

Studies towards *N*-trifluoromethylated amides

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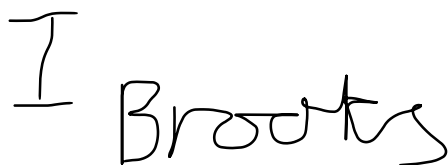
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On

September 2025

Authors Declaration

The work in this thesis was conducted at the Department of Chemistry at the University of Nottingham under the supervision of Dr Miriam O'Duill. All the work is my own, except where otherwise stated, and has not been submitted for any other degree at this or any other university.

A handwritten signature in black ink. It consists of a stylized capital letter 'I' followed by the word 'Brooks' in a cursive script.

Isaac Brooks

September 2025

Abstract

Trifluoromethylation is a potent tool for compound modulation from the fields of agrochemistry to pharmaceutical sciences, providing improved potency, modulation of lipophilicity and metabolic stability amongst other benefits. This project focuses on a niche trifluoromethyl moiety—*N*-CF₃ amides—that have promising potential, but few synthesis pathways have been published. We aim to use Togni I reagent to explore the synthesis of *N*-CF₃ amides following a ‘Ritter style’ reaction using mild conditions and reagents. Ultimately, some crude samples of *N*-CF₃ amides were obtained but isolation was unable to be carried out, in part, due to the instability of the produced *N*-CF₃ amides.

Acknowledgements

Thank you to Dr Miriam O'Duill for her tireless and enthusiastic support of me throughout this past year, I really appreciate the opportunity you have given me and the splendid team ethos you have imbued into the group.

Thanks go too to the O'Duill group for their patience with me and for being very friendly and welcoming, never a dull moment! Special thanks go to Suman for showing me the ropes at the start and to Charlotte for taking me under her wing and helping me develop as a hypervalent iodine chemist trainee. Further thanks and appreciation go to my fellow MRes colleague 'Wormy-bint-Babybell' across the corridor, lunchtime walks seem key to maintaining wellbeing during hypervalent hysteria.

As Iko Uwais says in 'The Raid' 2011, **"You learn more from failure than from success."**

A prescient lesson relevant to Ritter type trifluoroamidations. Thank you to Rory for introducing me to this masterpiece of a film.

Cheers everyone.

Abbreviations

FDA—food and drug administration

HIV—human immunodeficiency virus

ADME—absorption, distribution, metabolism and excretion

Bcr-Abl—the Philadelphia chromosome

CB₁—Cannabinoid receptor 1

cAMP—cyclic adenosine monophosphate

QSAR—quantitative structure activity relationship

THF—tetrahydrofuran

DCM—dichloromethane

DMAP—4-dimethylaminopyridine

DCC—N,N'-dicyclohexylcarbodiimide

PIDA—phenyliodine(III) diacetate

DMPU—N,N'-dimethylpropyleneurea

TFA—trifluoroacetic acid

PIFA—(bis(trifluoroacetoxy)iodo)benzene

NMR—nuclear magnetic resonance

mmol—millimole

mg—milligram

g—gram

kg—kilogram

mL—millilitre

μL—microlitre

h—hour

eq—equivalents

HSQC—heteronuclear single quantum coherence

DCE—dichloroethane

MHz—megahertz

HRMS—high-resolution mass spectrometry

J—coupling constant

IC₅₀—inhibitor concentration (where rate of reaction/binding reduced by 50 %)

ppm—part(s) per million

rt—room temperature

TLC—thin-layer chromatography

Å—angstrom

°C—degrees Celsius

δ —chemical shift

s—singlet

d—doublet

dd—doublet of doublets

t—triplet

td—triplet of doublets

m—multiplet

ESI—electrospray ionisation

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Introduction

The Trifluoromethyl group and Trifluoromethylation

The trifluoromethyl group $-\text{CF}_3$ is a synthetic functional group that is increasingly relevant to industries important to human life such as agrochemistry and pharmaceutical science.¹⁻⁴ From around 1979 there was a large increase in publications concerning this group, despite organofluorine compounds being recognised as biologically useful since the early parts of the 20th century.⁵⁻⁷ This is likely due to the extreme rarity of even singly fluorinated compounds in nature—only 13 have been identified, 8 of which are derivatives of fluoroacetic acid (fig 1)—coupled with the difficulty in achieving fluorination artificially.⁸⁻⁹

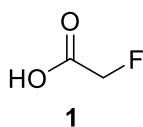
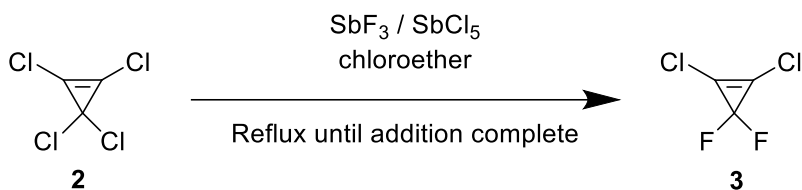


Figure 1: Structure of fluoroacetic acid, the basis for the majority of all naturally occurring organofluorine compounds identified.

Artificial fluorination was a process that originally required harsh, forcing conditions with toxic reagents as seen in the Swarts' reaction which involved the use of antimony trifluoride and antimony pentafluoride or chlorine to do a halogen exchange with chlorine atoms (scheme 1).¹⁰



Scheme 1: An example of a Swart's reaction.

Given the relative difficulty in trifluoromethylation, it is worth examining the moiety itself to see what makes it worth the cost of production. With regards to its utility, as mentioned before, it is widely used in pharmaceutical chemistry and agrochemistry for largely the same pharmacokinetic reasons with the statistics below outlining the impact the trifluoromethyl group possesses (fig 2).¹¹⁻¹²

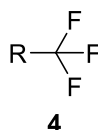


Figure 2: Structure of the trifluoromethyl group

With respect to pharmaceutical chemistry, the trifluoromethyl group is noteworthy given that out of a total of 66 FDA approved drugs in 2020, 19 contained the trifluoromethyl group covering ailments from tuberculosis to HIV.¹³

Regarding agrochemistry, as the global population grows and better access to food worldwide improves, more effective ways of protecting crops are needed to maximise yields to satisfy increasing demand. Protection from fungi, parasites, diseases and pests is one way of achieving this goal. The high level of prevalence of the trifluoromethyl group in pharmaceutical science is also seen in agrochemistry with half of all pesticides released since the turn of the millenium being fluorinated, of them, 40 % contain a

trifluoromethyl group, however, recently, there has been criticism of fluorinated agrochemicals due to their environmental persistence, thus the future of trifluoromethylated agrochemicals is at risk.¹⁴

The main feature of the trifluoromethyl group comes from fluorine being the most electronegative element. This means the C-F bonds in the trifluoromethyl group can exhibit semi-ionic character with the carbon bearing a partial positive charge and the fluorines, a partial negative.¹⁵ This makes this moiety one of the strongest electron withdrawing groups, and this quality imparts a great deal of this group's utility.¹⁶⁻¹⁷

The key qualities the trifluoromethyl group is appreciated for are its ability to: improve lipophilicity; improve binding selectivity through favourable interactions with surrounding molecules such as proteins; improve metabolic stability and overall favourable ADME (absorption, distribution, metabolism and excretion) ability largely due to high bond disassociation enthalpy and chemo-, thermo-, electro-, and photochemical stability.¹⁸⁻¹⁹ Moreover, due to these pharmacokinetic effects, the group also sees use as a bioisostere being a useful replacement functional group for moieties such as chlorine or a nitro group.²⁰⁻²¹

What this means is that the trifluoromethyl group is a potent tool with a proven positive impact—for instance, compound **5**, Prozac, the most prescribed anti-depressant in the world, contains a trifluoromethyl group that affords 6-fold potency relative to the non-trifluoromethylated compound—figure 3 shows a further selection of trifluoromethylated drugs.²²

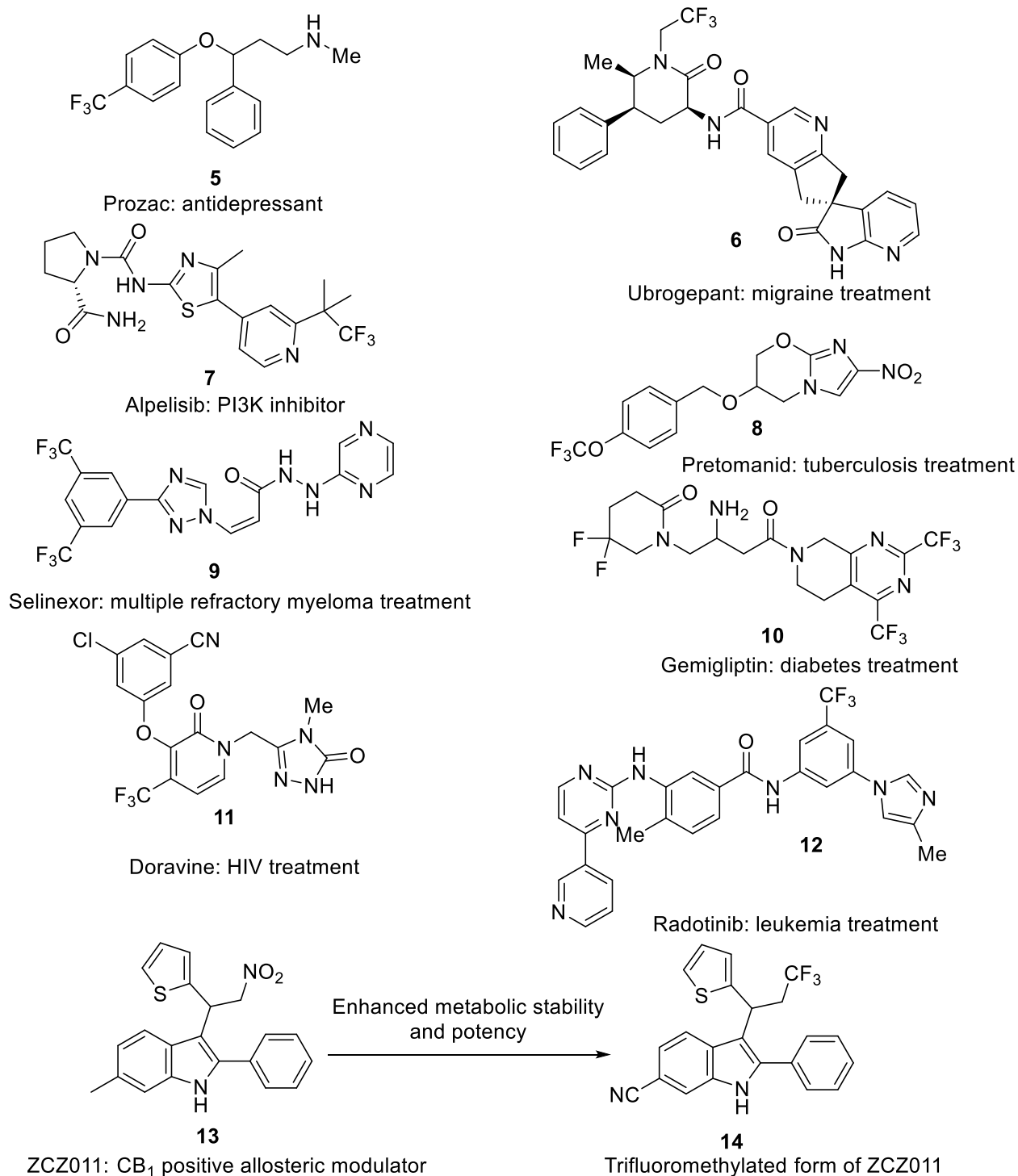


Figure 3: Trifluoromethylated drugs.^{13, 20-24}

An example of an improvement in selectivity is exemplified by compound **12**, Radotinib, a drug for leukemia in patients who do not respond well to other treatments. Here, the

