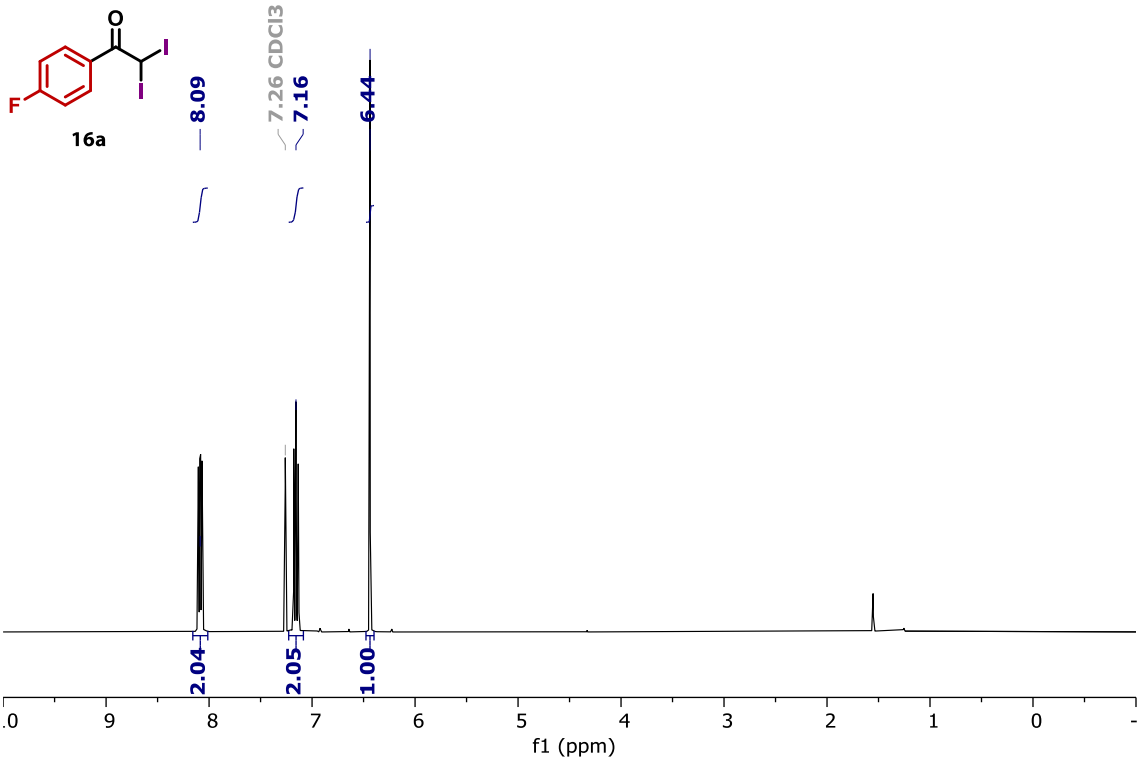


^{19}F NMR (376 MHz, $CDCl_3$)

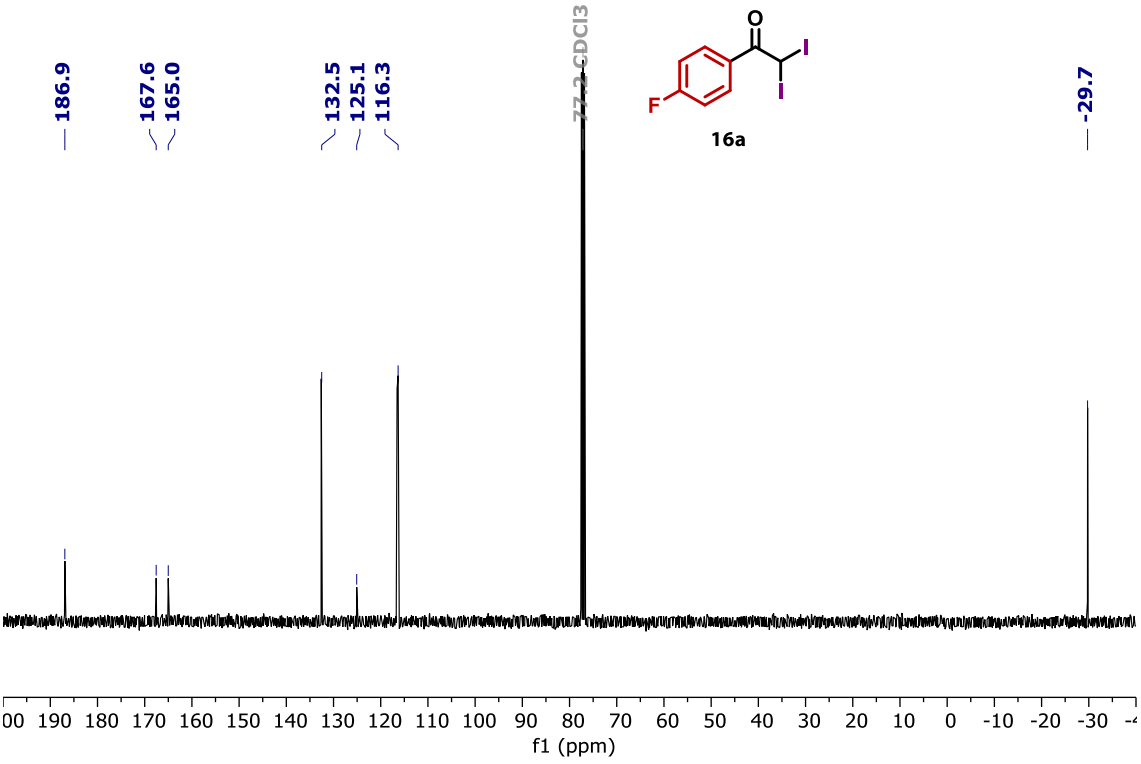


2,2-Diiodo-4’-fluoroacetophenone, **16a**

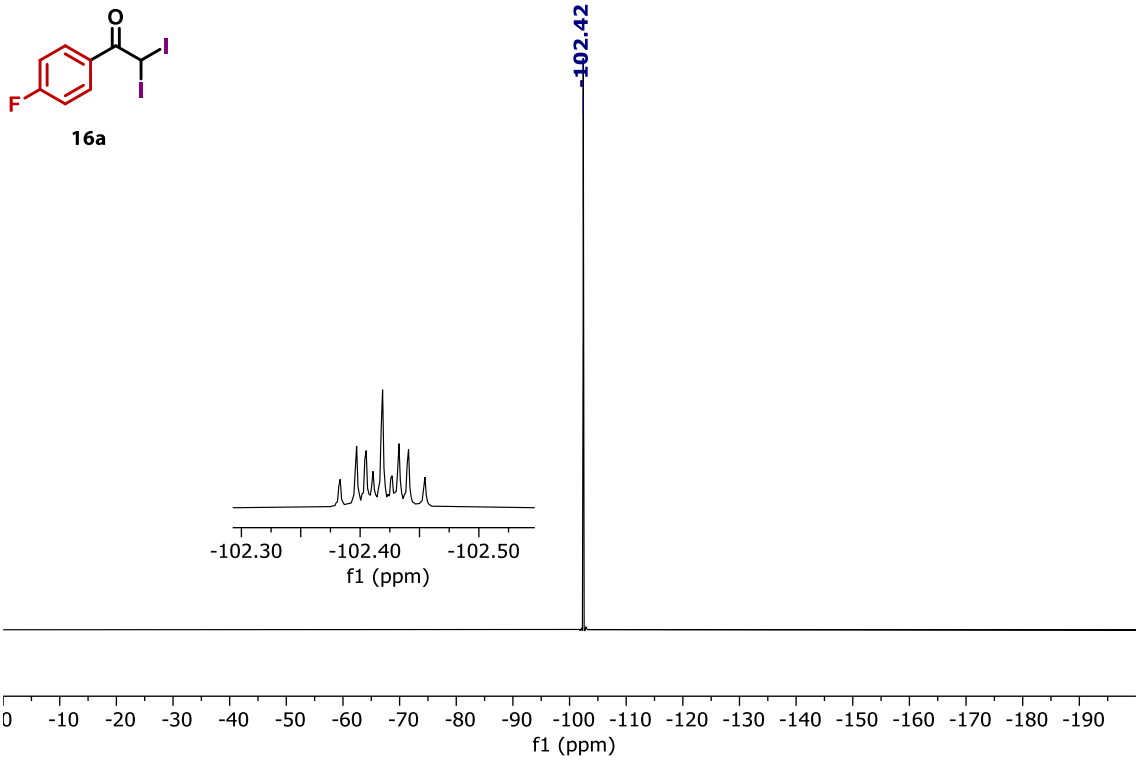
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

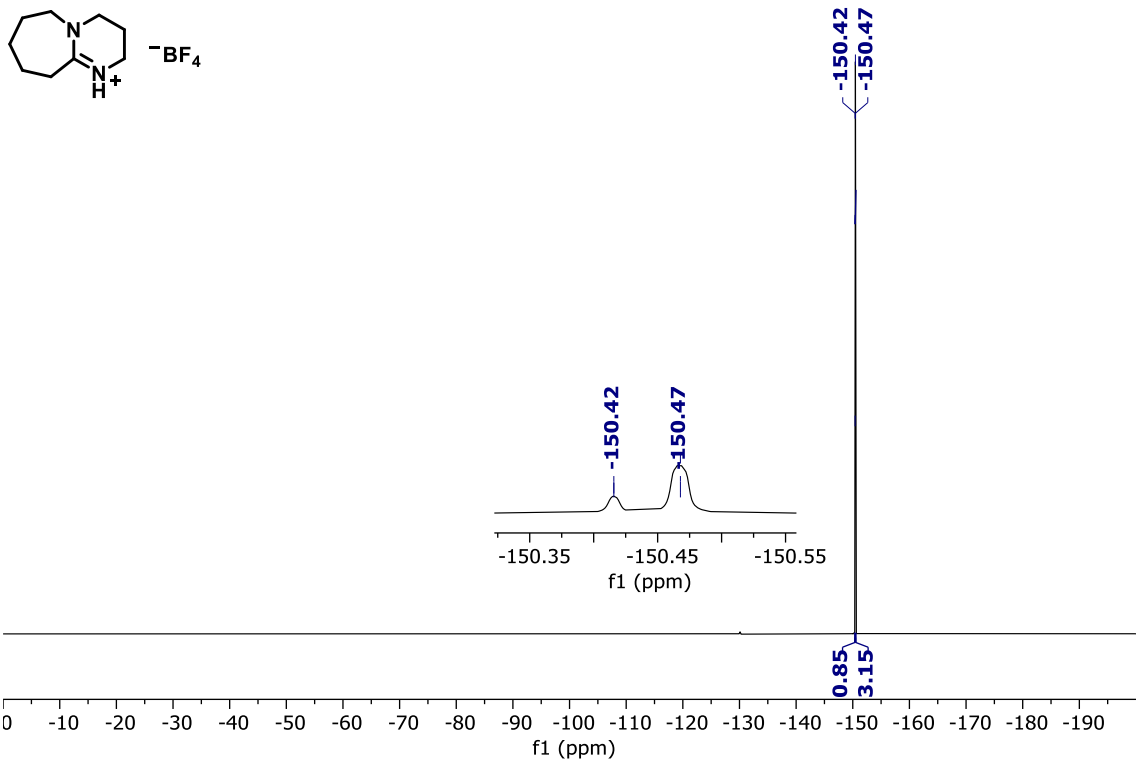


^{19}F NMR (376 MHz, $CDCl_3$)



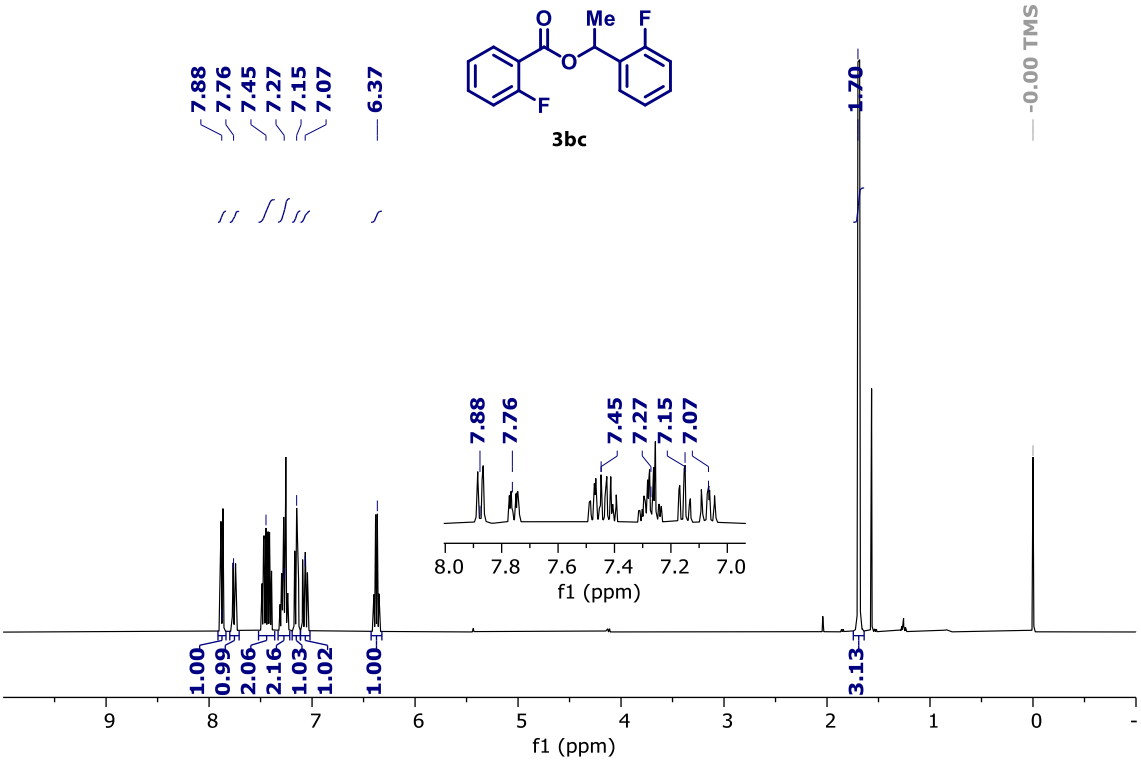
1,8-Diazabicyclo[5.4.0]undec-7-enium tetrafluoroborate (DBU.HBF_4)

^{19}F NMR (376 MHz, $CDCl_3$)

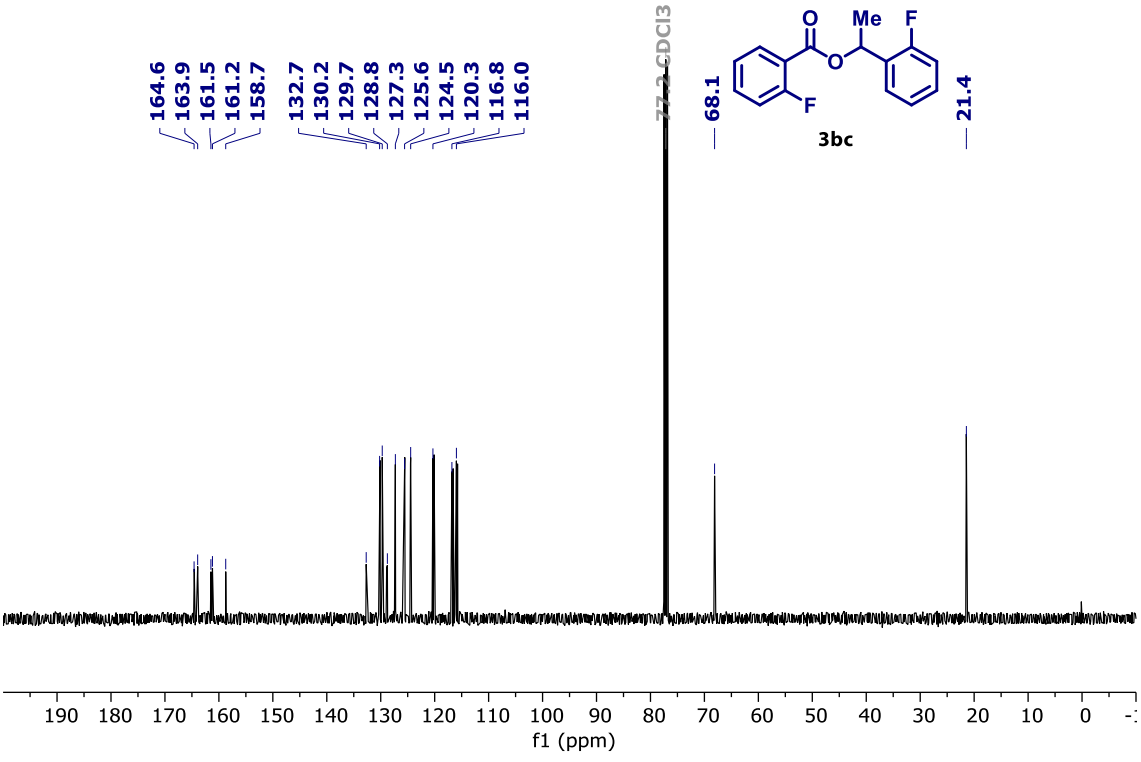


1-(2-Fluorophenyl)ethyl 2-fluorobenzoate, ***3bc***

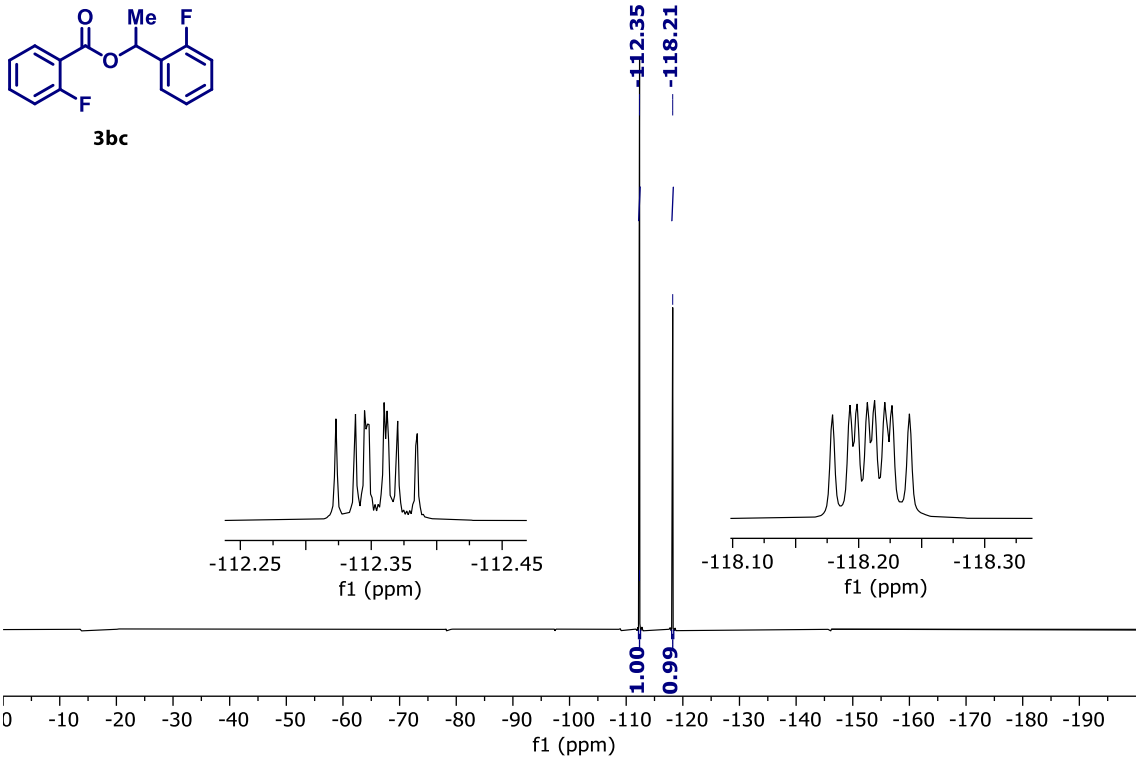
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