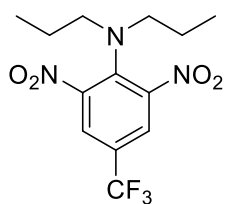
trifluoromethyl group is able to interact with a hydrophobic pocket in the binding region of the protein Bcr-Abl kinase affording increased potency.²⁴

The nitro group in drug discovery is rare and has been described as a 'nondrug-like moiety' due to its association with mutagenicity and genotoxicity. However, when used, there are few efficacious bioisosteric replacements. This is likely due to challenges in replicating the binding interactions of the greatly electron withdrawing nitro group.²⁰⁻²¹

Compound **14** is a trifluoromethylated form of the CB₁ positive allosteric modulator ZCZ011, compound **12**, with the nitro group swapped for the trifluoromethyl group, resulting in enhanced metabolic stability—one of the main use cases for a bioisostere—and even improved potency (cAMP EC₅₀ (nM) 18 ± 1 -> 40 ± 17) while overall activity is conserved.²⁰

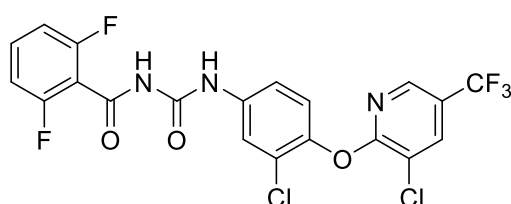
Regarding agrochemical specific uses, the trifluoromethyl group, due to its good binding selectivity, means that compounds in use as pesticides/herbicides/fungicides can have much narrower spectra of action—this is important in order to reduce 'collateral damage' to the wider ecosystem, outside of the parasite, for instance, being targeted.¹⁴

The trifluoromethyl group was first widely used in agriculture in the late 1950s with compound **15**, Trifluralin, a very popular herbicide that within 5 years of discovery was utilised to cover 10 % of the acreage used for soybean cultivation, shown in figure 4 alongside a selection of other trifluoromethyl containing agrochemicals:²⁵⁻²⁶



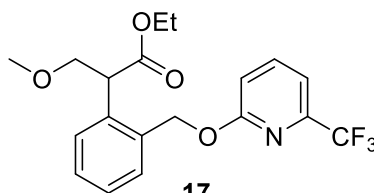
15

Trifluralin: herbicide



16

Fluazoron: pesticide



17

Picoxystrobin: fungicide

Figure 4: Trifluoromethylated agrochemicals.^{1, 27}

N-Trifluoromethylated (*N*-CF₃ amides), the focus of this project, are sparse in the general organic literature, likely due to previously difficult syntheses meaning they are passed over when designing a drug.²⁸ However, this moiety is worth investigating as it brings together two groups important to pharmaceutical science and agrochemistry. Amides are ubiquitous in nature and are present in ~40 % of all drugs, providing a large opportunity for modification by trifluoromethylation to create more effective drugs, as shown by one of the few *N*-CF₃ amides found in the literature.²⁹⁻³⁰ Compound **18** was discovered in 2007 by Sahu *et al.* when during QSAR analysis (quantitative structure activity relationship) of caffeoyl supported naphthelene sulfonamides, they found that a trifluoromethylated derivative provided enhanced activity and lipophilicity (figure 5):³¹

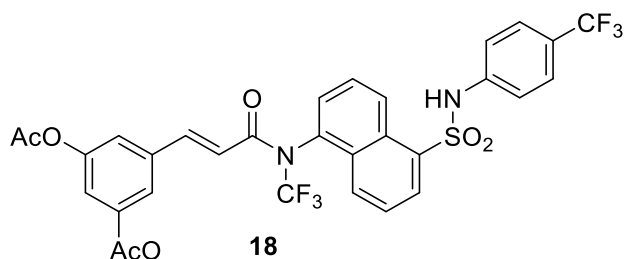
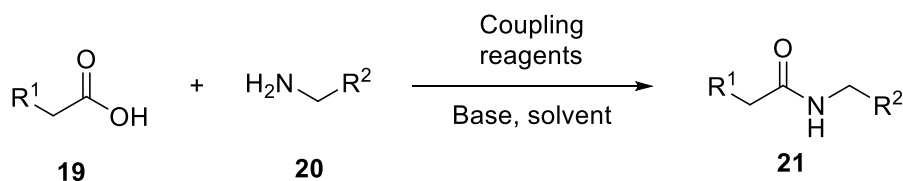


Figure 5: Structure of a caffeoyl based naphthalene sulfonamide derived N -CF₃ amide that shows promise as an HIV inhibitor based on QSAR analysis.

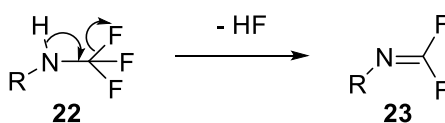
Existing Syntheses of N -CF₃ Amides

Currently, the standard way of making an amide is via a coupling of a carboxylic acid and an amine (scheme 2), however, this method has a certain level of problems associated with it when synthesising N -CF amides.³²



Scheme 2: Basic general reaction scheme for a classic synthesis of amides.

For instance, trifluoromethylated amines possess high instability leading to facile hydrodefluorination as shown in scheme 3.³³⁻³⁵



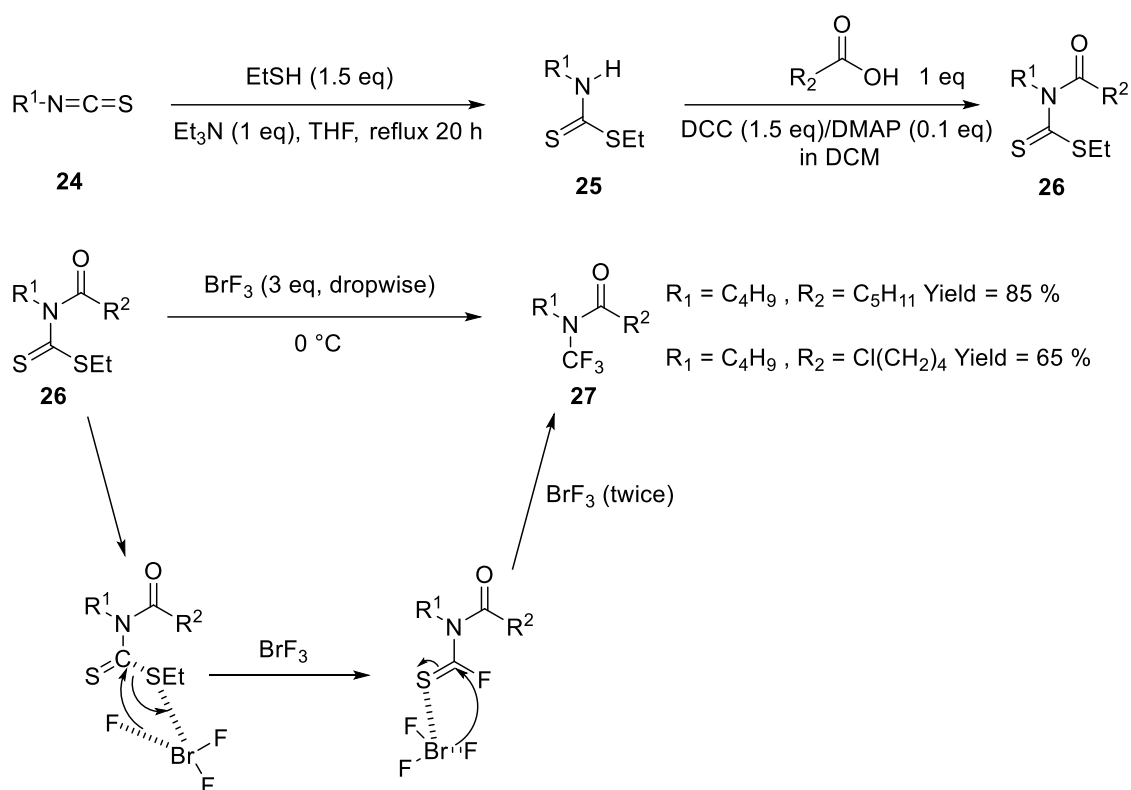
Scheme 3: Hydrodefluorination of an N -CF₃ amine.

Some ways around the potential impasse in $N\text{-CF}_3$ amide synthesis have been developed, however.

In this section, the various synthetic methods currently available to synthesise $N\text{-CF}_3$ trifluoromethylated amides will be discussed. One of the standard routes involves the use of isothiocyanate starting materials with multiple variations existing. Another route utilises electrophilic trifluoromethylation of an amide. The final synthetic method discussed involves using radical chemistry from an $N\text{-CF}_3$ imidate to generate the trifluoromethylated amide.

$N\text{-CF}_3$ Amides from Isothiocyanates

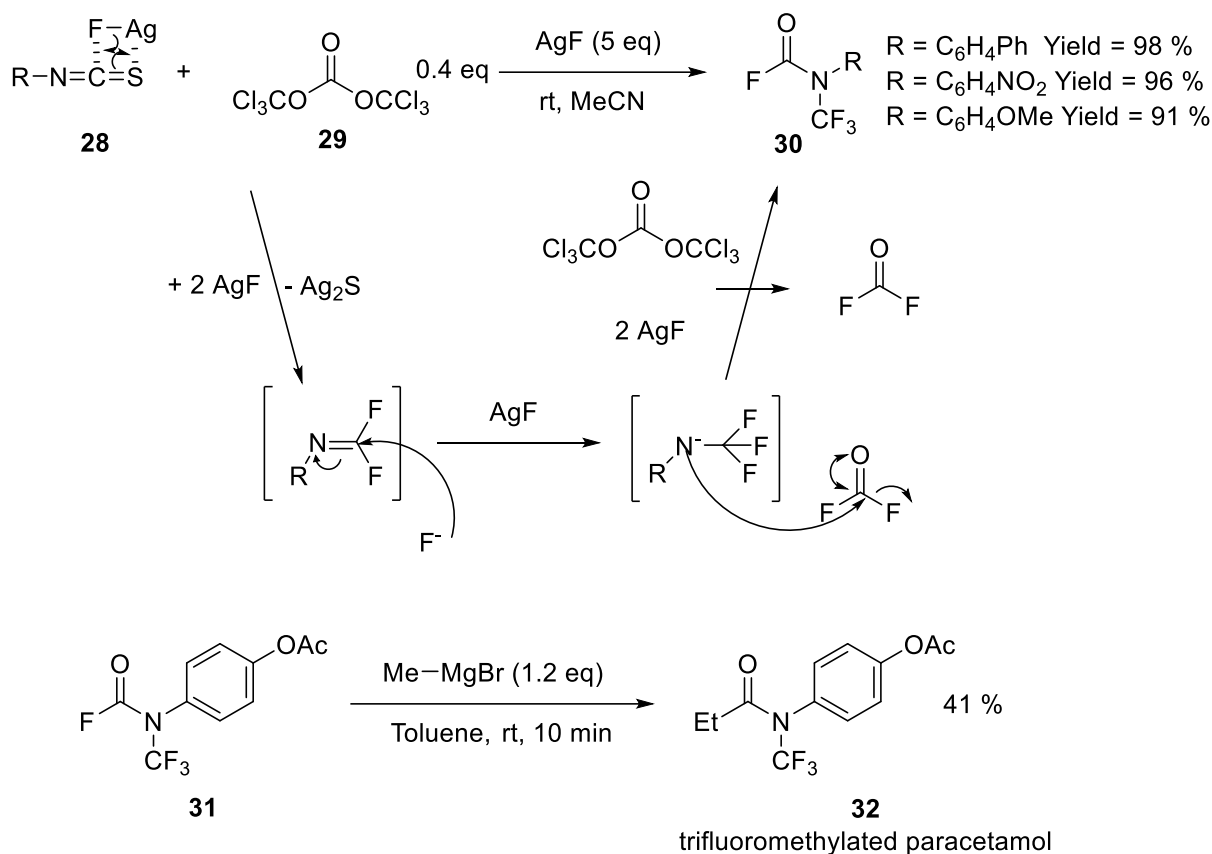
One of the first synthetically useful methods for $N\text{-CF}_3$ amide synthesis developed utilises an isothiocyanate starting material, compound **24**, with bromine trifluoride as a fluorinating material.²⁸ First, an isothiocyanate was treated with ethanethiol and then a carboxylic acid was added forming an alkyl(alkanoyl)dithiocarbamate which could complex to bromine trifluoride in order to afford an $N\text{-CF}_3$ amide, compound **27**, as laid out in scheme 4:



Scheme 4: Overall reaction scheme for one of the first *N*-CF₃ amide syntheses in the modern era with a selection of R groups and yields displayed.²⁸

An obvious disadvantage of this method is the use of bromine trifluoride, an explosive compound rarely used due to its reactivity and danger as acknowledged by Rozen in this article. Moreover, the reaction requires multiple steps whereas a more streamlined method would be more attractive to industry.