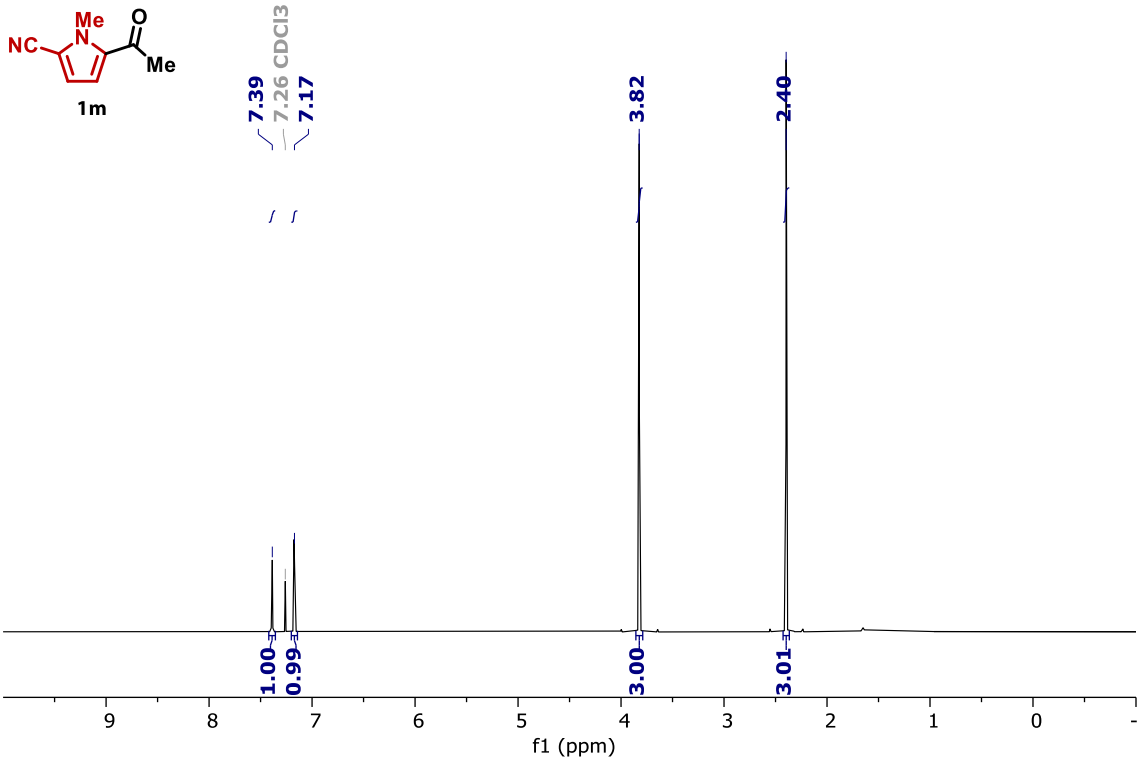


^{19}F NMR (376 MHz, $CDCl_3$)

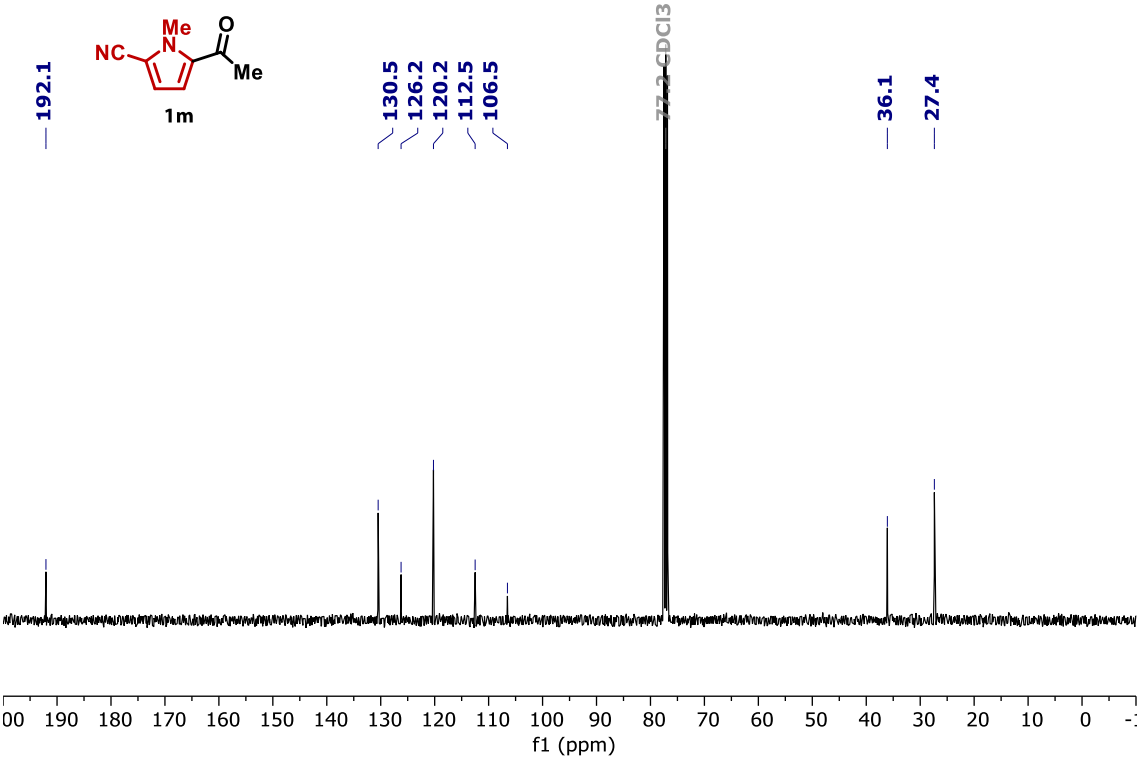


5-Acetyl-1-methyl-1H-pyrrole-2-carbonitrile, ***1m***

^{1}H NMR (400 MHz, $CDCl_3$)

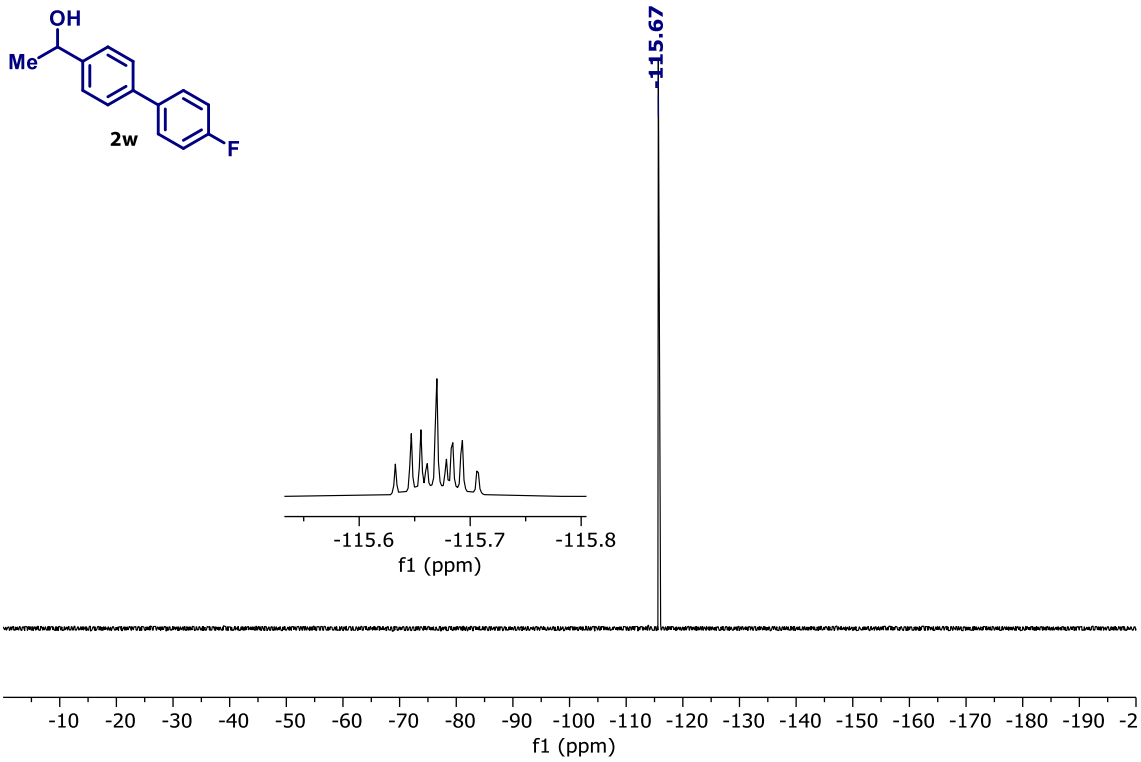


^{13}C NMR (101 MHz, $CDCl_3$)



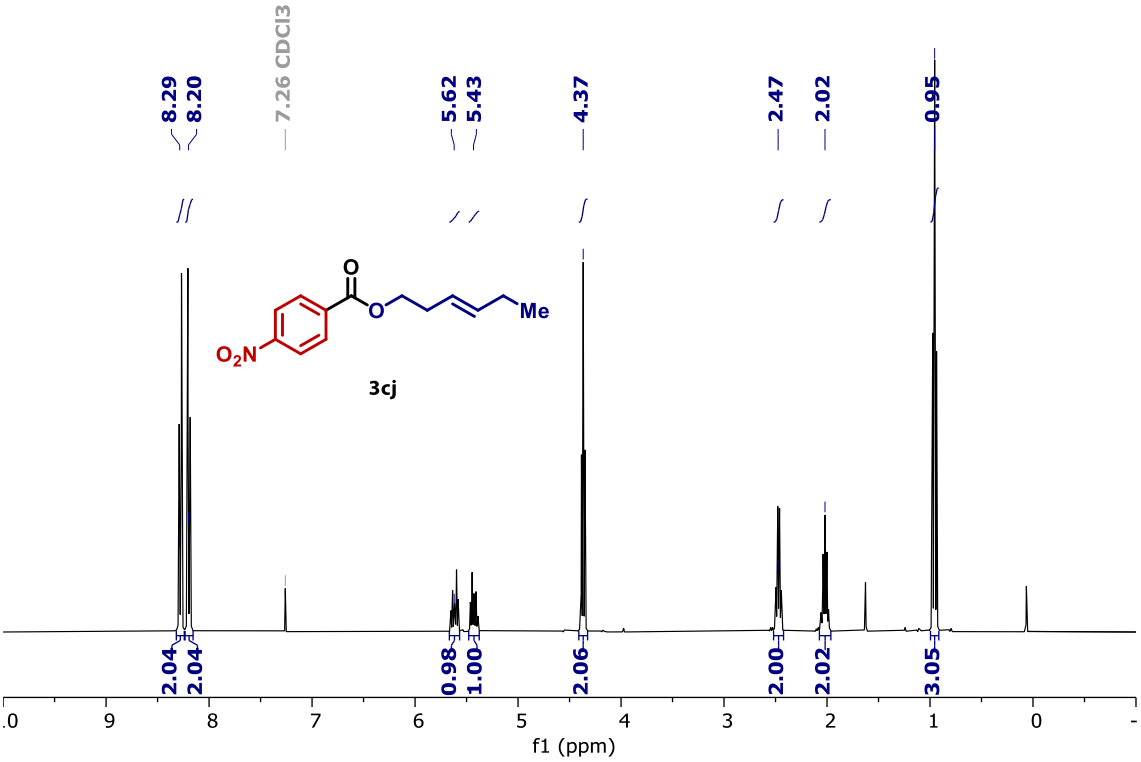
1-(4'-Fluoro-[1,1'-biphenyl]-4-yl)ethanol, **2w**