Another isothiocyanate based method was developed by Schoenebeck and coworkers via the ‘operationally simple’ preparation of carbamoyl fluoride precursors that can then be further modified.³⁶ The method hinges upon desulfurizing isothiocyanates with silver fluoride to a difluoromethyl imine, adding more silver fluoride and then trapping the resulting nucleophile with an electrophilic carbonyl as shown in scheme 5:

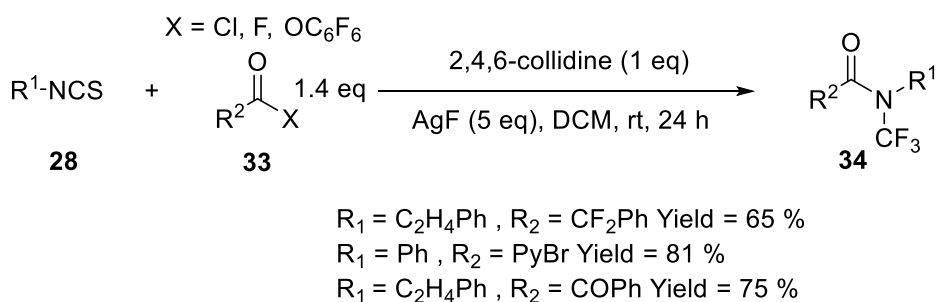


Scheme 5: Overall scheme for *N*-CF₃ amide formation created by Schoenebeck *et al* with a selection of R groups and yields displayed along with an example of a functionalisation via Grignard reagent.

This reaction tolerates many functional groups in the R position such as amides, nitriles, esters and sulfones and even free alcohols, acids and primary amines provided they were protected. From the building block *N*-CF₃ amide compound **30**, more complex *N*-CF₃ amides could be synthesised via use of Grignard reagents in toluene (bottom reaction of scheme 4) allowing *N*-trifluoromethylated forms of common drugs such as paracetamol, compound **32**, to be synthesised. However, one clear drawback for the reaction is the use of triphosgene, a highly toxic reagent.³⁷

Recently, in 2021, Wilson *et al* developed a synthetic method based on the classic way of making amides using carboxylic acids, combined with using an isothiocyanate starting

material.³⁸ This method uses the silver fluoride / isothiocyanate step from scheme 5 and then instead of using triphosgene, uses a variety of carboxylic acid halides and esters, also avoiding the need to use toxic Grignard reagents to reach further functionalisation with the general scheme shown in scheme 6:



Scheme 6: General reaction scheme for *N*-CF₃ amide synthesis by Wilson *et al.*³⁸

Triphosgene can be avoided due to 2,4,6-collidine being able to increase the reactivity of the silver stabilised R-N-CF₃⁻ anion. This is due to 2,4,6-collidine coordinating to the silver cation, reducing the strength of the silver cation's coordination to the R-N-CF₃⁻ anion thus increasing reactivity as shown in figure 6:

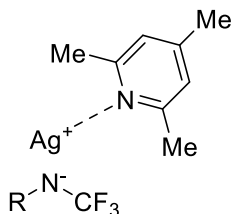
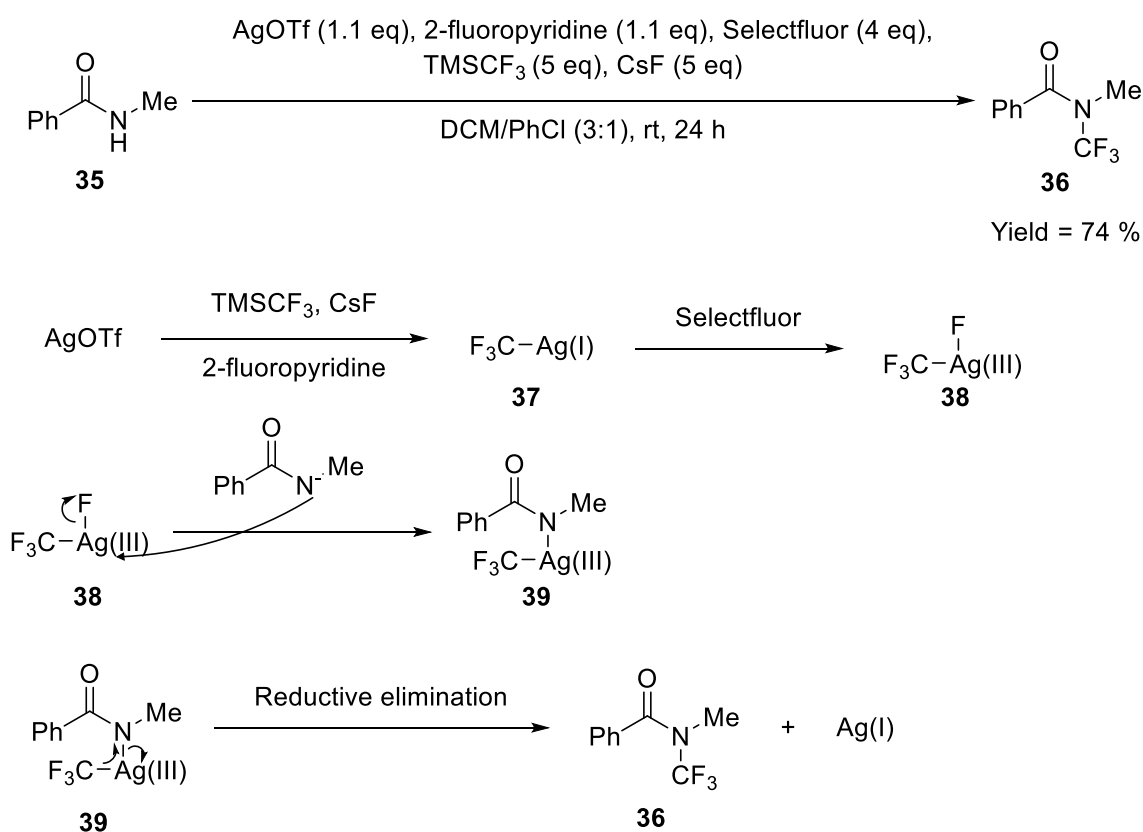


Figure 6: Simple diagram showing 2,4,6-collidine coordinating with a silver cation, reducing silver's stabilisation of the R-N-CF₃ anion.

N-CF₃ Amides through electrophilic trifluoromethylation

One shorter approach compared to the isothiocyanate routes skips the potentially awkward amine to amide synthesis route and involves a silver mediated electrophilic trifluoromethylation of an already formed amide promoted by AgOTf and 2-fluoropyridine via a reductive elimination with the overall scheme shown in scheme 7:³⁹



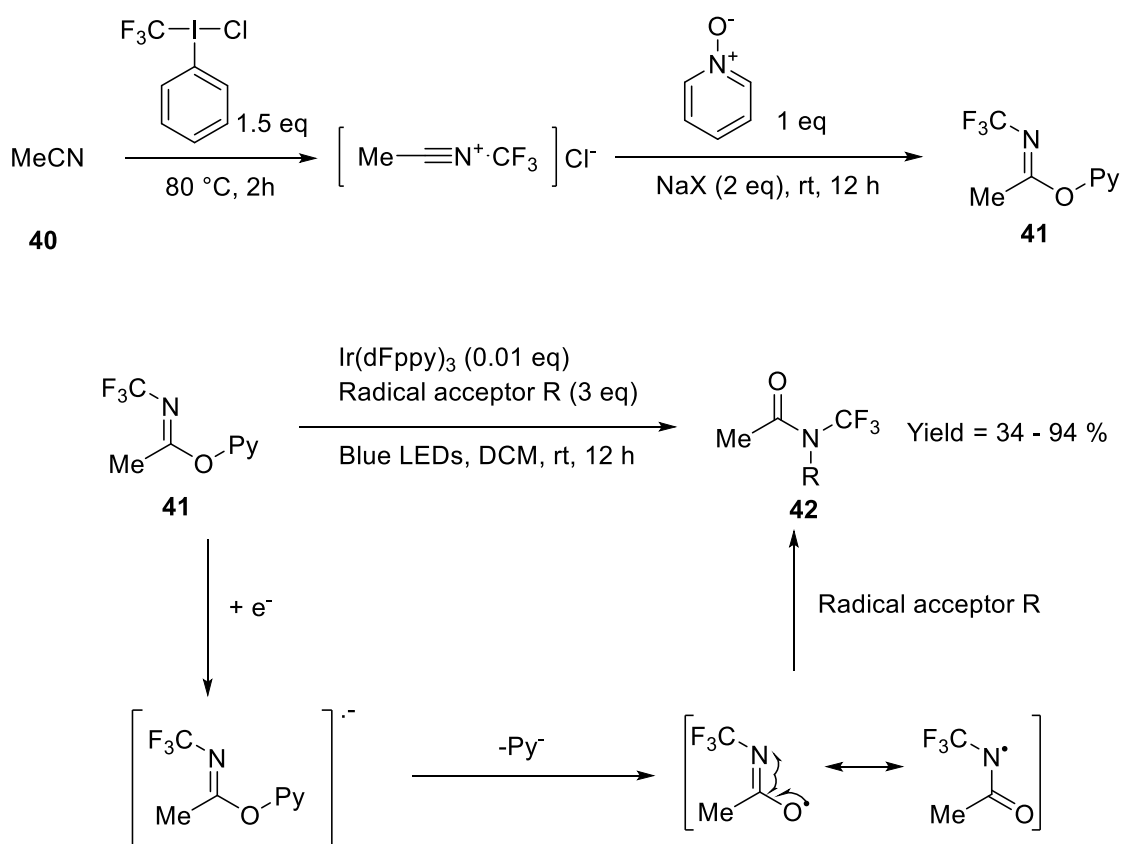
Scheme 7: General reaction scheme for the Li *et al* I-CF₃ amide synthesis.

The reaction scope was good with amides from benzamides to alkylalkanamides tolerating the reaction conditions, as well as a good range of functional groups such as ketones, nitriles and aryl halides meaning late-stage amide trifluoromethylation is

feasible. However, one downside of this method is the high excess of reagents required in this method.

N-CF₃ Amides Through a Radical Pathway

Unlike the previous methods, utilising a radical pathway forgoes isothiocyanates.⁴⁰ Firstly, a nitrile such as acetonitrile is used to form an *N*-CF₃ O-N imidate, compound **41**. This is done via the nitrile, compound **40**, coordinating to the hypervalent iodine -CF₃⁺ source PhICl₃ then reductively eliminating to form a trifluoromethylating nitrilium ion. This cation is then trapped by pyridine-*N*-oxide or another suitable *N*-oxide nucleophile which is in turn photocatalysed into the desired amide compound **42** via a radical pathway as shown in scheme 8:



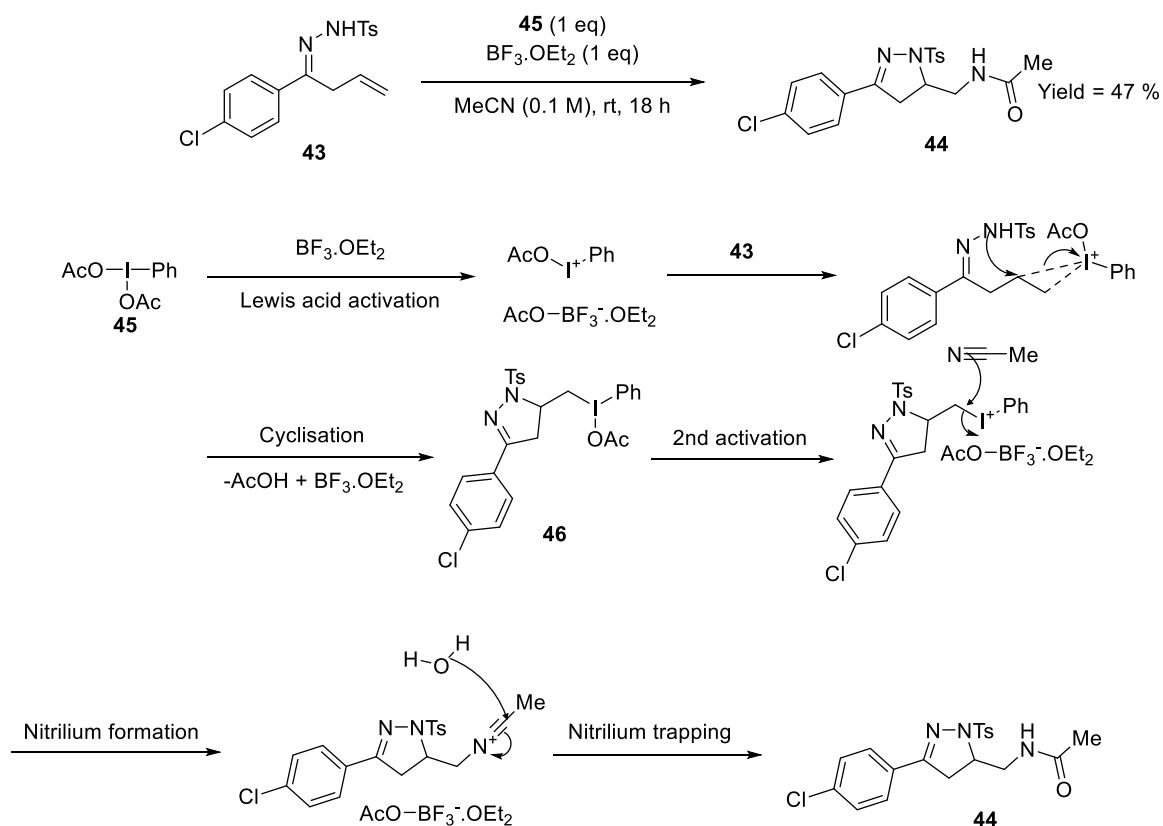
Scheme 8: Overall reaction scheme for the photocatalysed synthesis of *N*-CF₃ amides starting from a nitrile, with the example using acetonitrile.⁴⁰

This method provides very good yields of up to 94 %, a clear advantage compared to other methods. A key part of this method is the first step, which utilises hypervalent iodine as an electrophilic source of the trifluoromethyl cation which then forms a nitrilium ion intermediate.

Synthesis of Amides through Ritter Type Reactions

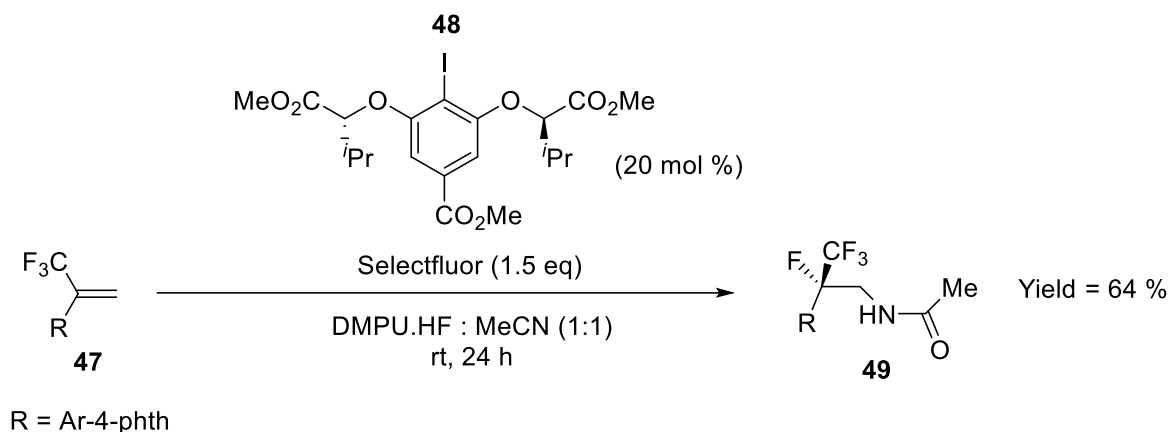
Although the two following synthetic methods do not afford *N*-CF₃ amides, they are relevant due to their use of a Ritter type reaction whereby a nitrilium ion is quenched by water acting as a nucleophile, leading to amide formation. This water based synthetic route could potentially lead to *N*-CF₃ amide formation via a simple scope expansion—using a trifluoromethylated *N*-CF₃ nitrilium ion.

One reaction involves a hypervalent iodine-mediated amidation of a terminal alkene.⁴¹ The reaction involves the use of a Lewis acid to activate the hypervalent iodine reagent PIDA, compound **45**. The activated reagent forms an electrophilic iodonium intermediate with the terminal alkene of an allyl ketone oxime or tosylhydrazone. After cyclisation via nucleophilic attack on the iodonium intermediate, the iodine can once again be activated via a Lewis acid. Acetonitrile then nucleophilically substitutes with the resultant iodonium ion, forming a nitrilium ion which is trapped by water to form an amide. The general scheme and mechanism is shown in scheme 9:



Scheme 9: Reaction scheme and mechanism for water-based amide formation via a Ritter type reaction.⁴¹

A second reaction involves the use of trifluoromethyl styrenes which are fluoroamidated via $\text{I}^{\text{I}}/\text{I}^{\text{III}}$ catalysis, with an iodonium intermediate being nucleophilically attacked by a nitrile and then quenched by water, with a similar mechanism as that of scheme 9 (overall scheme shown in scheme 10):⁴²



Scheme 10: Reaction scheme for Gilmour's amidation of alkenes via a similar mechanism to scheme 9.⁴²

One downside of this reaction compared to the previous is the use of HF, although higher yields are achieved: 64 % compared to 47 %.

Hypervalent Iodine

General Introduction to Hypervalent Iodine

As seen in scheme 8 and 9, hypervalent iodine is a potential route for synthetic success. Hypervalent iodine is a broad and growing topic with many books being published on the matter by highly prolific chemists such as V. V. Zhdankin.⁴³⁻⁴⁶ Hypervalent iodine reagents make use of the large size of iodine which allows for 3 centred four electron bonding (-L-I-L) formed by 5p orbital overlap of the iodine with two ligands (figure 7). This 'hypervalent' bond is weak and highly polarised providing strong reactivity.⁴⁷

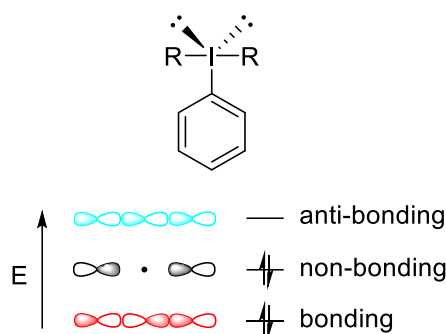


Figure 7: Structure of hypervalent iodine—T shaped geometry, 3 centre-4 electron hypervalent bond, equatorial lone pairs.

Hypervalent iodine reagents are often compared to transition metal catalysts—oxidative addition, reductive elimination, ligand exchange and ligand coupling are common features of hypervalent iodine reactions but iodine is more attractive based on both ecology and economics.⁴⁸ An iodine containing compound used as the main component in the synthesis of one such hypervalent iodine compound is in the region of £900 per kg—a fraction of the cost of popular transition metals such as platinum group metals. For instance, in 2011 the price of platinum fluctuated between EUR 45,000 and 61,000 per kg.^{49, 50} Moreover, iodine and its reagents are widely regarded as environmentally benign and moderately sustainable, with roughly 500 years supply remaining based on current levels of consumption.⁵¹

Hypervalent iodine reagents have multiple classes divided into two main segments—iodine (III) reagents and iodine (V) reagents (λ^3 -iodanes and λ^5 -iodanes respectively), with general structures of the classes based on Zhdankin's classifications shown in figure 8:

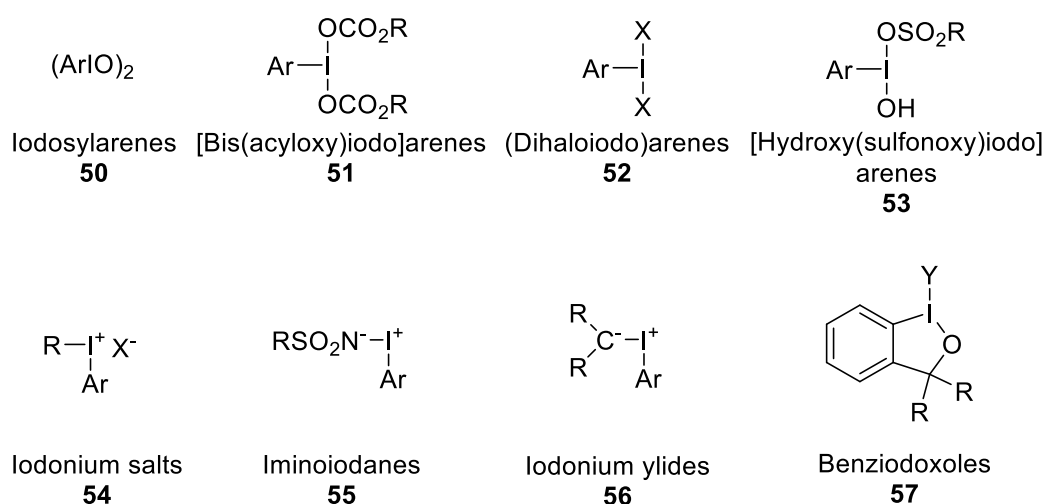
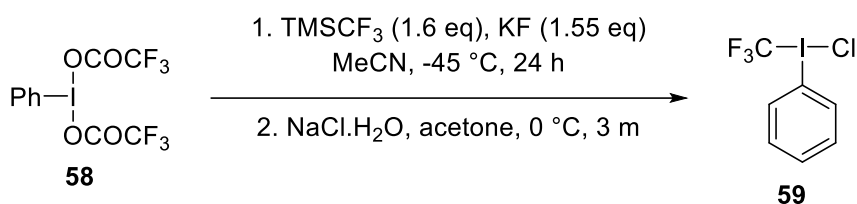