^{19}F NMR (376 MHz, $CDCl_3$), *recorded by Alex Atkins*

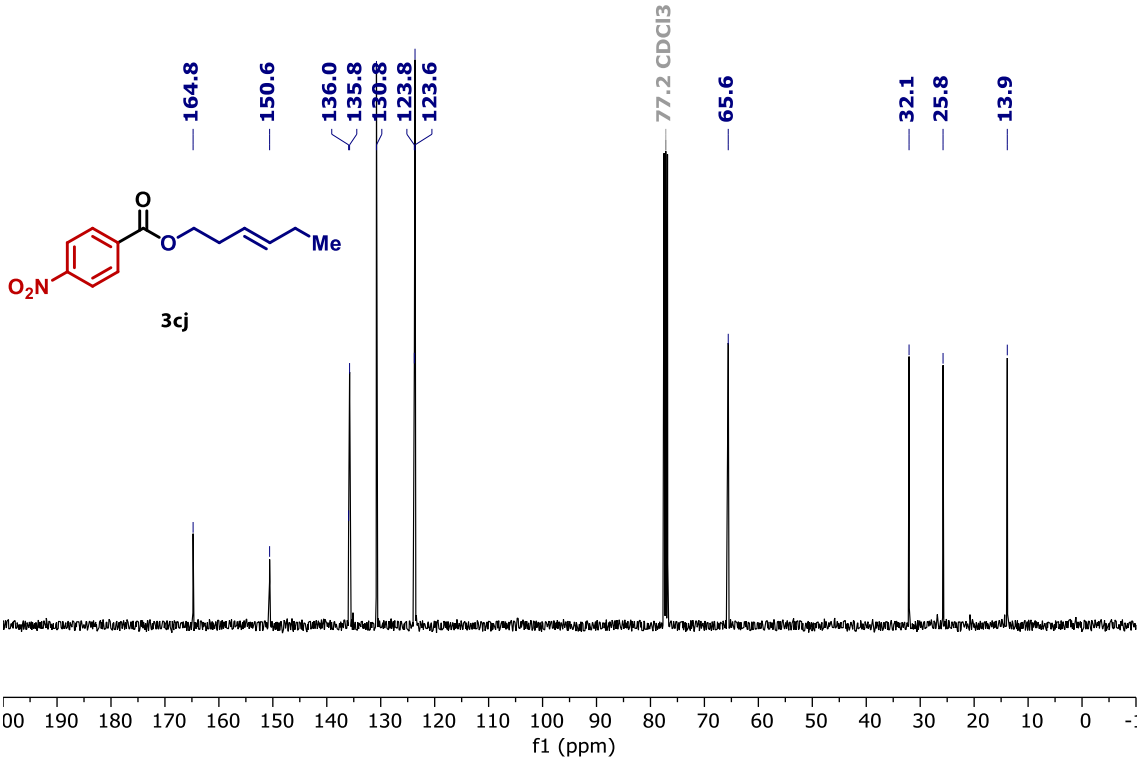


(E)-Hex-3-en-1-yl 4-nitrobenzoate, ***3cj***

^{1}H NMR (400 MHz, $CDCl_3$), *recorded by David Heard*

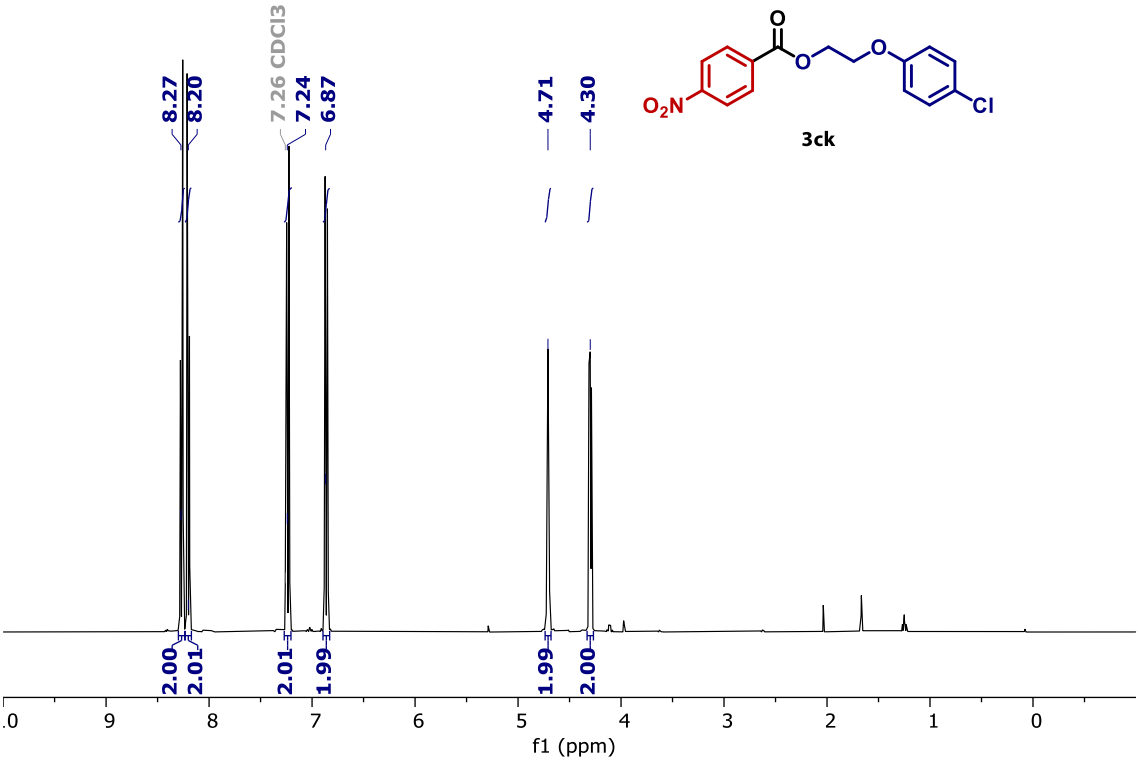


^{13}C NMR (101 MHz, $CDCl_3$), *recorded by David Heard*

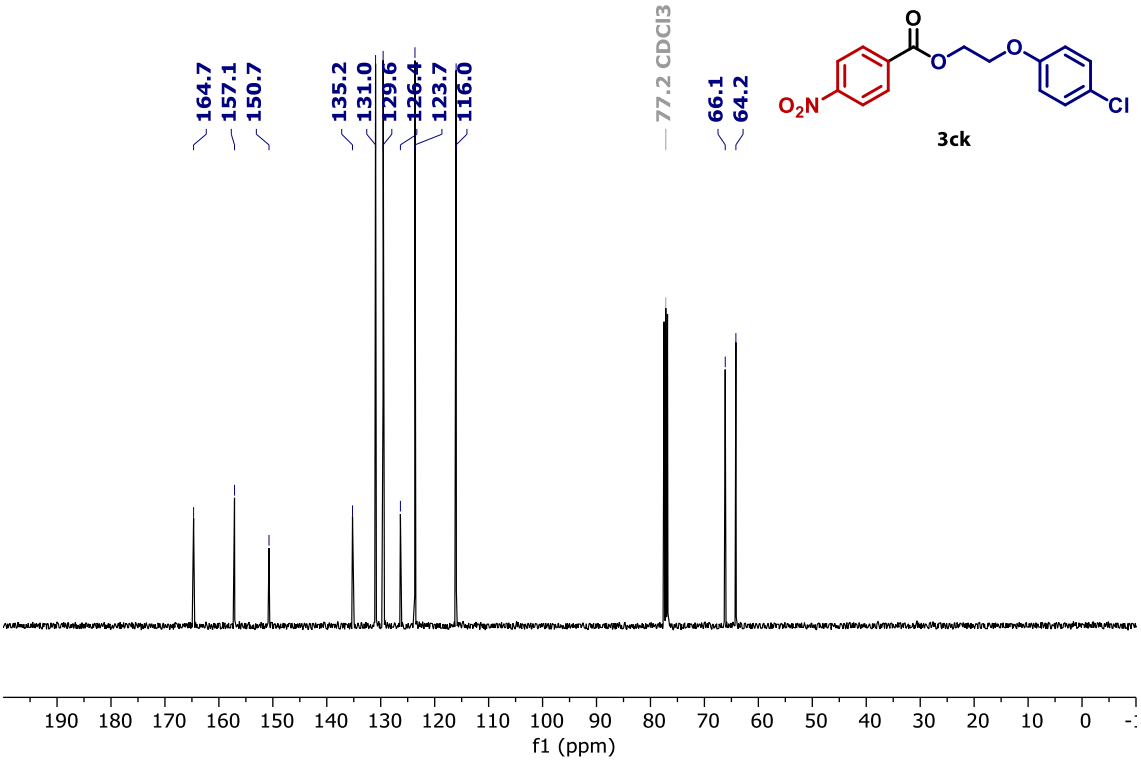


2-(4-Chlorophenoxy)ethyl 4-nitrobenzoate, ***3ck***

^{1}H NMR (400 MHz, $CDCl_3$), *recorded by David Heard*

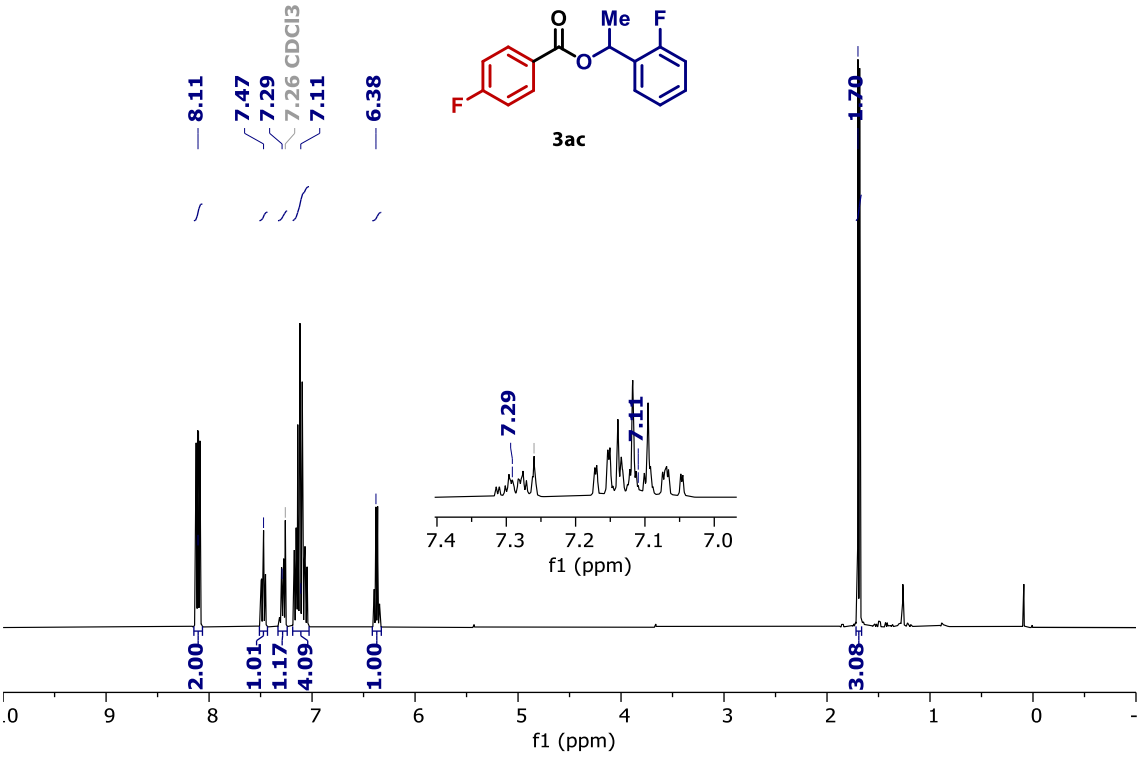


^{13}C NMR (101 MHz, $CDCl_3$), *recorded by David Heard*

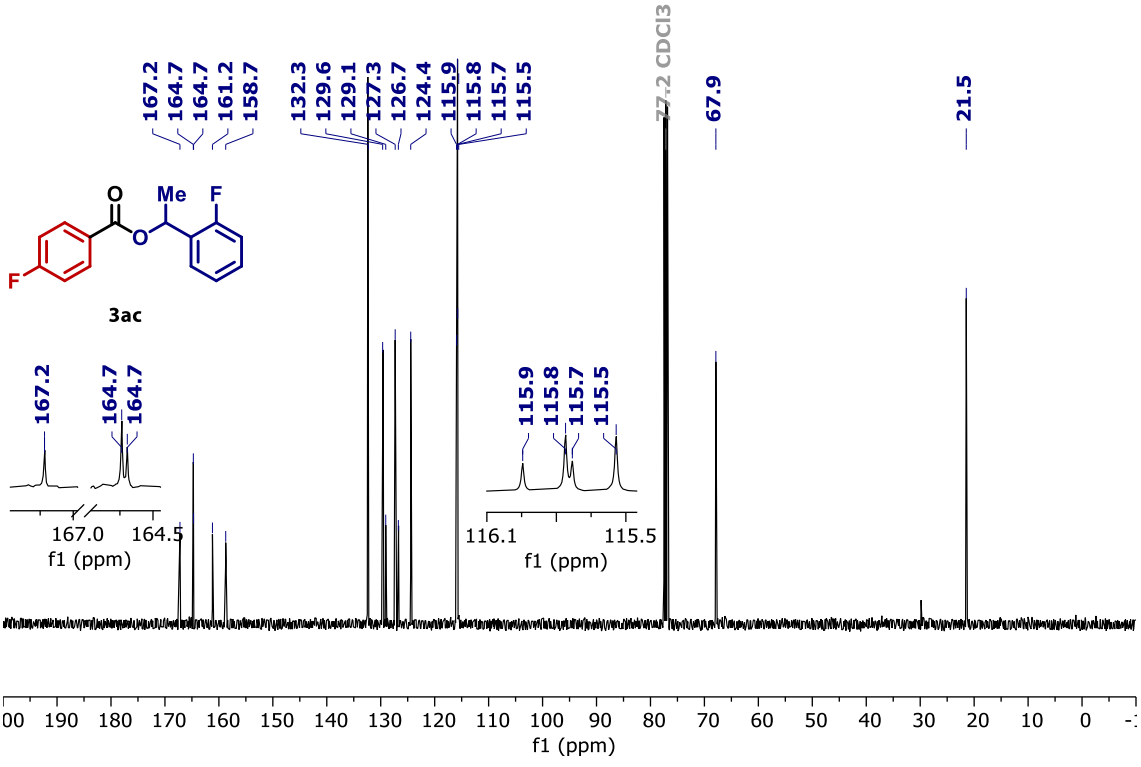


1-(2-Fluorophenyl)ethyl 4-fluorobenzoate, ***3ac***

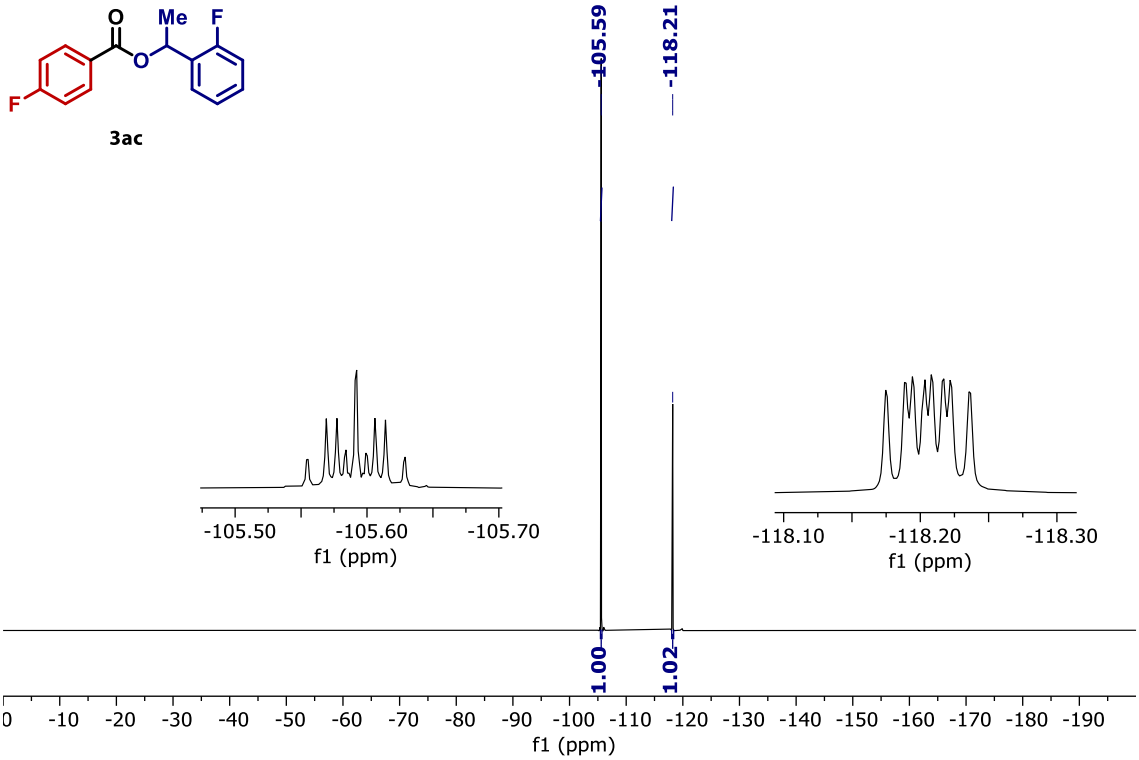
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

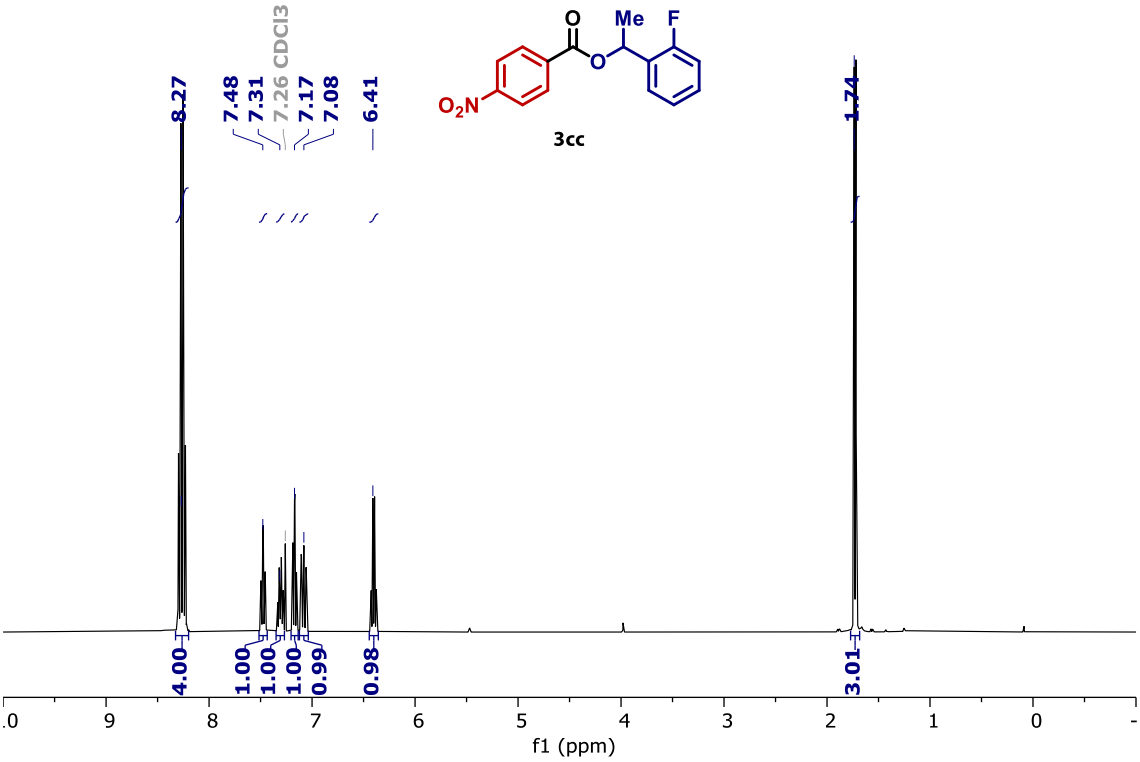


^{19}F NMR (376 MHz, $CDCl_3$)