Figure 8: The 8 main classes of hypervalent iodine reagents according to Zhdankin where X is a halide or pseudo halide and Y is a trifluoromethyl group.⁴⁷

Hypervalent Iodine Trifluoromethylation Reagents and their Use

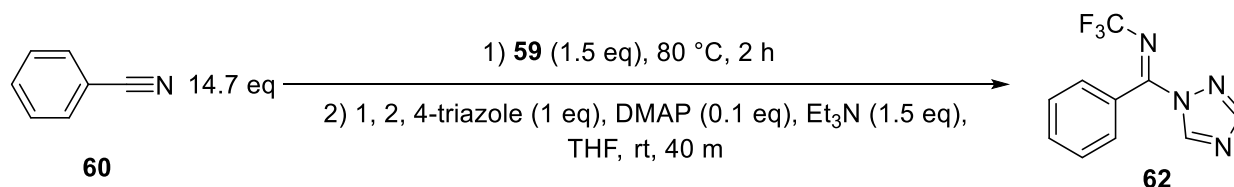
Of the classes of hypervalent iodine reagents in figure 8, (dihaloiodo)arenes, compound **52**, and benziodoxoles, compound **57**, are the ones used for trifluoromethylation chemistry. They possess a trifluoromethyl group attached to the iodine, and in the case of compound **52** usually a chlorine or triflate are also attached. Scheme 11 shows the preparation of an example of a (dihaloiodo)arene, PhICF_3Cl , compound **59**, utilised by Wang *et al* in the synthesis of *N*- CF_3 amidines, imidates and thioimidates and also seen before in scheme 8:⁵²⁻⁵³



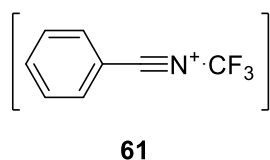
Scheme 11: Reaction scheme for preparation of the (dihaloiodo)arene **52** class reagent utilised by Wang *et al.*⁵³

One downside of this compound is the difficulty in synthesising it, requiring very low temperatures overnight (covered further in results and discussion).

(Dihaloiodo)arene **59** is used in conjunction with a nitrile, DMAP and Et₃N to form an *N*-CF₃ nitrilium ion, which is then ‘quenched’ with an *N*-/O-/S- centred nucleophile to form the desired amidine, imidate or thioimide respectively. One example is using 1,2,4-triazole as an *N*- centred nucleophile as shown in scheme 12:⁵²



Via DMAP stabilised nitrilium ion intermediate **61**:



Scheme 12: Synthesis of 1-phenyl-1-(1,2,4-triazol-yl)-*N*-(trifluoromethyl)methanimine using (dihaloiodo)arene **59** with 1,2,4-triazole as a ‘nitrilium cation quenching’ nucleophile and benzonitrile as the nitrile.

Much like the reaction in scheme 8, yields of the reaction are excellent, up to 91 %, and proceed via a two-step process. The nitrile is mixed with the PhICF_3Cl , (dihaloiodo)arene **59**, for 2 hours to form the nitrilium ion intermediate **61** like in scheme 8, upon which time the rest of the reactants are added.

However, the use of (dihaloiodo)arene reagents for trifluoromethylation is a recent development, owing to their perceived difficulty in isolation late in the 20th century, with Umemoto *et al* being unable to isolate their theoretical product under their reaction conditions.⁵⁴ This led to the development of cyclic hypervalent iodine trifluoromethylating reagents of the benziodoxole class due to the higher stability of cyclic hypervalent reagents compared to their acyclic counterparts.⁵⁵⁻⁶⁰

Benziodoxoles are a lot more varied with their substituents, possessing a trifluoromethyl group attached to the iodine and a variety of potential R groups. Figure 9 shows five trifluoromethylating benziodoxole class reagents:

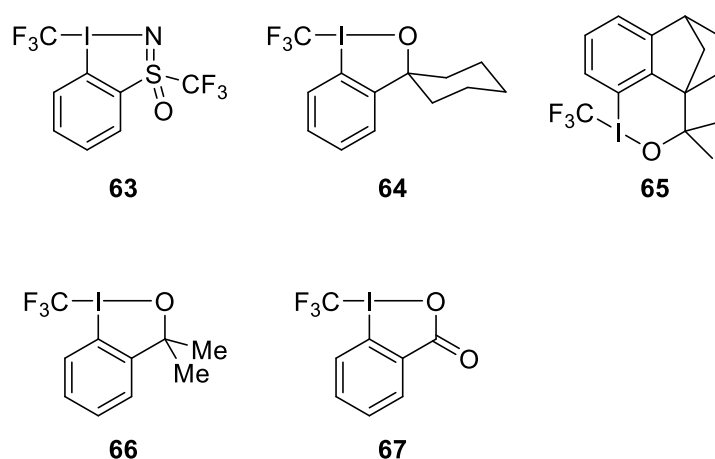
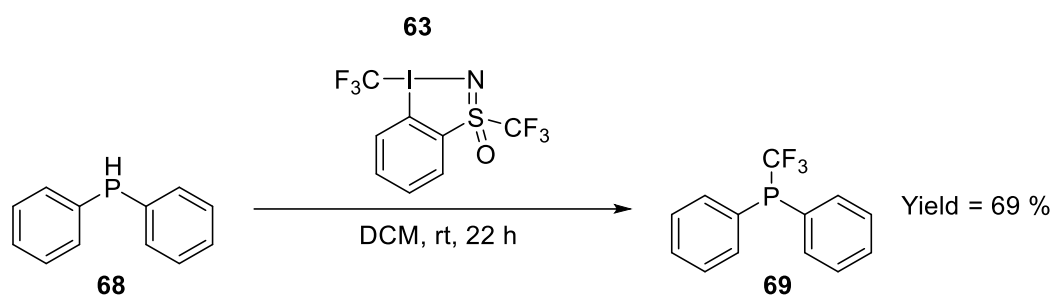


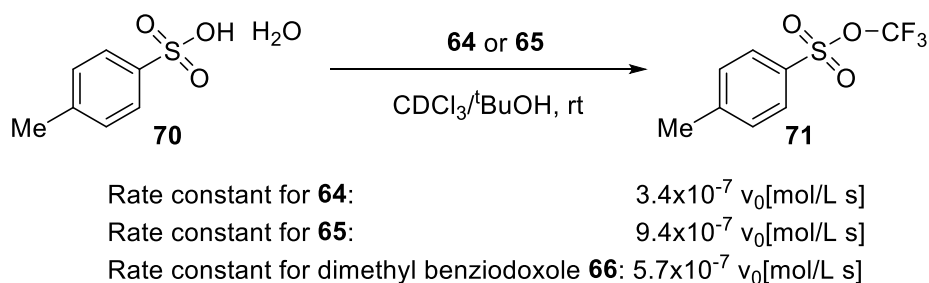
Figure 9: Five benziodoxole class reagents with varied R groups and one of which, compound **63**, being a derivation of the benziodoxole class, it itself being an iodosulfoxime.

Compound **63** is a hypervalent iodosulfoximine which falls into the category of a benziodoxole reagent under Zhdankin's classification, and is competent at trifluoromethylating S-, C-, O- and P- centred nucleophiles with good yields as shown in scheme 13:⁵⁷



Scheme 13: Iodosulfoxime **63** in use as a trifluoromethylating agent with a P- centred nucleophile demonstrating a good yield.

Compounds **64** and **65** are based upon work by Togni *et al* covered in more detail in the section below.⁵⁸ These two reagents were attempts at broadening the catalogue of cyclic trifluoromethylating hypervalent iodine reagents, and were evaluated based on rate constants of a previously reported simple reaction as shown in scheme 14:



Scheme 14: The simple and well reported reaction used to assess compound **64** and **65** plus their respective rate constants with those of the more established reagent, dimethyl benziodoxole **66**.

These rate constants are of a similar magnitude to those of the original two Togni reagents and thus show promise for future work, however, owing to the experimental nature of these compounds, and low yield of reagent synthesis, this project focused on compound **66** and **67**.

Exploring Togni's Reagents

Compound **66** and **67**, Togni I (dimethyl benziiodoxole) and its sister Togni 2 (carbonyl benziiodoxole) respectively, are two benziiodoxoles which can afford facile trifluoromethylation under mild conditions.^{55, 59-60}

These two reagents were developed in 2006 from a failed attempt to synthesise an acyclic hypervalent iodine reagent which was alleged to have failed due to the vulnerable I-CF₃ bond (although in more recent years Wang *et al* have found success with such a reagent class).⁵² The overall goal was to synthesise a trifluoromethylating hypervalent iodine reagent due to relatively cheap starting materials (methyl 2-iodobenzoate is less than £20 for 10 g) and due to potential for recycling the de-trifluoromethylated side-product which is an intermediary material in the synthesis of the reagents.⁵⁵

When determining reactivity of Togni-style reagents the main factor involved is the length of the I-CF₃ bond, with a shorter bond increasing the electrophilicity of the reagent. This is linked to the trans effect. In general terms, given the hypervalent iodine 3-centre-4-electron bond Y-I-X, if X is a strong sigma donor it will donate a high proportion of electron density thus strengthening and therefore shortening the I-X bond. However, since the bond order of Y-I-X is constant, this necessitates a weakening and therefore lengthening

of the trans I-Y bond. Key in the trifluoromethylation reactions compounds **66** and **67** are involved in is a long I-X bond (X = O for these compounds) which correlates to an increased electrophilicity for the iodine centre.⁶¹

This theory has been shown in reactivity studies: dimethyl benziodoxole **66** has a shorter I-O bond and a reaction free energy of 63.7 kcal mol⁻¹ versus carbonyl **67**, which has a longer I-O bond and a lower reaction free energy than dimethyl benziodoxole **66**: 63.7 kcal mol⁻¹.⁶¹

Table 1 using data from Schaefer *et al* showing the relationship between bond length and reaction free energy of dimethyl benziodoxole **66** and carbonyl benziodoxole **67** is reproduced below with compound **67** having a lower reaction free energy and thus being more reactive (and unstable) (where reaction free energy is the energy required to decompose):

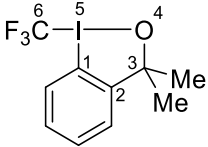
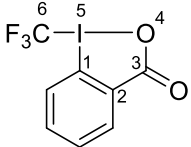
Compound:	 66	 67
Bond length (Å) 4-5	2.105	2.263
Bond length (Å) 5-6	2.257	2.212
Reaction free energy (kcal mol ⁻¹)	63.7	37

Table 1: The bond lengths and corresponding free energies of the two original Togni reagents.