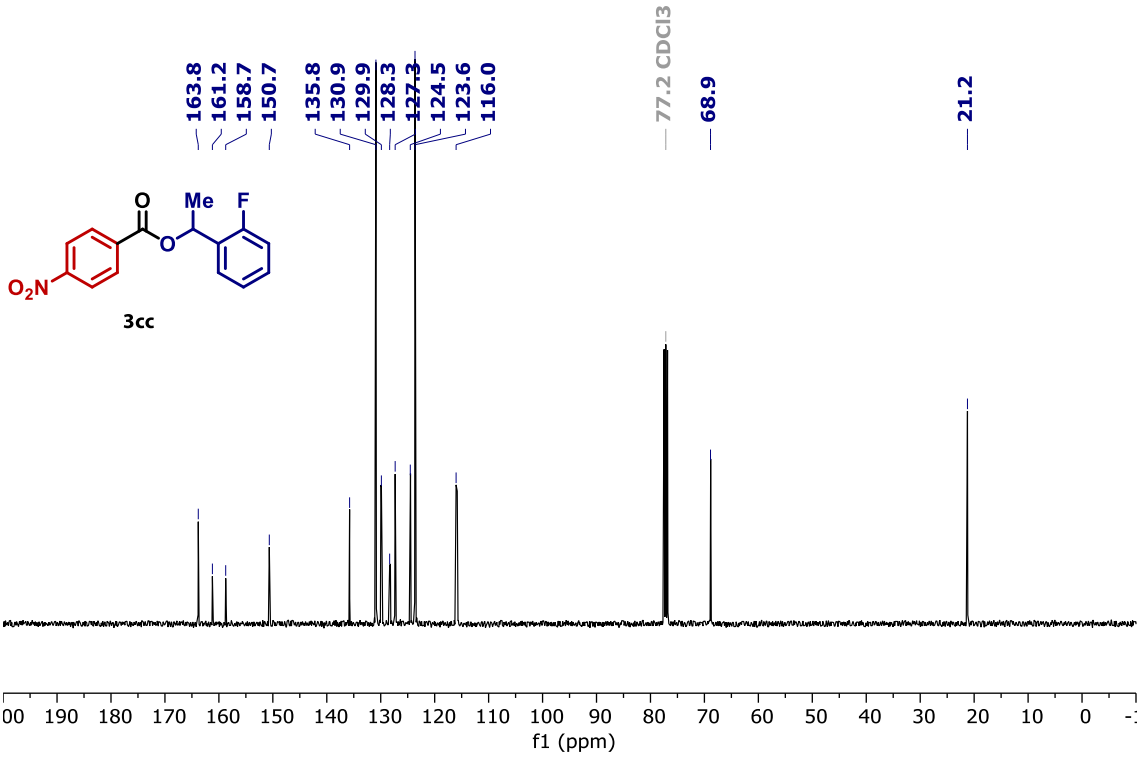


1-(2-Fluorophenyl)ethyl 4-nitrobenzoate, ***3cc***

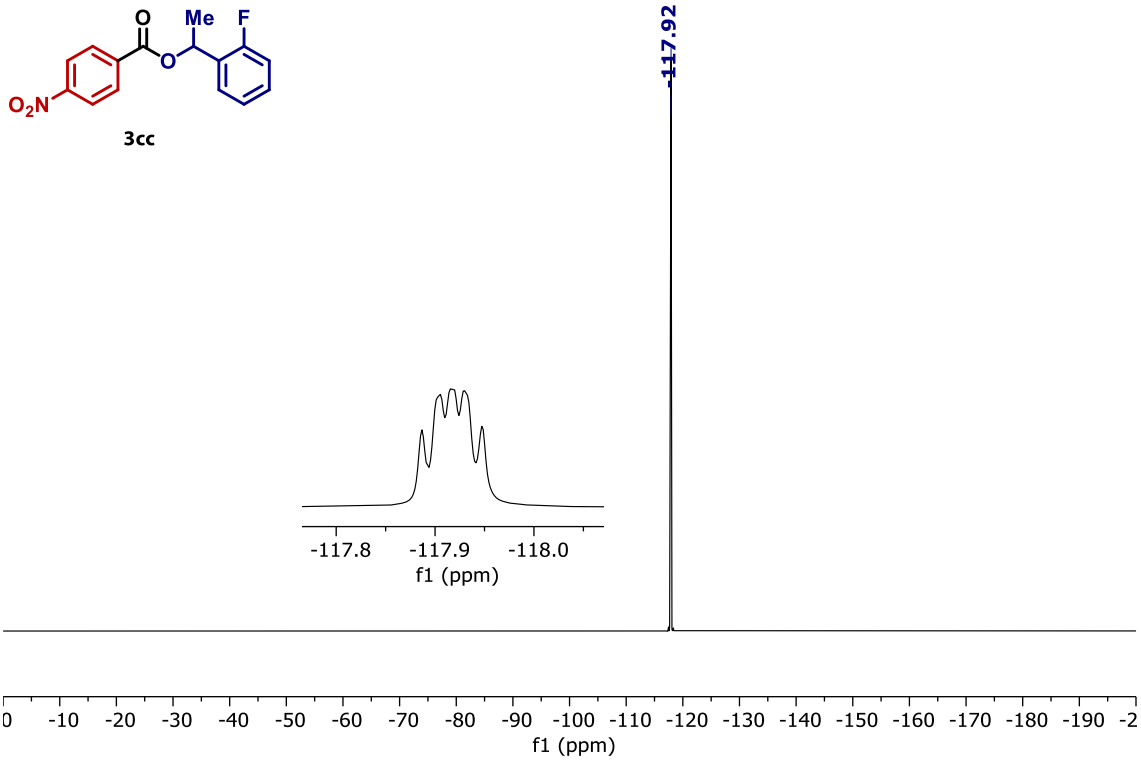
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

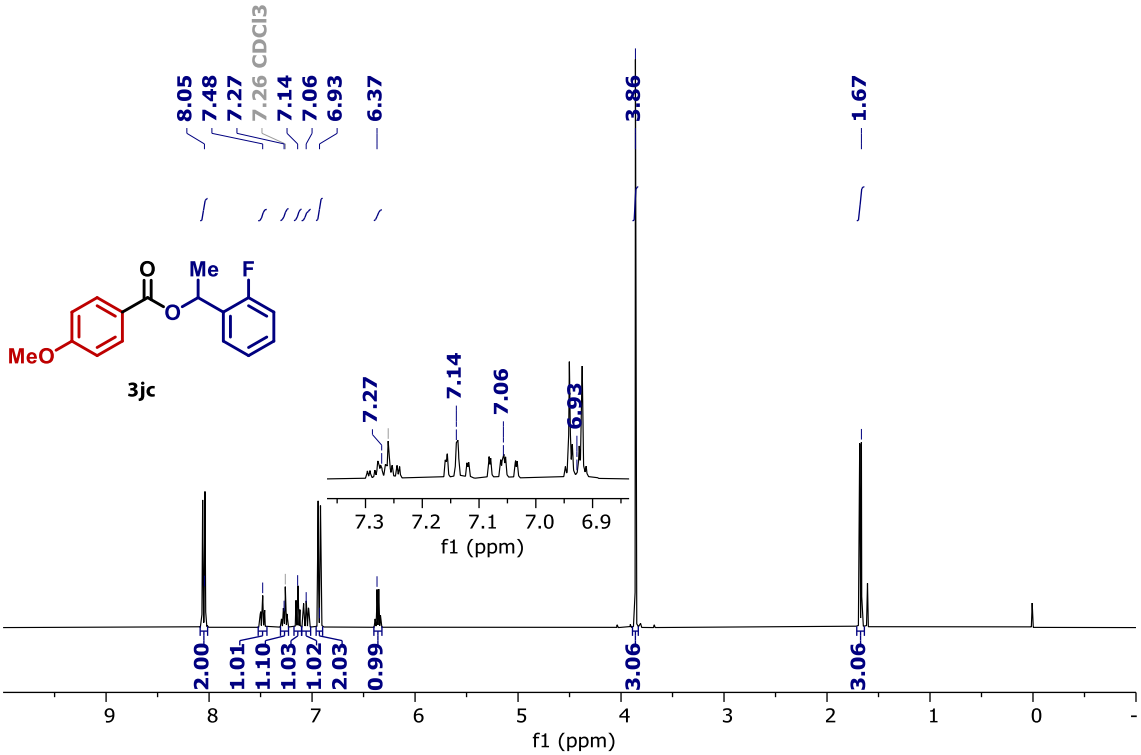


^{19}F NMR (376 MHz, $CDCl_3$)

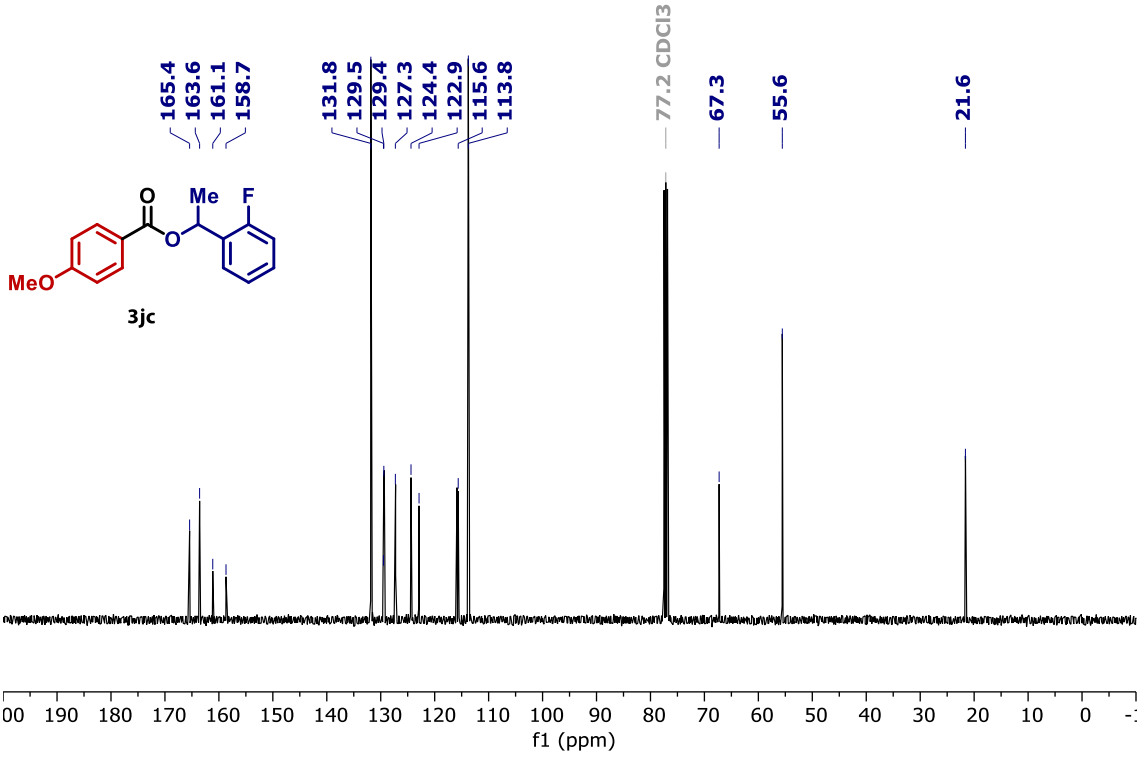


1-(2-Fluorophenyl)ethyl 4-methoxybenzoate, ***3jc***

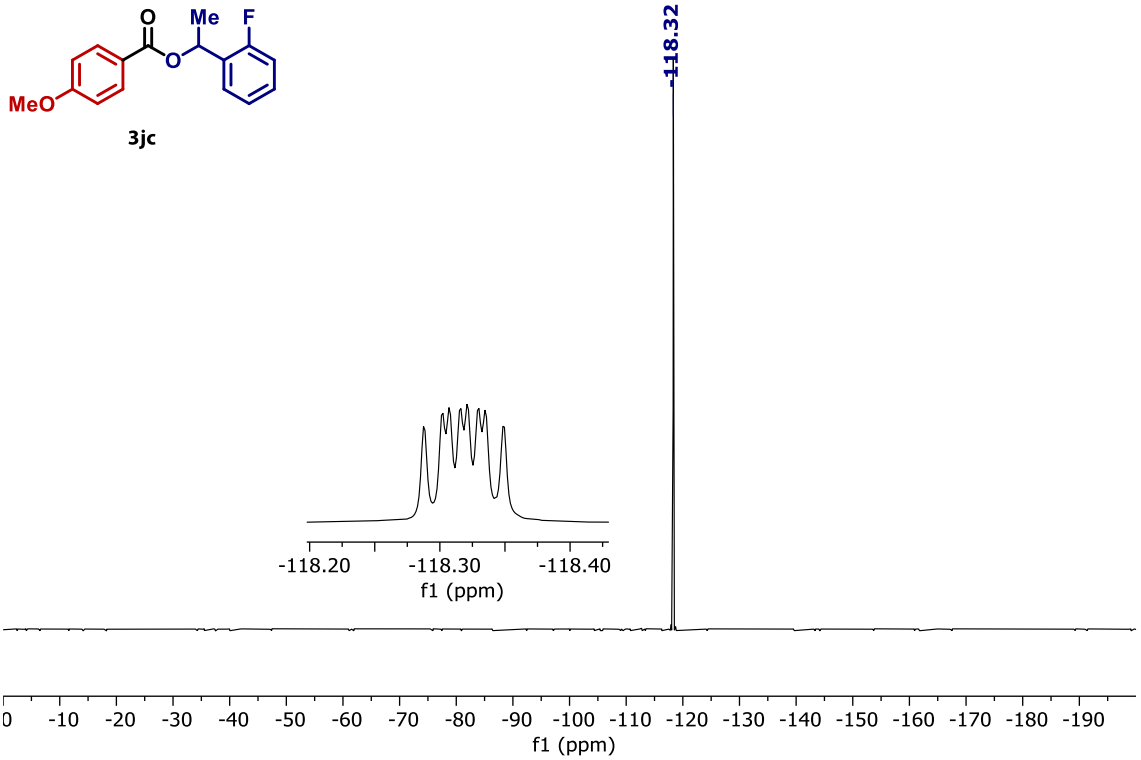
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

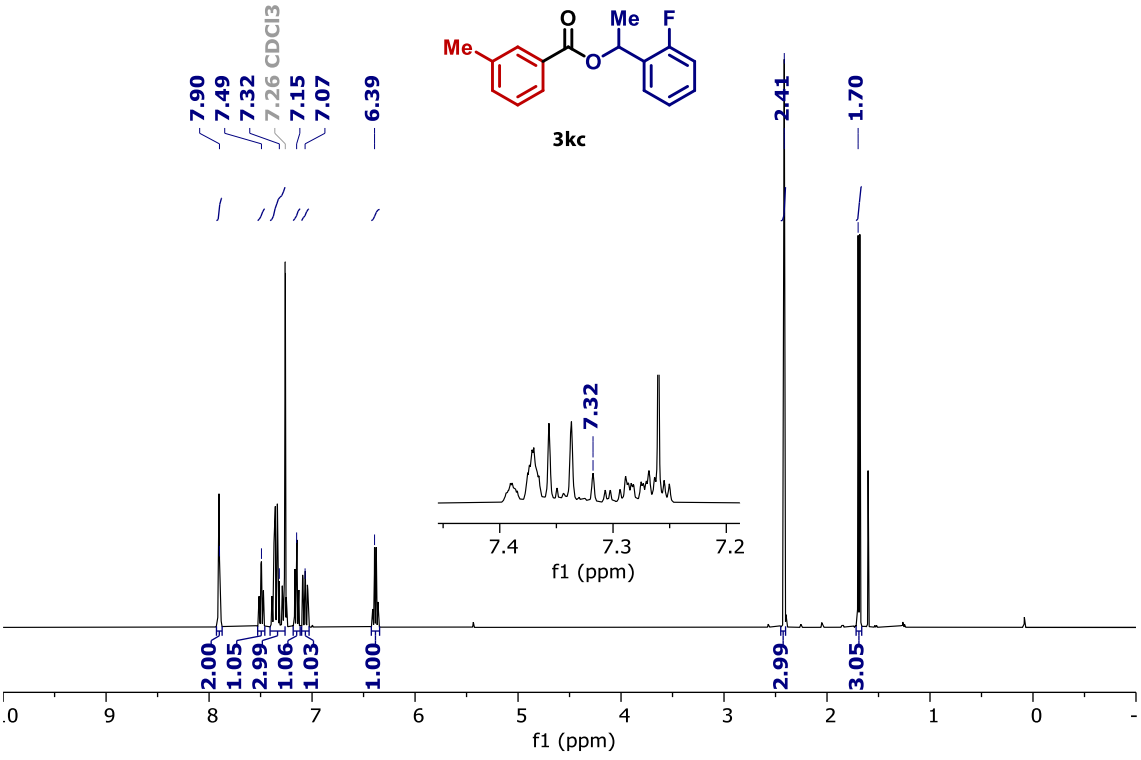


^{19}F NMR (376 MHz, $CDCl_3$)

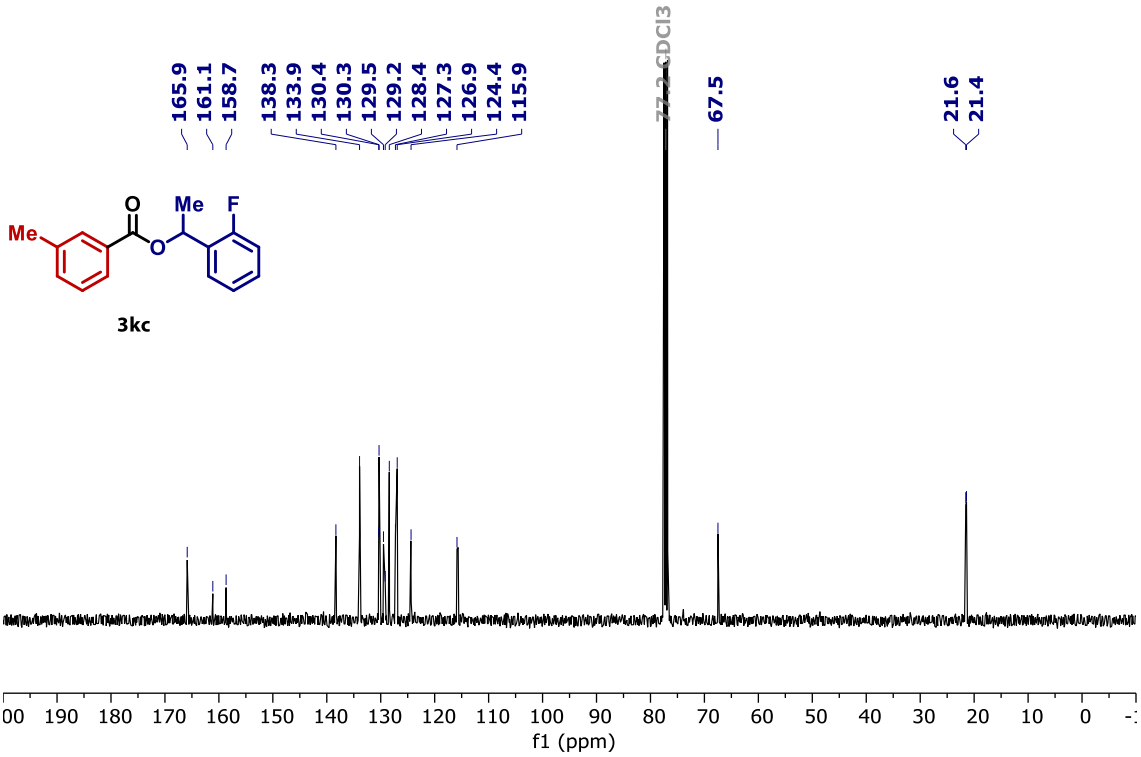


1-(2-Fluorophenyl)ethyl 3-methylbenzoate, ***3kc***

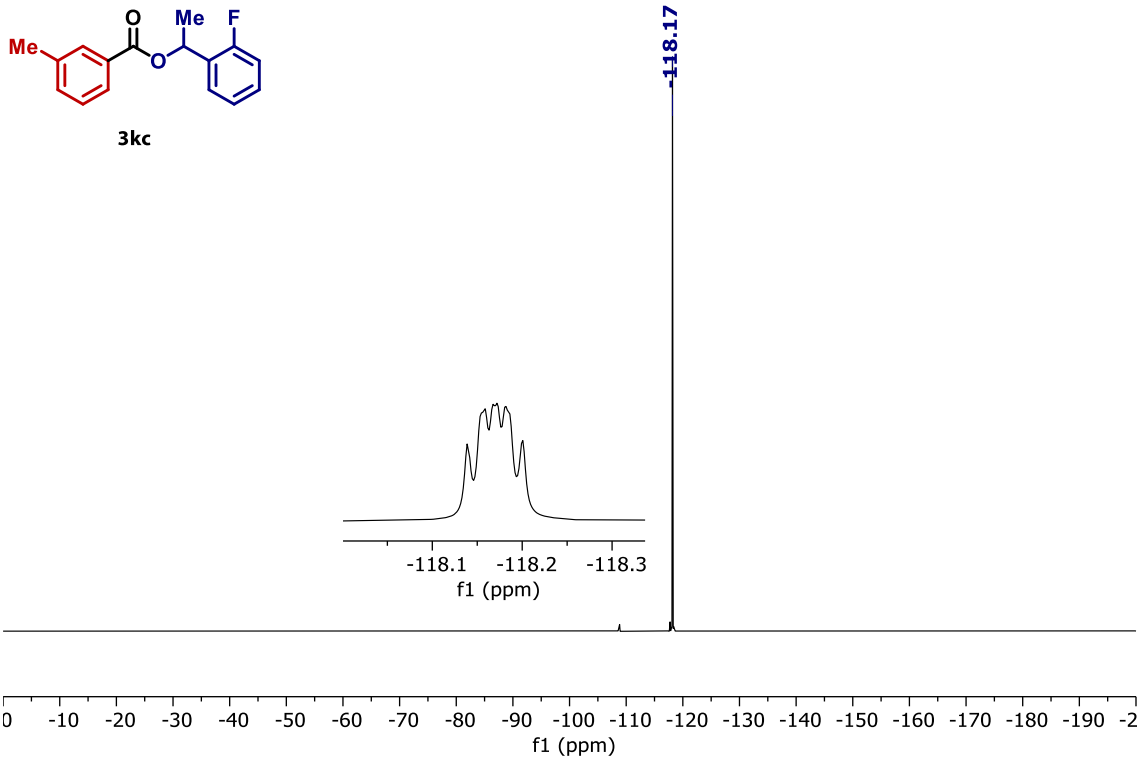
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

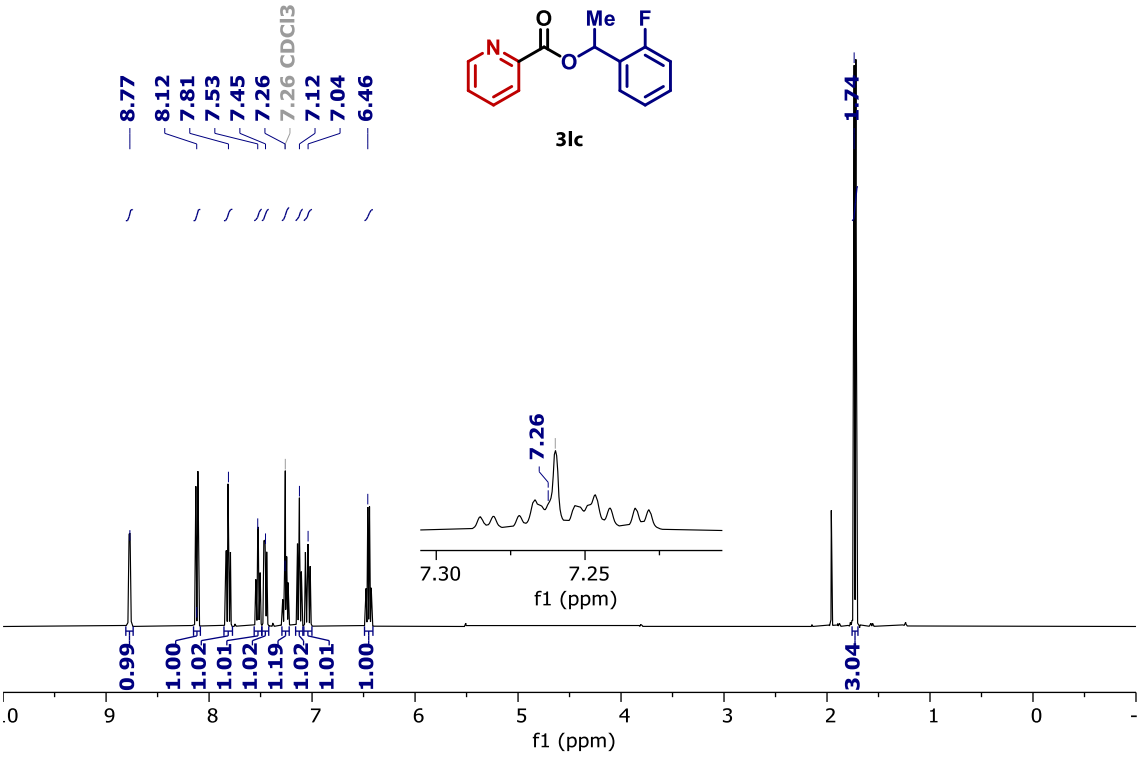


^{19}F NMR (376 MHz, $CDCl_3$)

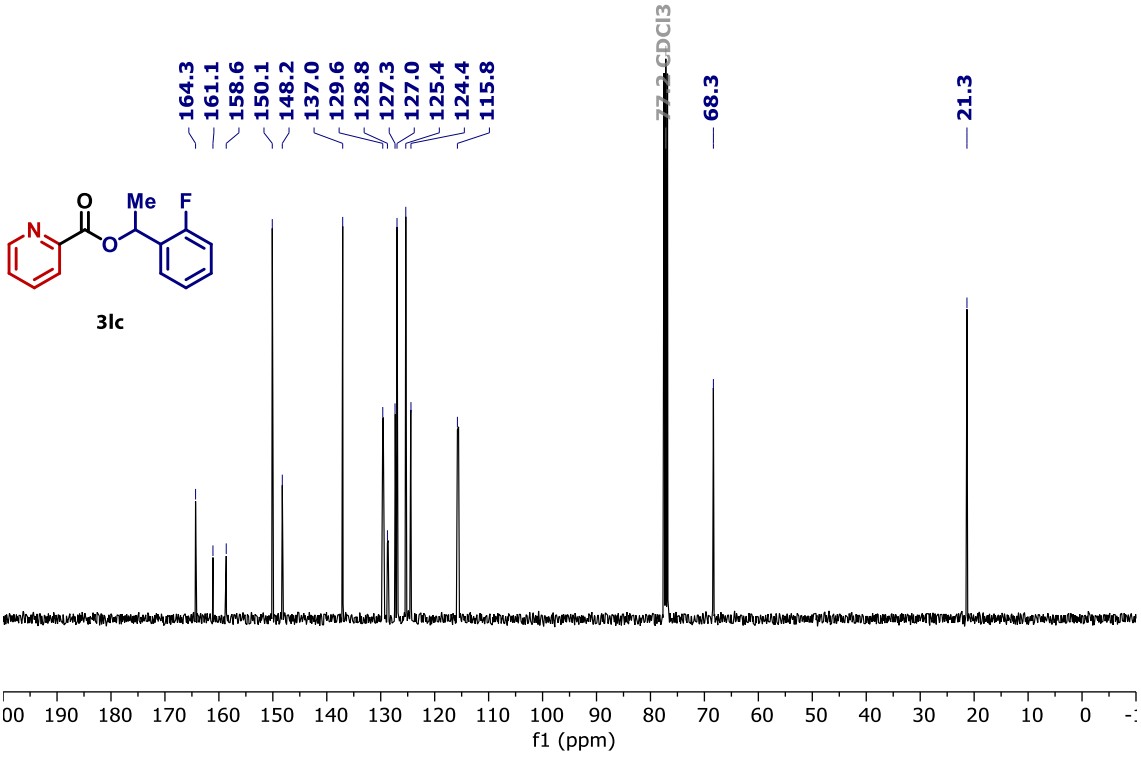


1-(2-Fluorophenyl)ethyl picolinate, ***3lc***

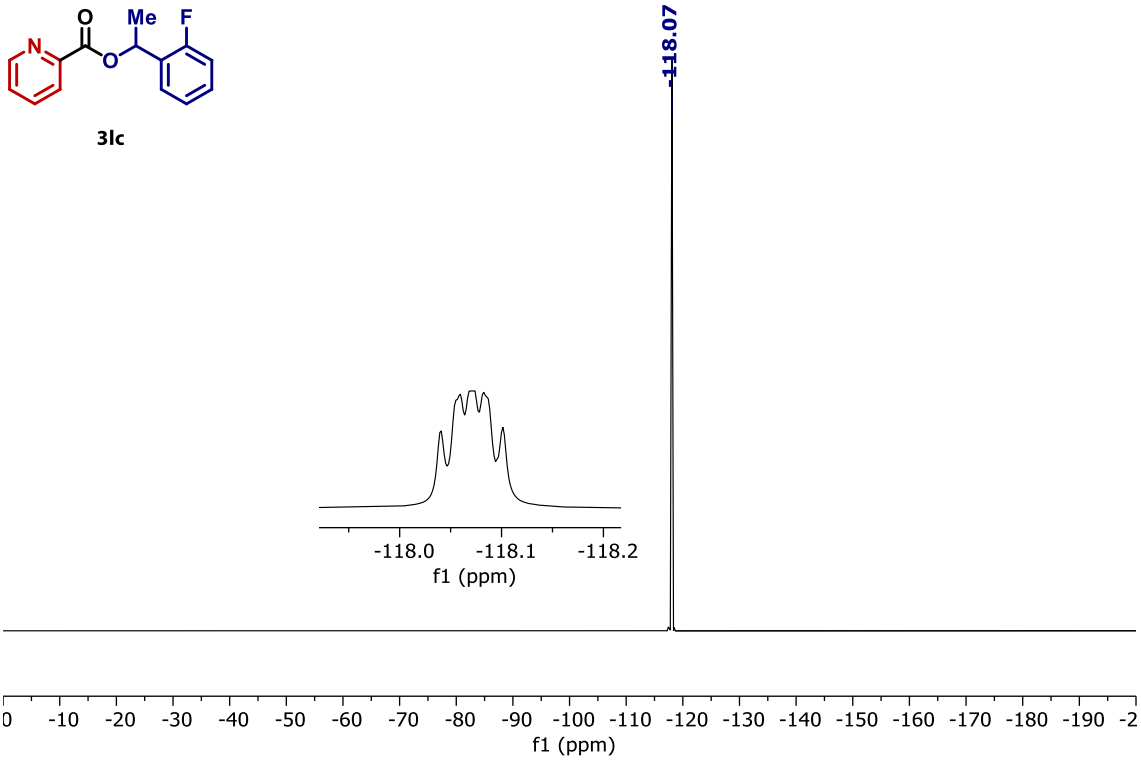
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

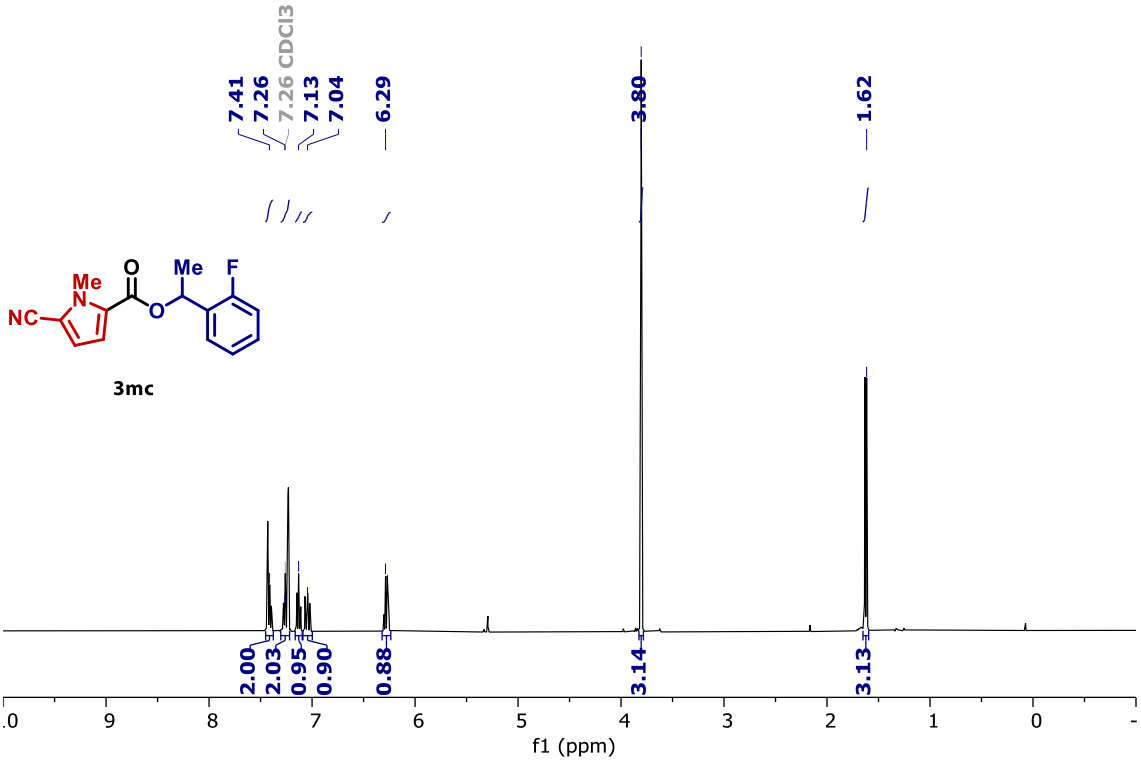


^{19}F NMR (376 MHz, $CDCl_3$)