Dimethyl benziodoxole **66** is more stable than carbonyl benziodoxole **67** and thus theoretically easier to handle in the context of this project (MRes student). Of note also are the potential safety concerns for carbonyl benziodoxole **67**—it has been classed as

an explosive and thus additional safety precautions would need to be implemented. Although the same report that highlighted these concerns also tested dimethyl benziodoxole **66** and found some level of danger, it was not to the scale of carbonyl benziodoxole **67**.⁶²

Dimethyl benziodoxole **66** has been used to carry out a large variety of electrophilic trifluoromethylations, showing efficacy with N-, P-, S-, O- and C-centred nucleophiles.⁶³⁻

⁶⁵ Figure 10 shows a small selection of some of the nucleophiles trifluoromethylated using dimethyl benziodoxole **66** and their respective products:

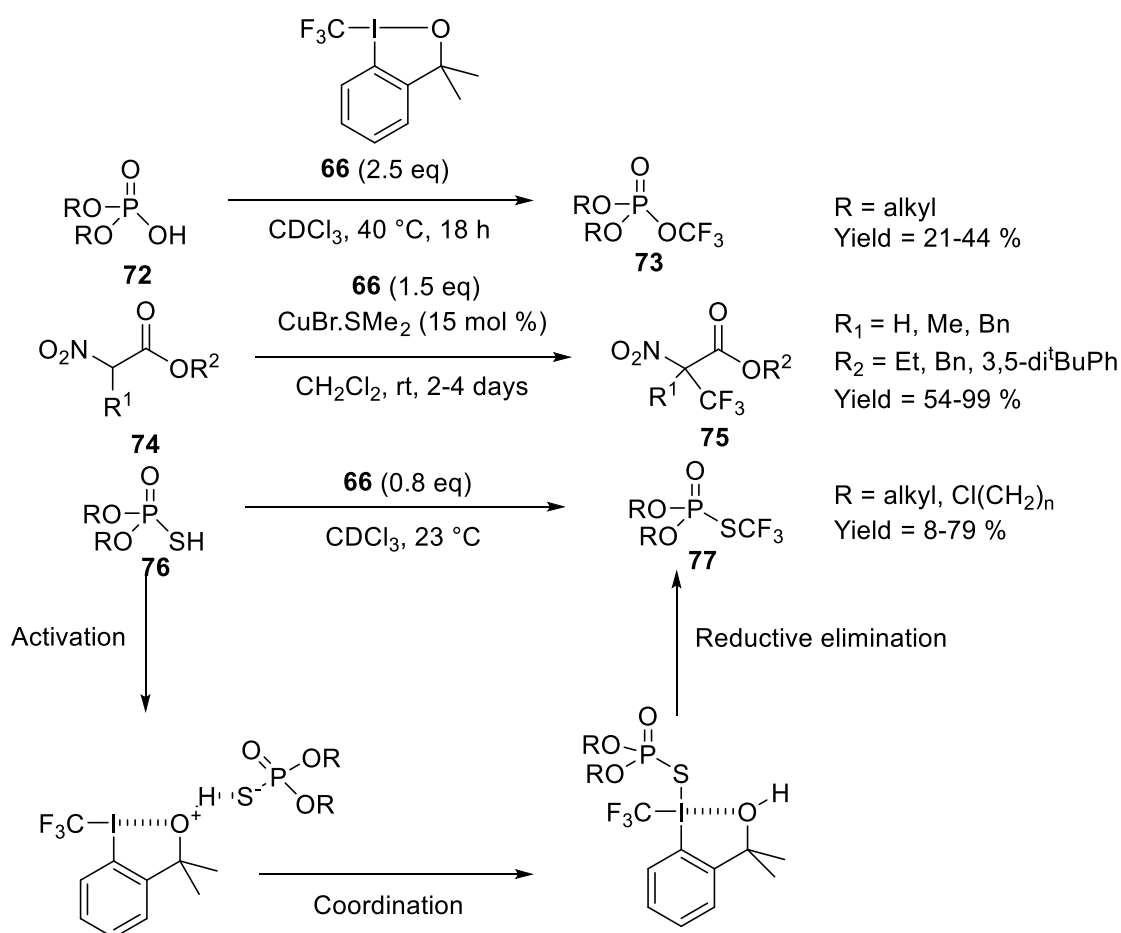
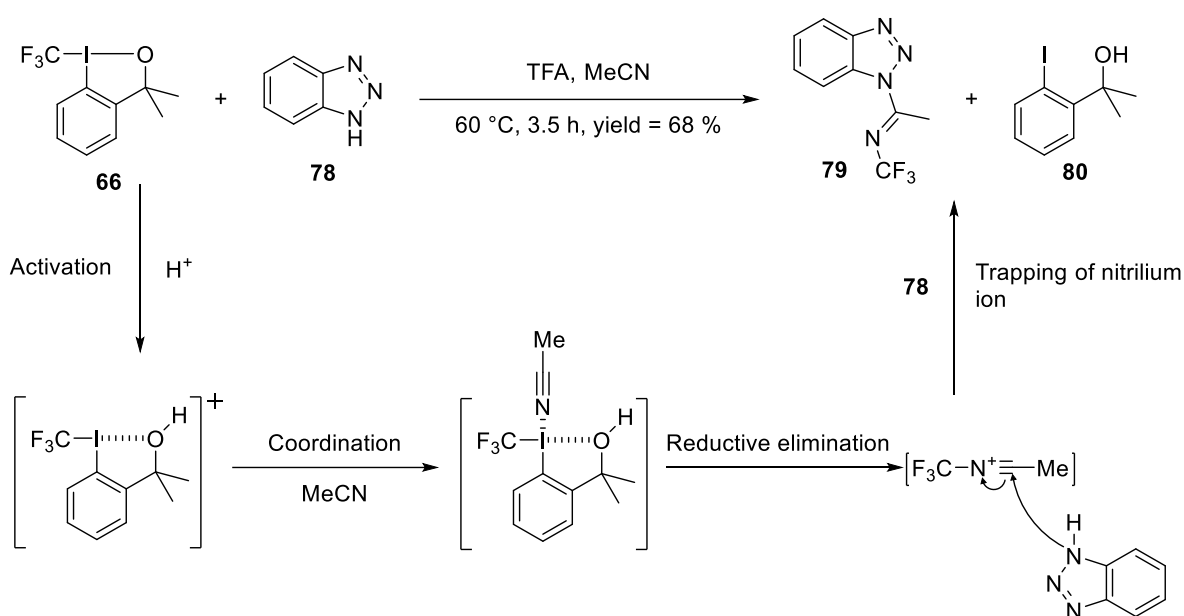


Figure 10: A small selection of the scope of electrophilic trifluoromethylation with dimethyl benziodoxole **66** including a reaction mechanism of one of the reactions.⁶⁰

With respect to forming trifluoromethylated amides, dimethyl benziodoxole **66** has seen use in the formation of *N*-CF₃ nitrilium ions in a similar manner to the (dihaloiodo)arene **59**, used in a Ritter type reaction in 2011 (scheme 143).⁶⁶ Here, a nitrile coordinated to a trifluoromethylated dimethylbenziodoxole which had been activated by a Bronsted acid. Then, there was a reductive elimination leaving an *N*-trifluoromethyl nitrilium cation and a decyclised form of the hypervalent iodine reagent minus the trifluoromethyl group (iodo alcohol **80**) as shown in scheme 15:

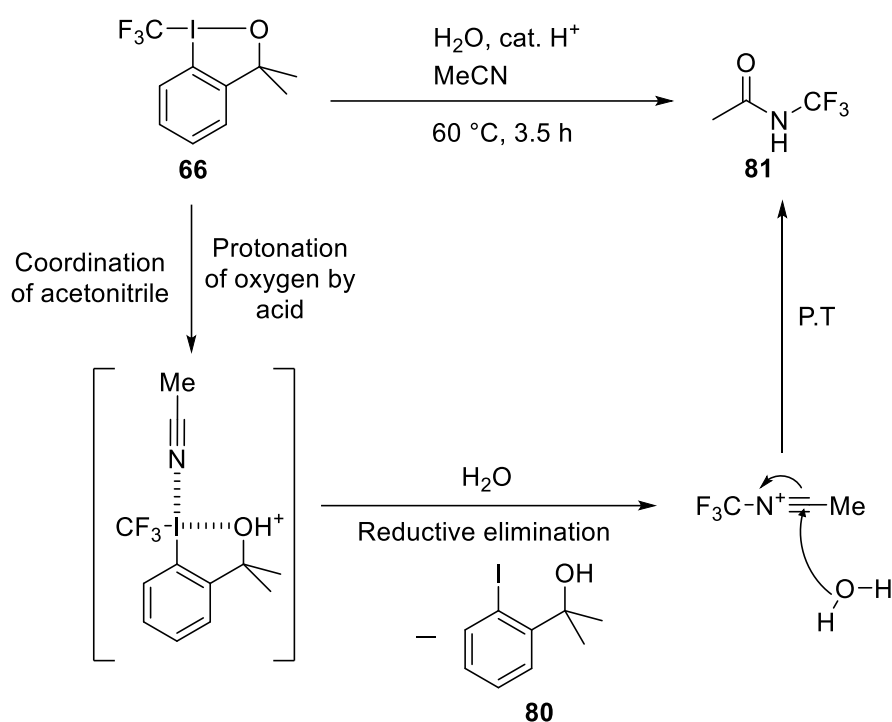


Scheme 15: The Ritter style reaction developed by Togni *et al* using dimethyl benziodoxole **66**, benzotriazole and acetonitrile with TFA as an acid catalyst.⁶⁶

This reaction proceeded with relatively high yields as shown in scheme 15, showing potential for use as the first step of an *N*-CF₃ amide synthetic route based on addition of water as an O-centred nucleophile, something dimethyl benziodoxole **66** has shown a tolerance of.⁶⁰

Aims

This project aims to build upon the *N*-CF₃ nitrilium ion Ritter pathway introduced by Wang and Togni and introduce water as a nucleophile to ‘quench’ the electrophilic nitrilium ion—generated *in-situ* from a nitrile coordinating to dimethyl benziodoxole **66** then reductively eliminating—to afford a trifluoromethylated amide (scheme 15).^{52, 66} The nitrilium ion is formed through dimethyl benziodoxole **66** being activated by an acid catalyst on the oxygen thus weakening the I-O bond and making the iodine more electrophilic. This then allows a nitrile to coordinate to the iodine and subsequently reductively eliminate with the trifluoromethyl group, leaving an electrophilic nitrilium ion susceptible to nucleophilic attack from water. This is based on not only Togni and Wang showing that nitrilium ions are vulnerable to a wide variety of nucleophiles but also recent research utilising water or oxidants to form standard amides from Hong and Gilmour. Where this research differs is that none of them were able to make trifluoromethylated amides through this Ritter type mechanism.⁴¹⁻⁴² The general mechanism of the plan to achieve trifluoromethylated amide synthesis is as below with acetonitrile as an exemplar nitrile (scheme 16):



Scheme 16: Mechanism for the proposed project showing formation of *N*-CF₃ nitrilium ion and then attack of water followed by proton transfer and catalyst reformation to produce the *N*-CF₃ trifluoromethylated amide.

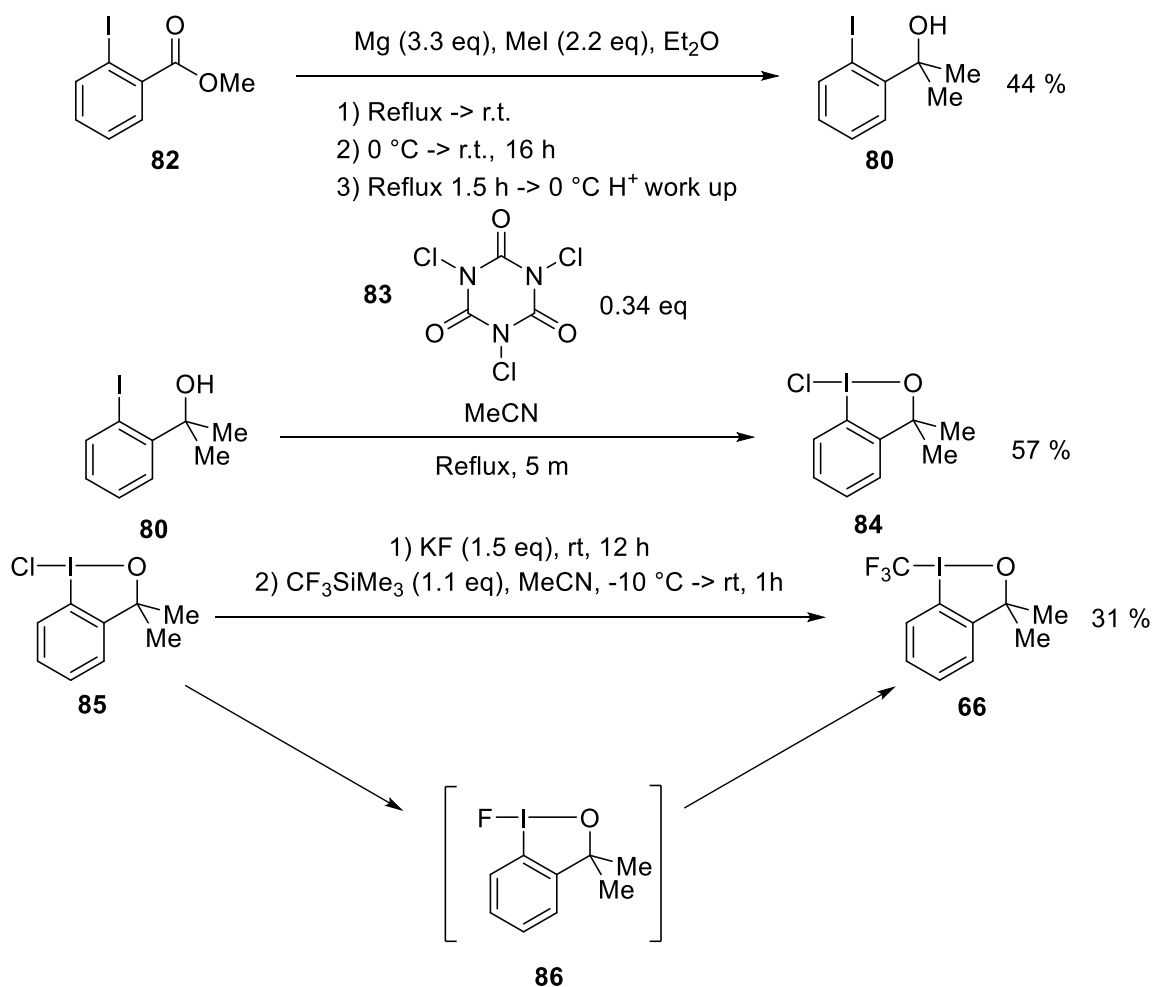
The novelty of this work would be forming the *N*-CF₃ bond and making an amide through this Ritter style reaction pathway which previously has not been reported. This would provide a simple and easy to execute one-pot strategy from readily available starting materials—a nitrile, a Bronsted or Lewis acid, water and dimethyl benziodoxole **66** (which can be purchased or manufactured in the lab). It builds upon previous work in both *N*-CF₃ coupling and amide synthesis through addition of water to a nitrilium ion respectively, yielding a novel approach. Of note also, is that of the previous methods explored, very few involve synthesis of an *HN*-CF₃ secondary amide—the vast majority are concerned with tertiary amide synthesis, this is likely due to perceived instability and subsequent hydrodefluorination as shown in scheme 3.

Results and Discussion

Synthesis of Togni's Reagent **66** and (Dihaloiodo)arene **59**

Togni's Reagent Dimethyl Benziiodoxole **66**

The main scope of the project involved the use of dimethyl benziiodoxole **66** for the source of CF_3^+ . First, an attempt was made to synthesise it following Togni *et al*'s work with alterations made to steps 2 and 3 based on a later revision.⁶⁷⁻⁶⁸ This synthesis involves three steps as laid out in scheme 17:



Scheme 17: Overall reaction scheme for synthesis of dimethyl benziiodoxole **66**.

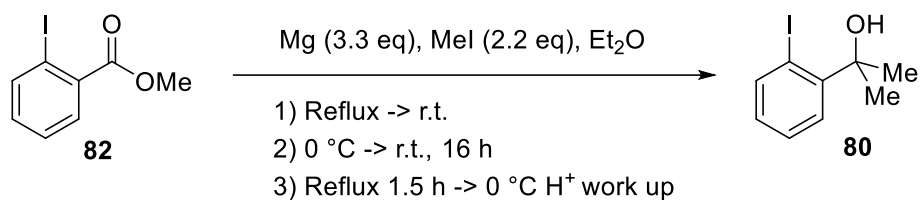
The first step involves *in-situ* synthesis of a Grignard reagent, MeMgI, utilising magnesium (3.3 eq) and methyl iodide (2.2 eq) which is then used, upon addition of iodo ester **82**, methyl 2-iodobenzoate, to form the tertiary alcohol **80**, 2-(2-iodophenyl)propan-2-ol, a slightly viscous brown oil. It was found that the yield of experiment 1 (table 2, entry 1) was 35 % —below literature expectations of 83 % with several reasons theorised.

Grignard reagents are very air and moisture sensitive and despite using oven-dried equipment and flushing the apparatus with argon, the rubber septa used are not wholly reliable as they age and stretch. To this end, fresh septa were sought and every joint covered with Teflon although the septum tops remained uncovered for needle access.

Another source of error could have come from poor synthesis of the Grignard / poor efficacy of *in-situ* Grignard, hence a commercial Grignard was tried for comparison. However, it was found via titration the Grignard in stock had greatly deteriorated, and when used was decomposed and insignificant reactivity was observed compared to previous attempts using an *in situ* prepared Grignard reagent. This is likely due to the Grignard containing experimentally significant amounts of water; thus, the attempt was aborted and no work up carried to avoid further waste of material.

An adaptation to the first step made was to increase the amount of magnesium used (5.25 eq) and MeI used (3.5 eq). This was to create ‘forcing conditions’ as compound **82** could be seen in TLC analysis. With a greater excess of Grignard reagent it was hoped this would be increase conversion of iodo ester **82** to iodo alcohol **80**. The idea of titrating the *in-situ* Grignard made was unfortunately not thought of, an idea that could have provided valuable information as to the difficulties being faced in this step.

The results of the standard conditions and the adapted conditions are shown in table 2:



Entry	Conditions	Yield
1	Standard	35 %
2	Magnesium (5.25 eq) Methyl iodide (3.5 eq)	44 %

Table 2: Yields of step 1 upon variation of reaction conditions: initial conditions being 3.3 equivalents of magnesium and 2.2 equivalents of methyl iodide. Entry 2 increased the equivalencies of magnesium (to 5.25 eq) and methyl iodide (to 3.5 eq).

With these efforts a slight increase to yield, 44 % was observed (table 2, entry 2) along with iodo ester **82** being 96 % used up. Despite the change of conditions and increased yield however, the yield remained low compared to literature precedent. Furthermore, despite only 4% of iodo ester **82** remaining, the yield was still less than half of theoretical indicating loss of mass somewhere in the reaction process, potentially due to procedural error from inexperience, alongside iodo alcohol **80**'s instability to light and heat leading to the potential for degradation before analysis could be done.⁶⁷

For the second step, iodo alcohol **80** was used unpurified as recommended to avoid storage overnight due to the compound's instability.⁶⁷ After 5 minutes under reflux conditions after addition of the chlorinating agent trichloroisocyanuric acid, compound **83**, chloro benziiodoxole **84** was synthesised and isolated in an acceptable 57 % yield providing a crop of yellow crystals after an acetonitrile recrystallisation.

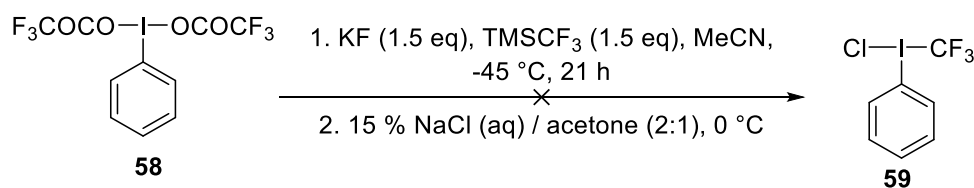
The final step involved an overnight halogen exchange using KF followed by a 1-hour nucleophilic trifluoromethylation using Ruppert-Prakash reagent.⁶⁹ Unfortunately, this step's yield was only 31%. A similar yield was encountered by a colleague when synthesising dimethyl benziiodoxole **66** for their respective experiment. The hypothesised culprit is inadequately dried KF despite attempts at reaching anhydrous conditions using a Schlenk line, for instance, during one attempt, the KF despite drying was seen to aggregate in the reaction vessel despite vigorous stirring and submerged in MeCN defying solvation with deleterious effects on reactivity.

These problems with yield led to purchase of commercially available dimethyl benziiodoxole **66** for further reactions.

This part of the project provided a useful introduction to hypervalent iodine chemistry and while yields were not at literature level, valuable experience was gained.

(Dihaloiodo)arene **59**

A synthesis of (dihaloiodo)arene **59**, used in Wang's $N\text{-CF}_3$ amide synthesis, was also attempted. The method used involved PIFA, dried KF, Ruppert-Prakash reagent and NaCl as shown in scheme 18:



Scheme 18: Synthetic route for synthesis of hypervalent iodine reagent (dihaloiodo)arene **59**.⁵³

The main downside of the reaction was the need to cool the reaction to -45 °C overnight which was unable to be reached even closely by the equipment used (chiller)—the lowest seen temperature was -26 °C and the temperature the morning after was -23 °C. Furthermore, as in the synthesis of dimethyl benziodoxole **66**, inadequately dry KF contributed to an even further reduction in reaction efficacy despite the KF being dried on a Schlenk line for 2 hours. These two factors combined meant that the crude mixture contained only trace (<1 %) amounts of (dihaloiodo)arene **59** alongside unreacted starting material **58** as assessed by ¹⁹F NMR—trace peak at -35.6 and large peak at -75.5, thus no isolation was carried out.

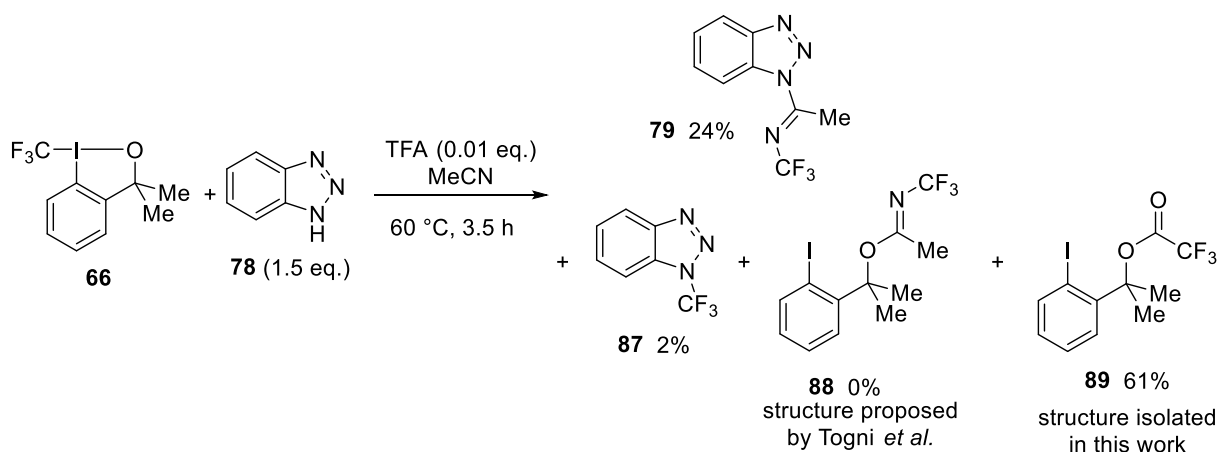
Testing the Ritter Type Reaction

As mentioned in the introduction, the overall project aims to employ a Ritter type reaction to form an *N*-CF₃ amide based on the work by Togni *et al.*,⁶⁶ and Wang *et al.*'s work.⁵² It was thus decided to carry out an exemplar Ritter style reaction as an introduction to trifluoromethylation and to practice the use of dimethyl benziodoxole **66**.