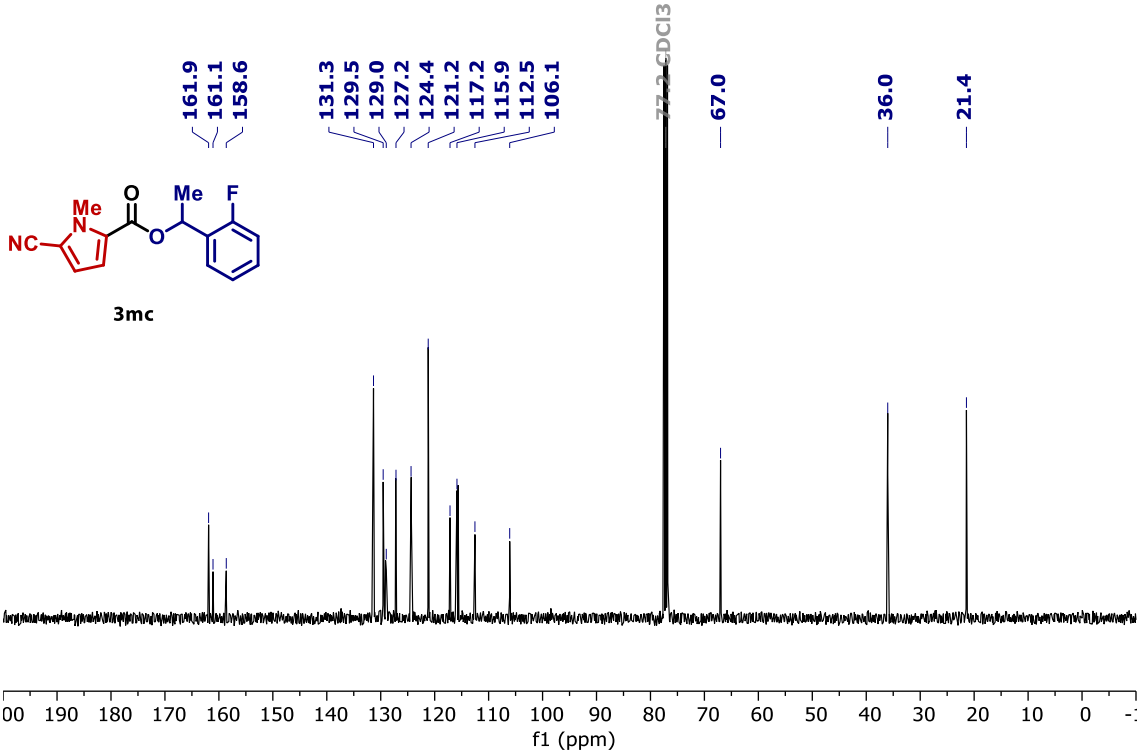


1-(2-Fluorophenyl)ethyl 5-cyano-1-methyl-1H-pyrrole-2-carboxylate, ***3mc***

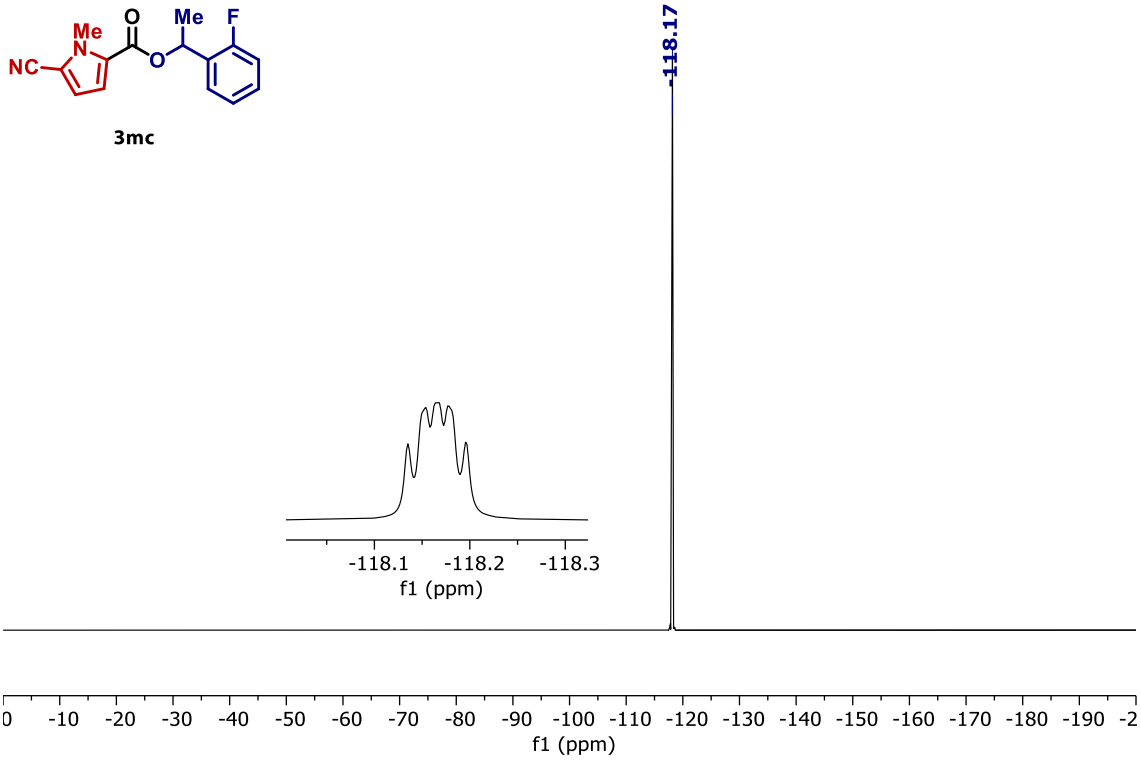
^{1}H NMR (400 MHz, $CDCl_3$), *recorded by David Heard*



^{13}C NMR (101 MHz, $CDCl_3$), *recorded by David Heard*

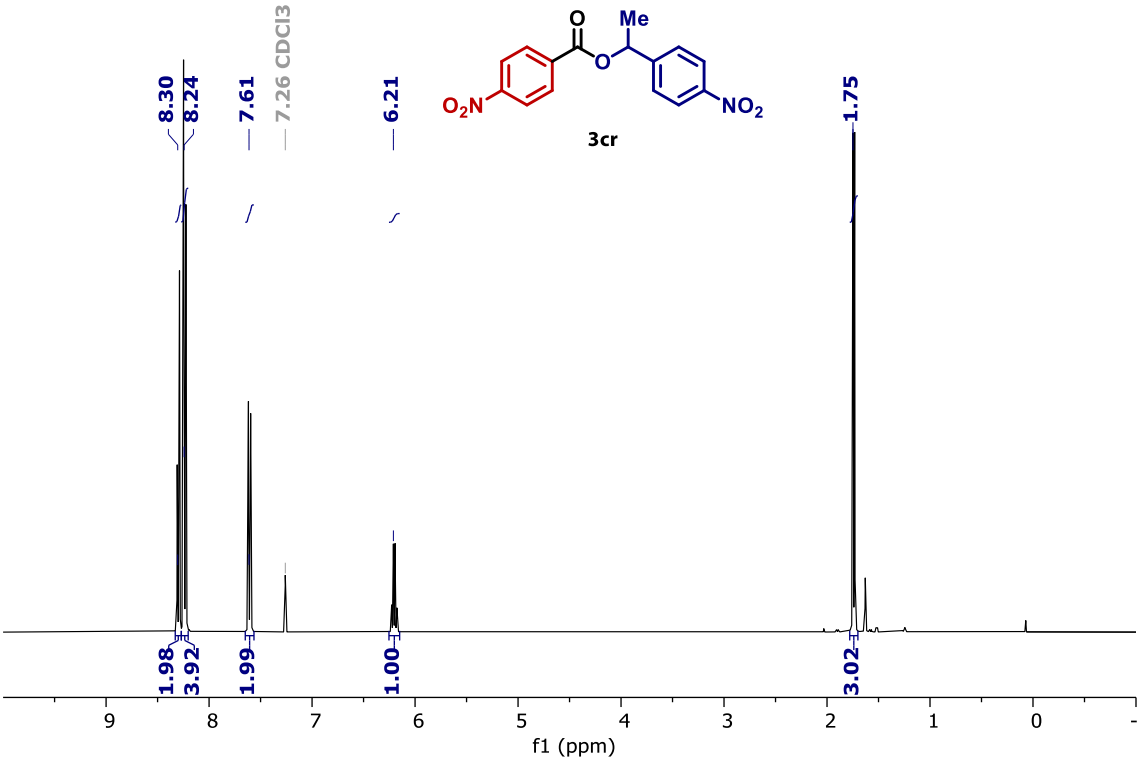


^{19}F NMR (376 MHz, $CDCl_3$), *recorded by David Heard*

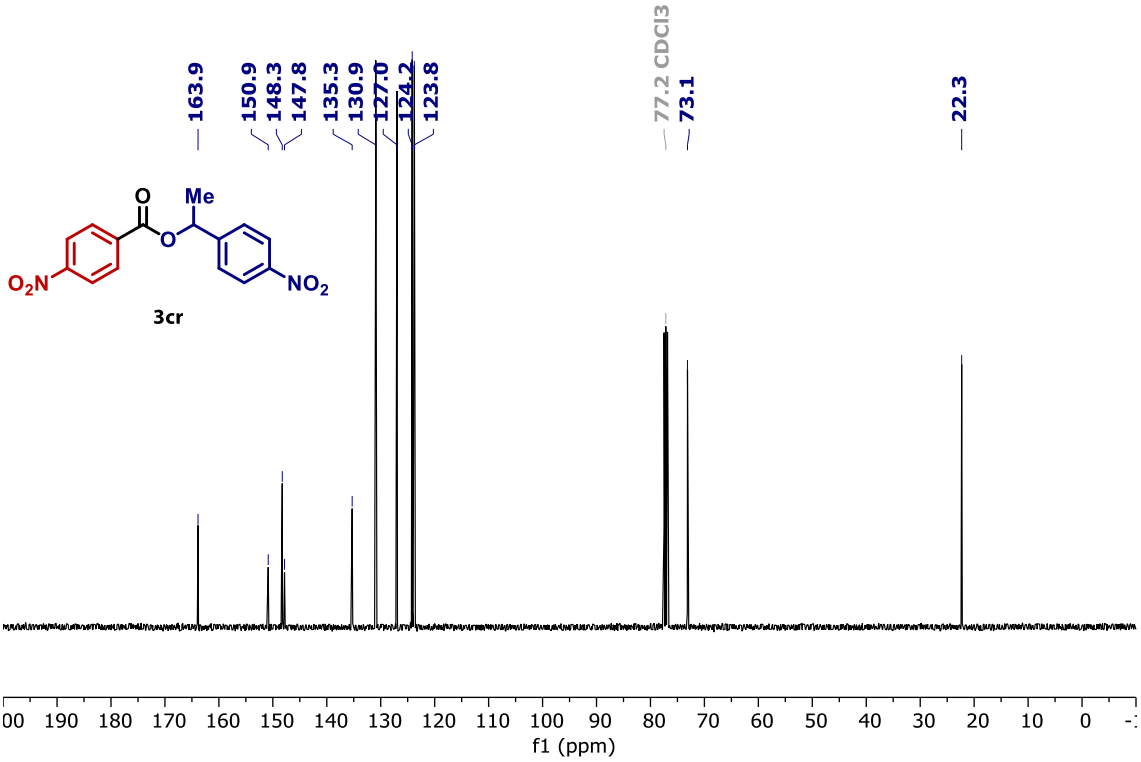


1-(4-Nitrophenyl)ethyl 4-nitrobenzoate, ***3cr***

^{1}H NMR (400 MHz, $CDCl_3$)

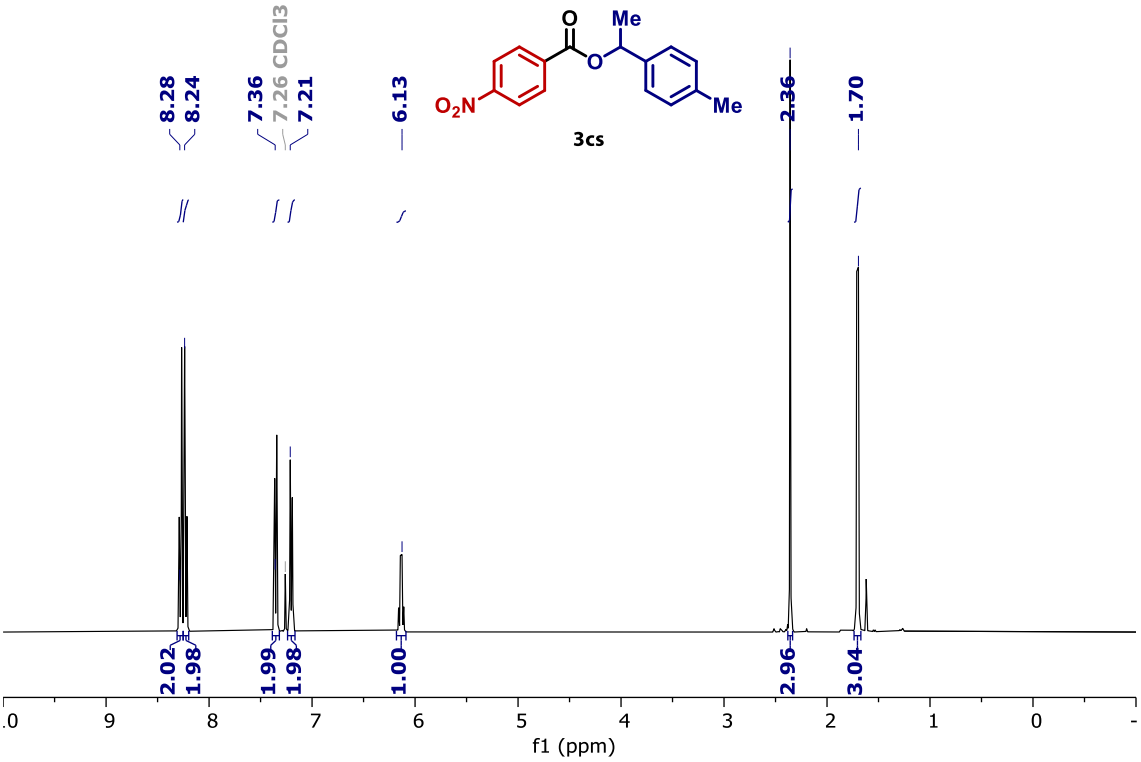


^{13}C NMR (101 MHz, $CDCl_3$)

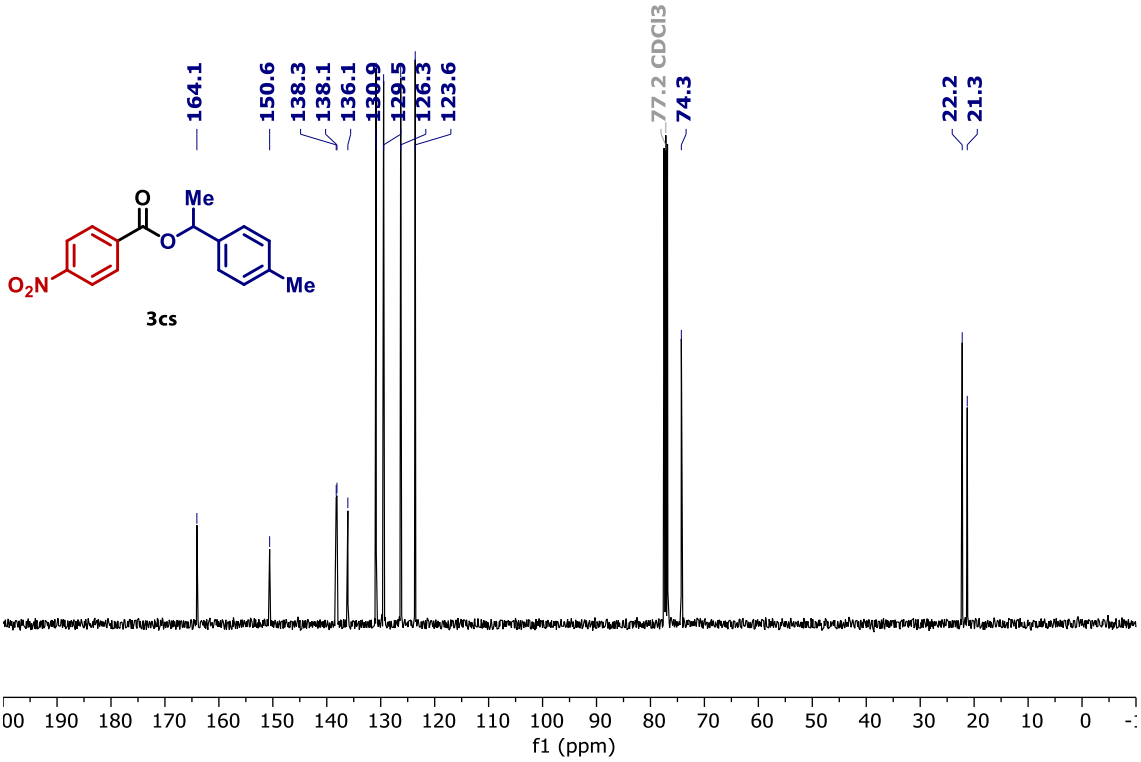


1-(4-Methylphenyl)ethyl 4-nitrobenzoate, **3cs**

^{1}H NMR (400 MHz, $CDCl_3$)

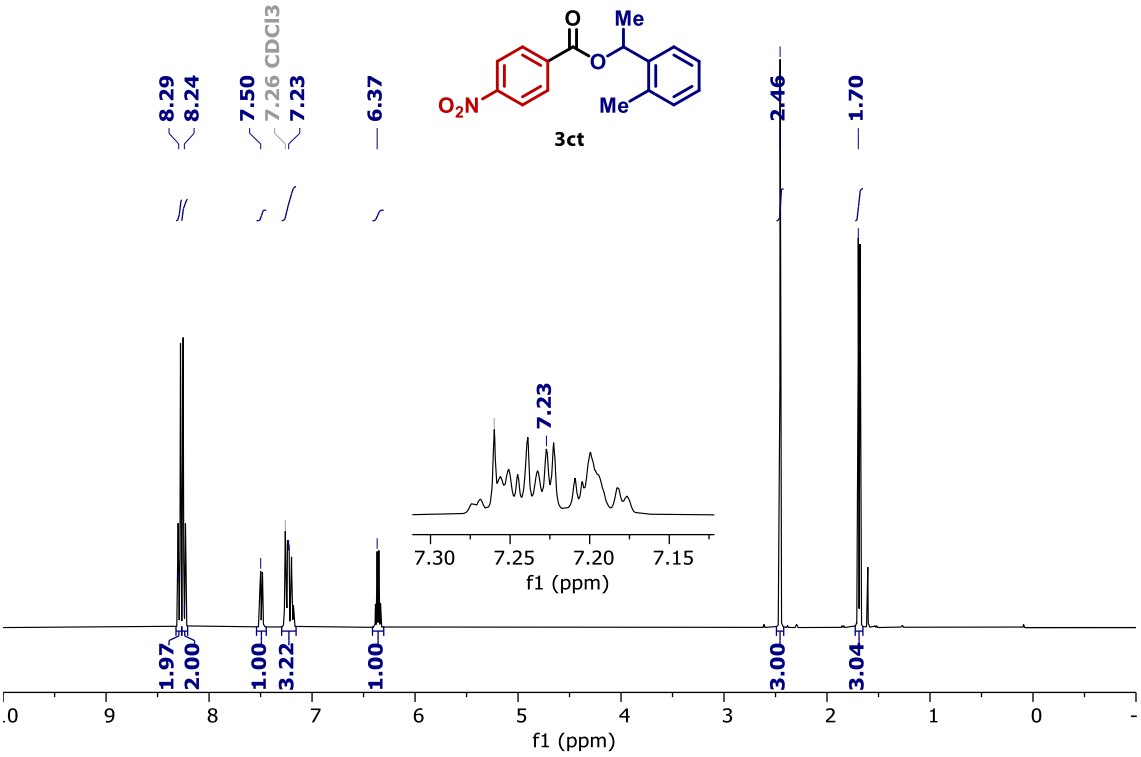


^{13}C NMR (101 MHz, $CDCl_3$)

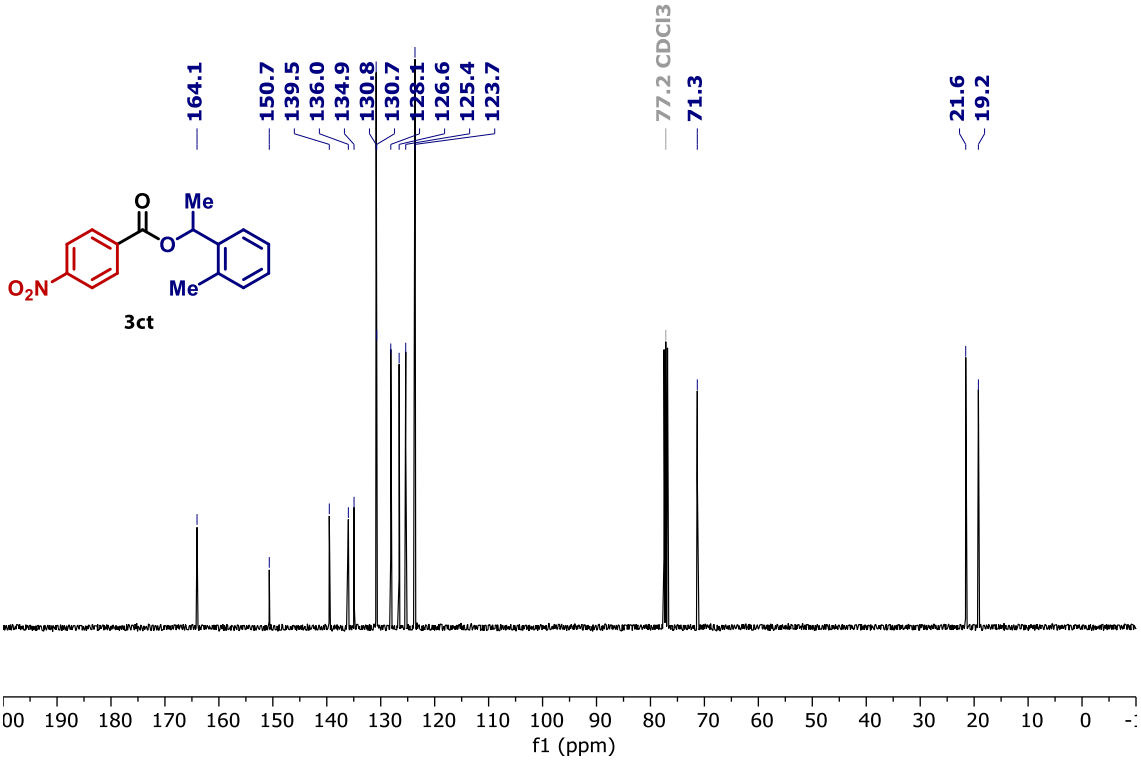


1-(2-Methylphenyl)ethyl 4-nitrobenzoate, ***3ct***

^{1}H NMR (400 MHz, $CDCl_3$)

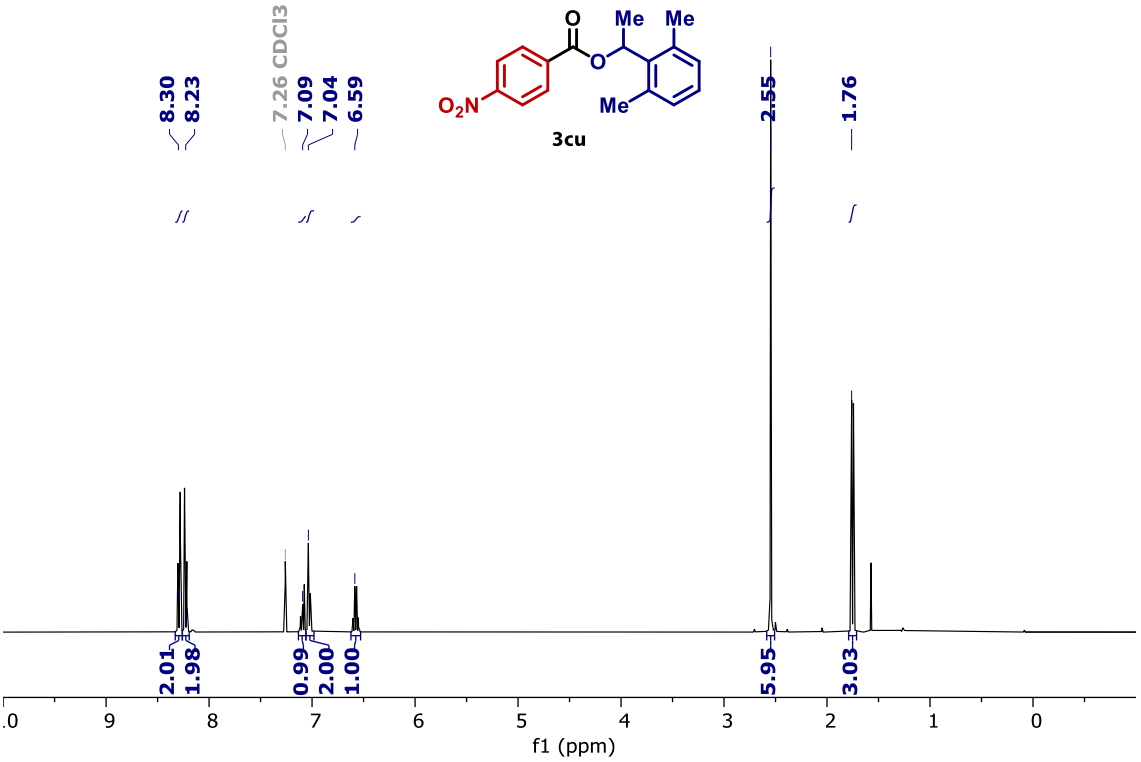


^{13}C NMR (101 MHz, $CDCl_3$)

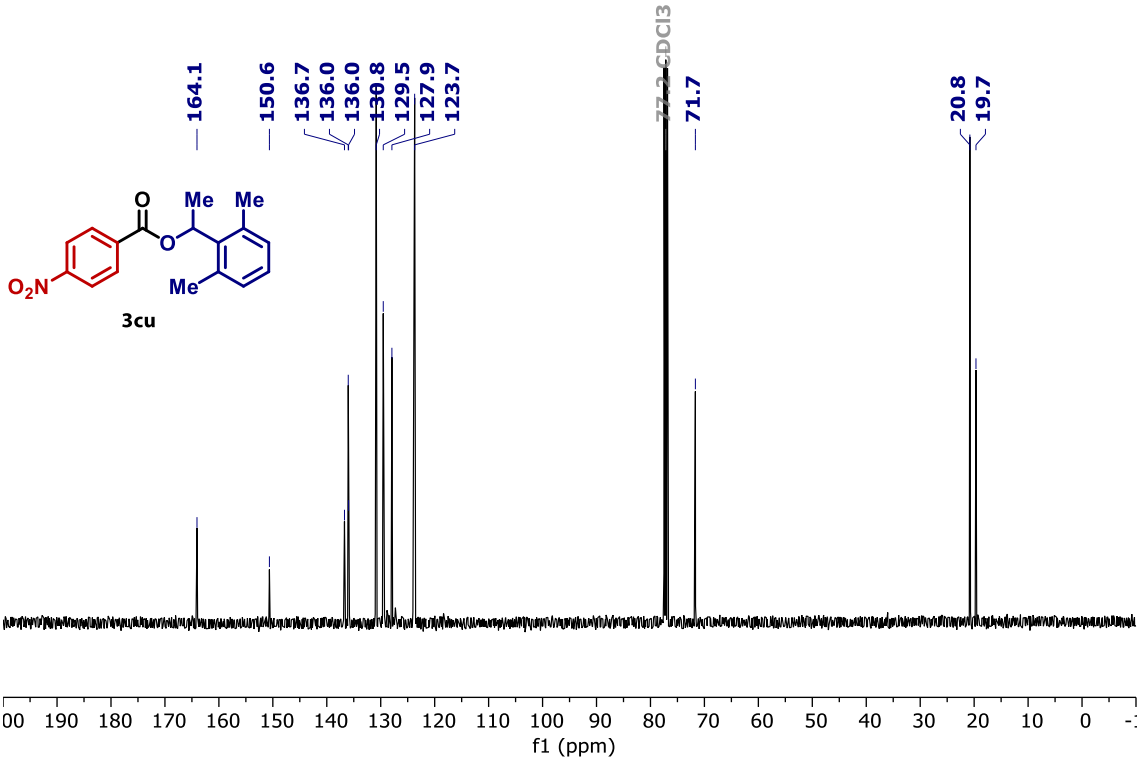


1-(2,6-Dimethylphenyl)ethyl 4-nitrobenzoate, ***3cu***

^{1}H NMR (400 MHz, $CDCl_3$)

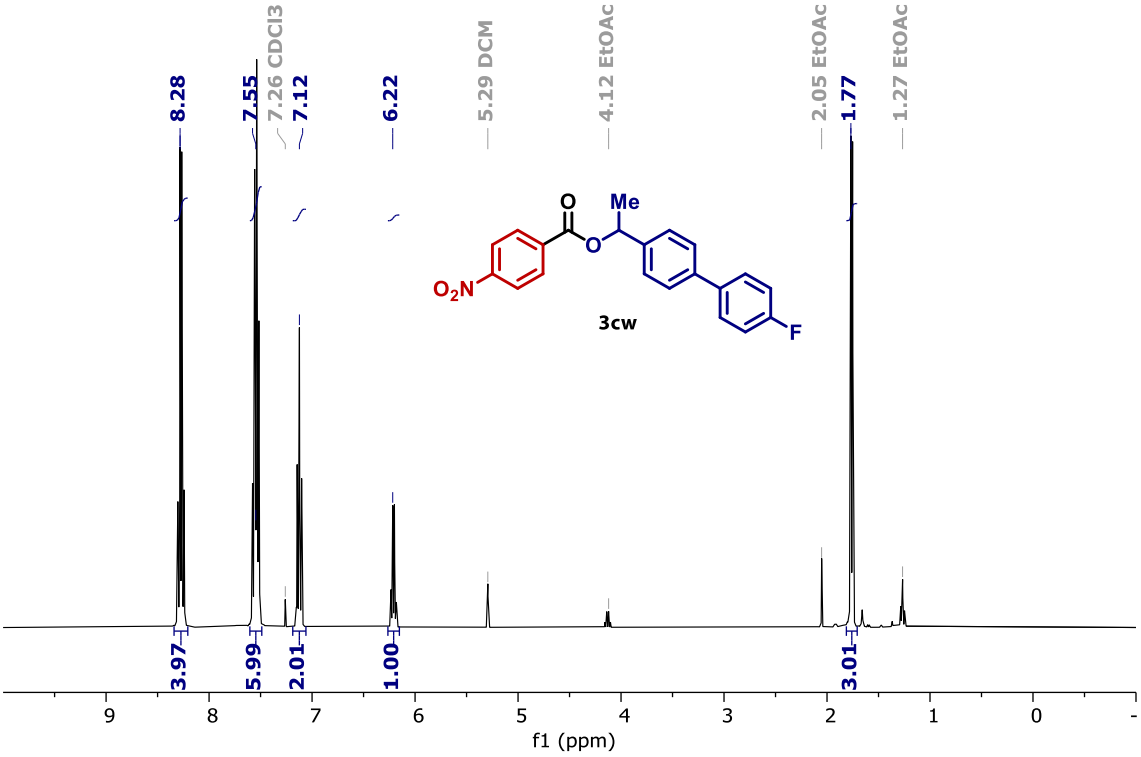


^{13}C NMR (101 MHz, $CDCl_3$)

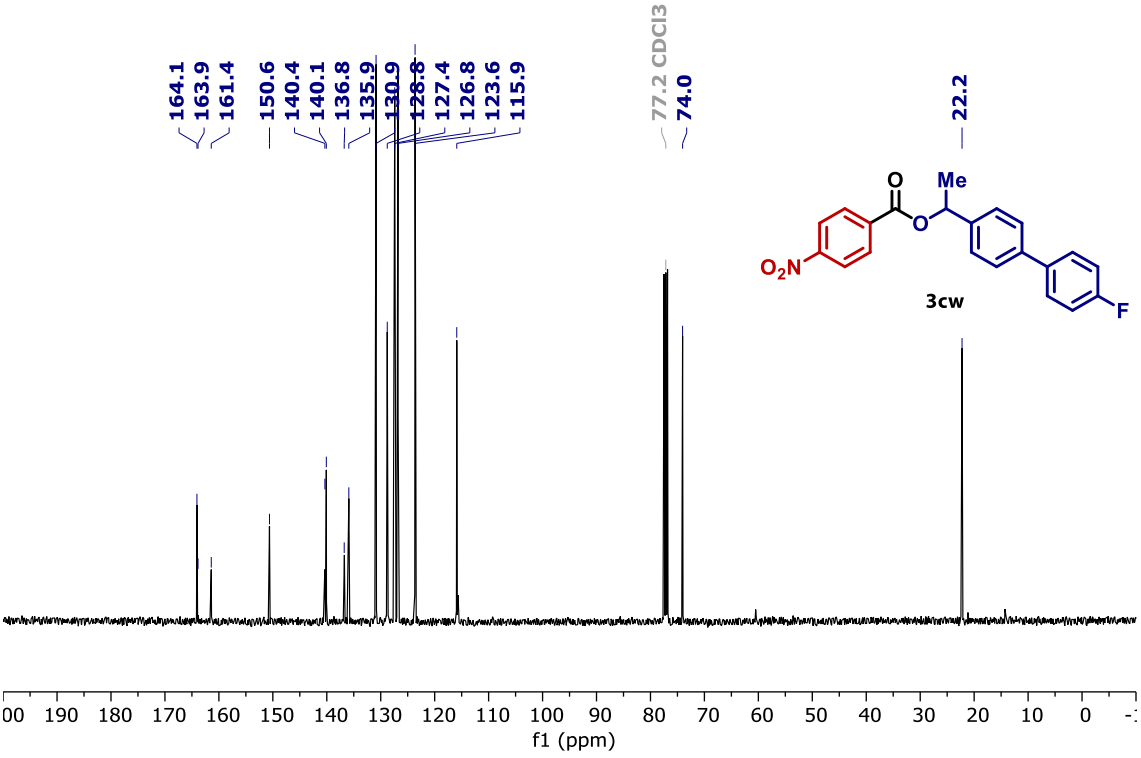


1-(4'-Fluoro-[1,1'-biphenyl]-4-yl)ethyl 4-nitrobenzoate, ***3cw***

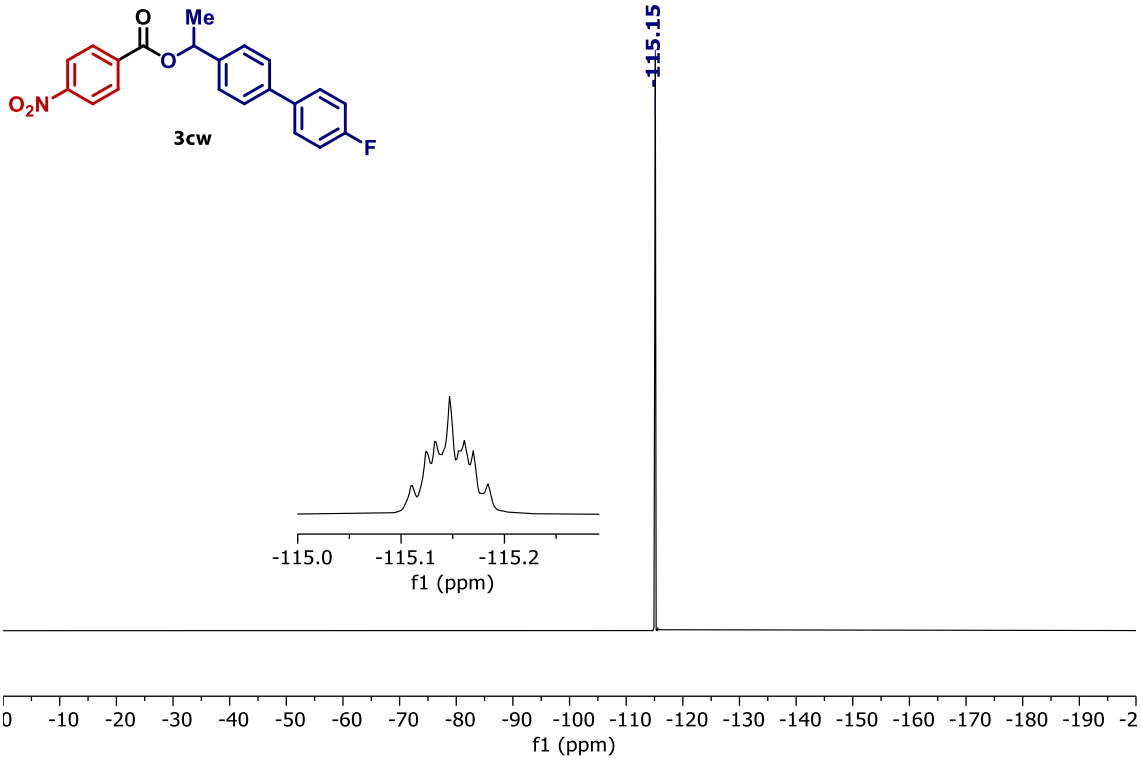
^{1}H NMR (400 MHz, $CDCl_3$), *recorded by David Heard*



^{13}C NMR (101 MHz, $CDCl_3$), *recorded by David Heard*

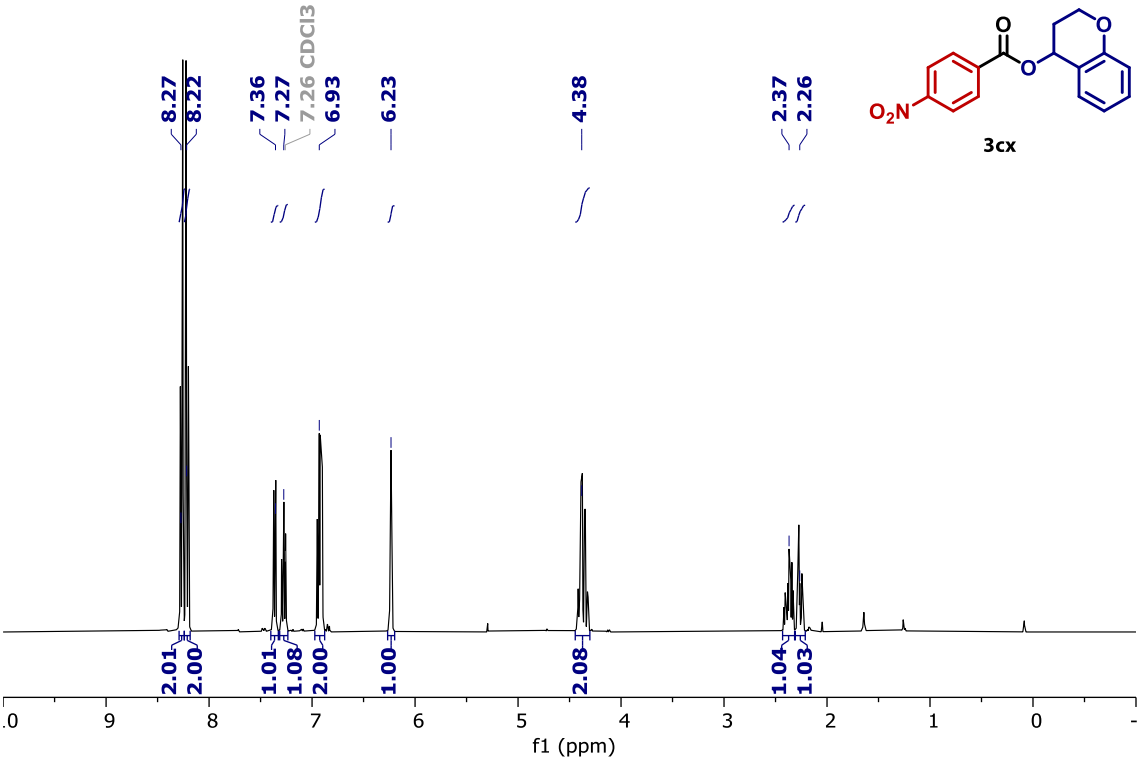


^{19}F NMR (376 MHz, $CDCl_3$), *recorded by David Heard*

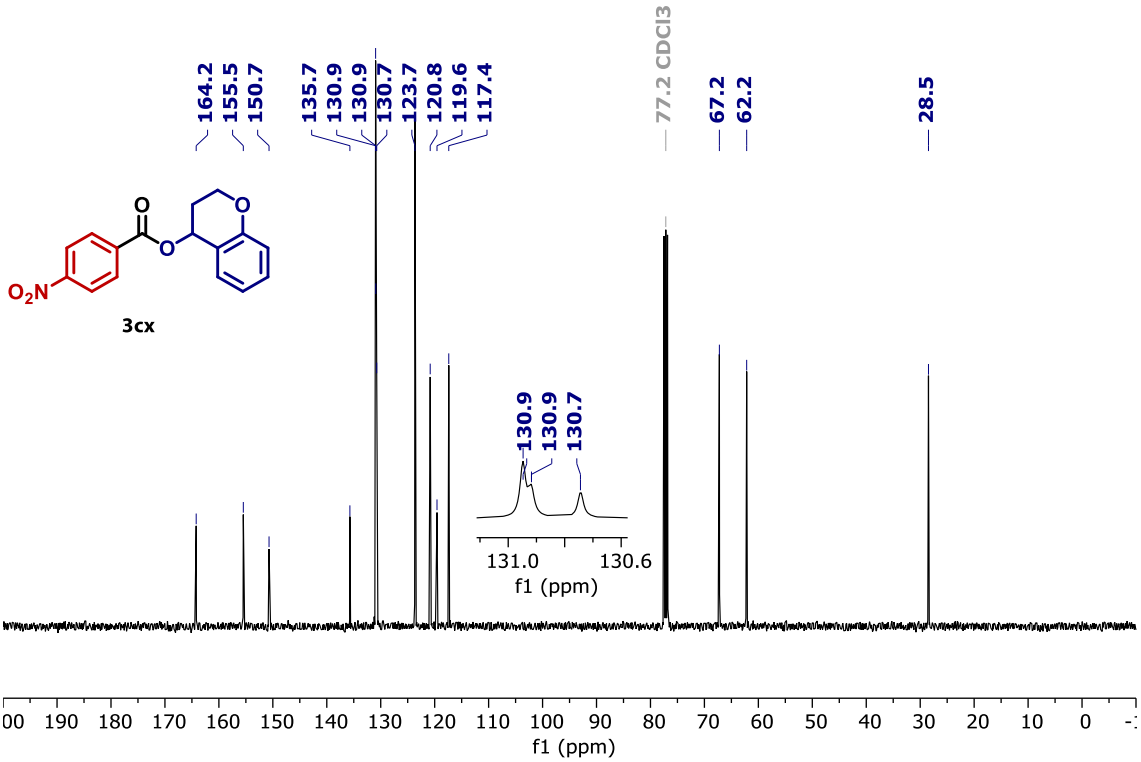


Chroman-4-yl 4-nitrobenzoate, ***3cx***

^{1}H NMR (400 MHz, $CDCl_3$), *recorded by David Heard*

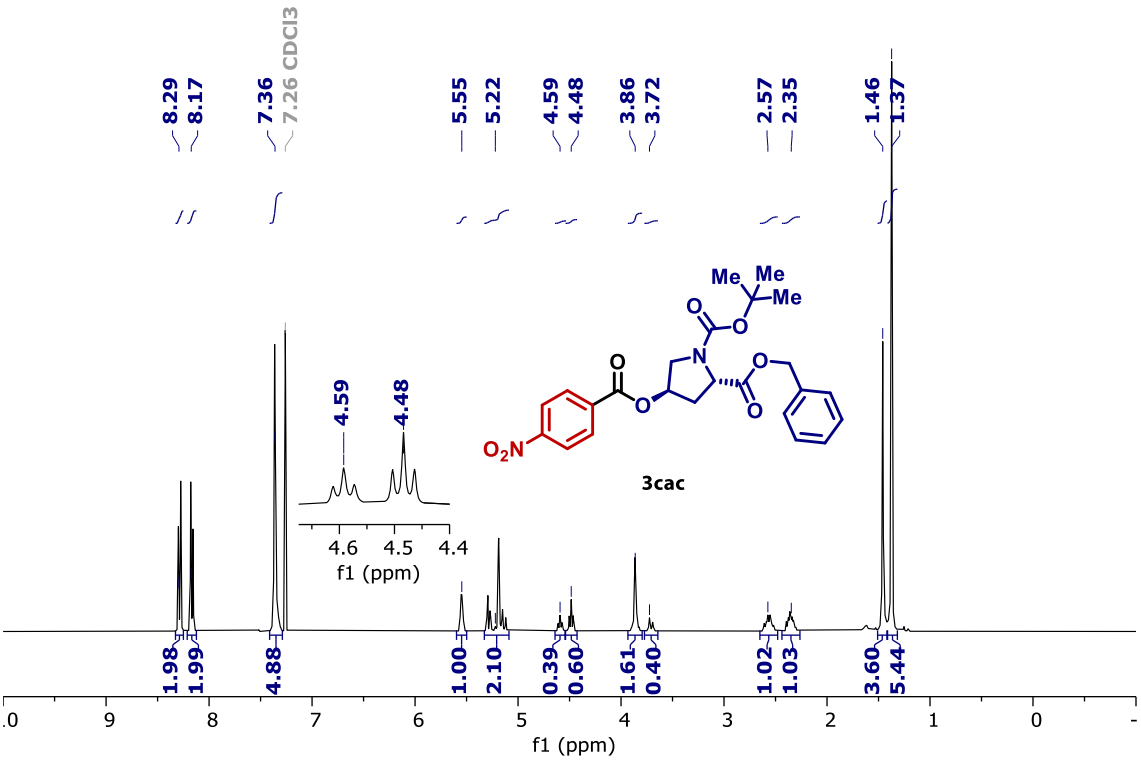


^{13}C NMR (101 MHz, $CDCl_3$), *recorded by David Heard*

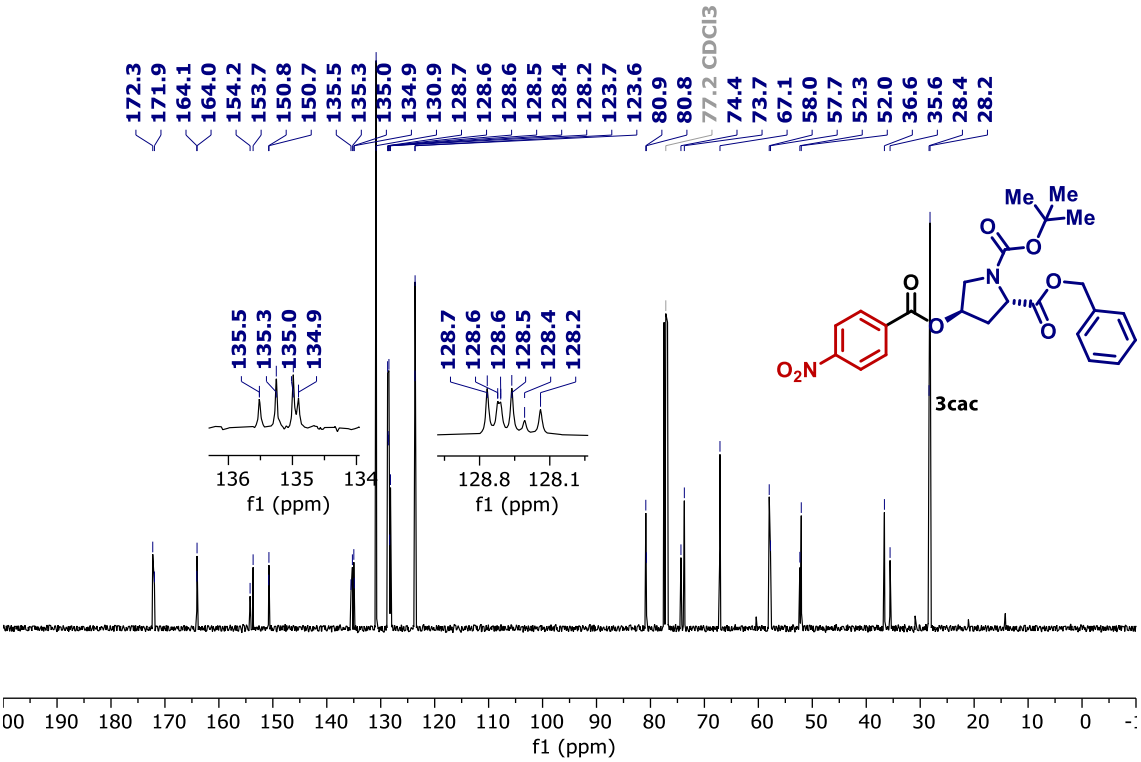


2-Benzyl 1-(tert-butyl) (2S,4R)-4-((4-nitrobenzoyl)oxy)pyrrolidine-1,2-dicarboxylate, ***3cac***

^{1}H NMR (400 MHz, $CDCl_3$), *recorded by David Heard*

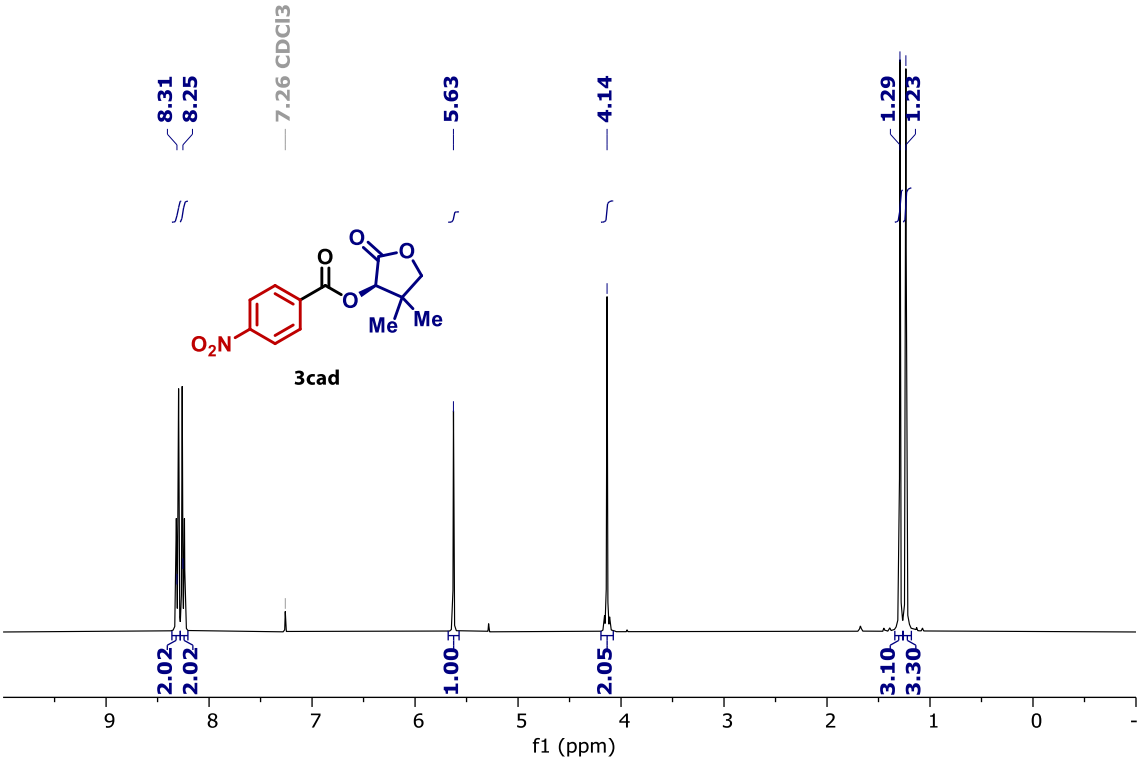


^{13}C NMR (101 MHz, $CDCl_3$), *recorded by David Heard*

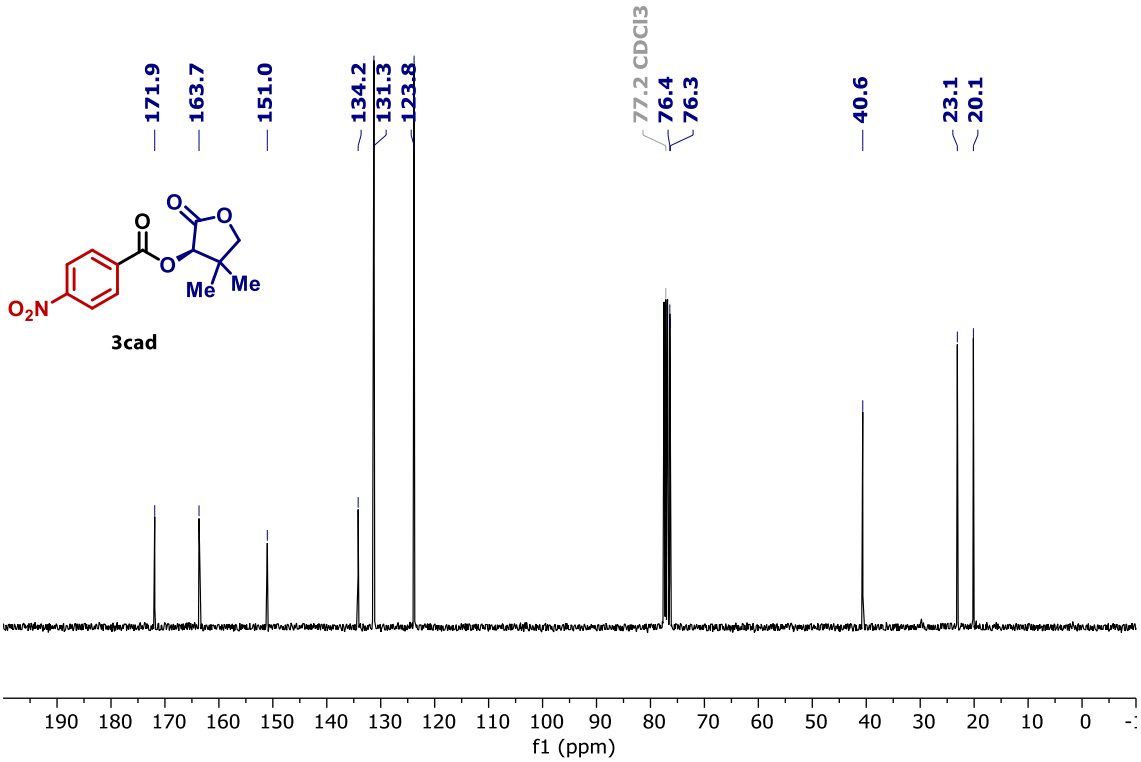


O-(4-Nitrobenzoyl)-D-pantolactone, ***3cad***

^{1}H NMR (400 MHz, $CDCl_3$), *recorded by David Heard*



^{13}C NMR (101 MHz, $CDCl_3$), *recorded by David Heard*



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