The conditions used were as those laid out in scheme 13 with 0.2 mmol of dimethyl benziodoxole **66** used, 0.3 mmol of benzotriazole, 0.02 mmol of TFA and 2 mL of MeCN

for 3.5 hours at 60 °C. While the original paper utilises HNTf₂, TFA was used due to logistical constraints—HNTf₂ would have required access to a glovebox whereas TFA was readily available in the laboratory. This substitution according to Togni *et al* only has a minor impact on yield: 68 % with HNTf₂ and 60 % with TFA.⁶⁶

Unfortunately, similarly to the synthesis of dimethyl benziodoxole **66**, the literature yield of 60 % was not replicated with a final yield of imine **79** of 24 % (Scheme 19). However, two side products formed as predicted by the Togni paper that provide a reason for the lower-than-expected yield.



Scheme 19: Overall reaction scheme for the benzotriazole Ritter type reaction with product compound imine **79** and side products triazole **87** and ester **88**.

Side product triazole **87** was theorised by Togni *et al* to be a result of direct trifluoromethylation of benzotriazole, with benzotriazole taking the place of MeCN coordinating to dimethyl benziodoxole **66**. This compound was isolated and assigned by Togni *et al* and was seen in the ¹⁹F NMR of this project's reaction with a yield of 2 %.

Side product ester **88** was theorised by Togni *et al* to be a result of dimethyl benziodoxole **66** acting as a nucleophile on the *N*-CF₃ nitrilium ion. However, no data was reported for this compound was not reported so we could not cross-reference our result. We observed a peak in the crude ¹⁹F NMR of our reaction corresponding to a yield of 61% which we initially assumed was this product (ester **88**).

However, when the compound was isolated, the spectroscopic data acquired did not match the theorised structure provided by Togni *et al* such as only having five unique proton environments compared to ester **88**'s six. Hence, further analytical attempts were made to ascertain the structure of this 'mystery' compound with a ¹³C NMR and an HSQC recorded along with a sample being analysed via mass spectrometry.

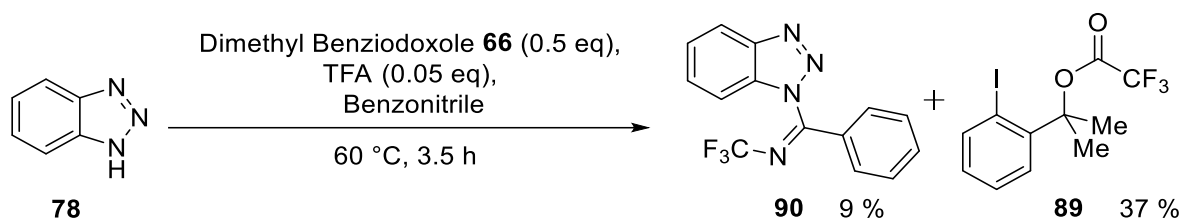
Based on this data, and after considerable consultation with colleagues, the by-product in the reaction was believed to be 2-(2-iodophenyl)propan-2-yl 2,2,2-trifluoroacetate **89** (Scheme 19) pending further developments from a reaction between dimethyl benziodoxole **66** and TFA. However, this was only an assumption—a definitive structure could not be decided upon. For instance, the mass spectrometry data did not show the expected value. Moreover, no IR was carried out before the sample was lost—this is disappointing as an IR would have been able to show if a carbonyl was present or not. However, the ¹⁹F NMR signal is at -74.3, which appears to line up with the ester theory with most trifluoromethylated esters being in the range of -70 to -80 ppm. Unfortunately, further analysis is complicated due to the complete absence of data available for ester **88** thus no side-by-side NMR comparisons can be carried out which could have helped in identification. ¹H NMR data lends credence to the ester theory with 4 proton signals characteristic of an iodo aryl ring (8.00, 7.45, 7.37, 6.97) similar to iodo alcohol **80**'s, and

then a 5th representing the protons on the two methyl groups at 2.00 ppm. This 5th signal being at 2.00 ppm is interesting as it is much higher than the comparable dimethyl signal for dimethyl benziiodoxole **66** at 1.48 ppm or that of iodo alcohol **80**, at 1.76 ppm which makes sense considering the greater electron withdrawing effect of the trifluoromethylated ester which would de-shield the dimethyl protons more than the oxygen of dimethyl benziiodoxole **66** and iodo alcohol **80** lending further credence to the ester theory.

Further experimental data and discussion involving the identity of 'presumed ester' **86** is located at the end of section '*N*-CF₃ Amide Synthesis via Ritter Type Reaction', whereby it is shown that the compound requires the presence of TFA to form—further evidence in favour of the proposed structure of ester **89**. This is due to the tentative theory that the structure forms in a reaction between TFA and dimethyl benziiodoxole **66**, although this is currently conjecture.

As an addendum to this Ritter type reaction, a change in nitrile was attempted using benzonitrile. This was done to assess the viability of benzonitrile as the nitrile source for an *N*-CF₃ nitrilium ion for making an *N*-CF₃ amide. Benzonitrile was chosen for the *N*-CF₃ amide synthesis due to having a higher molecular mass than MeCN thus the final product will have a higher boiling point hence making rotary evaporation less likely to evaporate the product—a worry with fluorinated compounds; for instance, methanol has a boiling point of 65 °C and trifluoromethanol a much lower one at -20 °C.⁷⁰⁻⁷¹

Scheme 20 shows the overall reaction scheme using benzonitrile in place of MeCN:



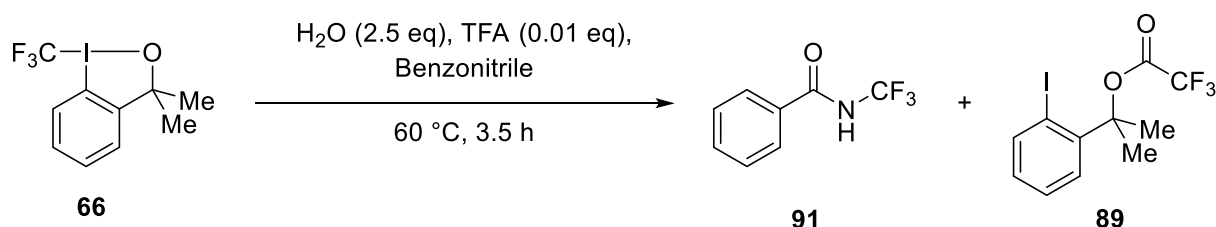
Scheme 20: Reaction scheme for a Ritter type reaction involving benzotriazole as a nucleophile used to trap an $N\text{-CF}_3$ nitrilium ion produced by the reductive elimination of coordinated benzonitrile from dimethyl benziodoxole **66**.

Similar to when MeCN was used, the yield of the desired product triazole imine **90**, 9 %, was lower than that of ester **89**, 37 %. Furthermore, the yield of 9 % was lower than that of the yield of imine **79** implying that benzonitrile is less effective than acetonitrile at coordinating to dimethyl benziodoxole **66** and/or reductively eliminating to form a nitrilium ion which is then rapidly trapped by the waiting nucleophile triazole **78** according to the reaction mechanism devised by Togni *et al.*⁶⁶ This could be explained by benzonitrile being less basic than acetonitrile and thus less able to coordinate to dimethyl benziodoxole **66**.⁷²

Synthesising $N\text{-CF}_3$ Amides via the Ritter Type Reaction

Within this section, multiple compounds have had attempts at synthesis with conclusions on success being based on quantitative ^{19}F NMR—a limited basis. This is due to difficulty in isolation of these compounds despite myriad attempts. A more senior colleague attempting to synthesise and isolate the main compound of interest, benzamide **91**, as a control on multiple occasions, but isolation and thus better characterisation remained unsuccessful. Hence, conclusions made do not have full backing.

As previously mentioned, and shown in scheme 16, the focus of this project was on the synthesis of *N*-CF₃ amides via a Ritter type reaction. Conditions for the synthesis were slightly altered from scheme 16 to use benzonitrile over MeCN despite the results of the benzotriazole experiments, due to the aforementioned worries concerning the potential volatility and difficult isolation of amide **81**. Moreover, owing to the volume of water utilised following the Togni *et al* Ritter conditions, 9 μ L, it was decided to halve the volume of benzonitrile to avoid an overly dilute reaction conditions impacting reactivity. This decision was based on research by Mayr *et al* concerning the decrease in reactivity resulting from increased dilution of water in acetonitrile—for instance going from a water: acetonitrile mix of 33 : 67, to 91 : 9 leads to a reduction in reaction rate of 8.95×10^5 to 7.99×10^5 based on an exemplar reaction of a benzhydrylium with a water/acetonitrile mix.⁷³ This therefore led to the conditions shown in scheme 21:



Scheme 21: Reaction scheme for the synthesis of *N*-CF₃ amide compound **91** using dimethyl benziiodoxole **66** and benzonitrile to form an *N*-CF₃ nitrilium ion *in situ* and water as the trapping nucleophile.

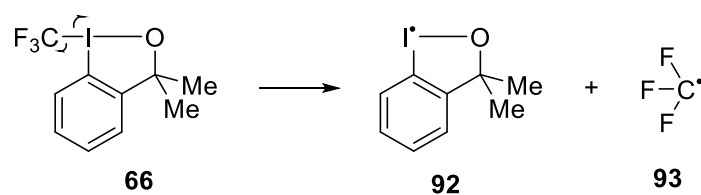
Table 3 includes the optimisation data for this reaction:

Entry	Conditions	Dimethyl Benziodoxole 66	Benzamide 91	Ester 89
1	Standard	0 %	16 %	22 %
2	2 mL PhCN	83 %	2 %	<1 %
3	500 μ L PhCN	0 %	3 %	2 %
4	500 μ L / 500 μ L PhCN / DCM	0 %	6 %	6 %
5	200 μ L / 800 μ L PhCN / DCM	0 %	2 %	8 %
6	100 μ L / 900 μ L PhCN / DCM	0 %	4 %	22 %
7	50 μ L water	0 %	10 %	7 %
8	100 μ L water	0 %	13 %	7 %
9	200 μ L water	0 %	1 %	1 %
10	500 μ L water	0 %	1 %	1 %
11	40 $^{\circ}$ C	78 %	1 %	32 %
12	80 $^{\circ}$ C	0 %	13 %	14 %
13	2 h	0 %	11 %	10 %
14	5 h	0 %	15 %	9 %
15	24 h	0 %	11 %	10 %
16	No TFA	100 %	0 %	0 %
17	2 mg Sc(OTf) ₃	0 %	5 %	0 %
18	2 mg Cu(OTf) ₂	69 %	4 %	0 %
19	0.4 mmol scale,	2 %	21 %	18 %

	18 μ L water			
20	0.4 mmol scale, 200 μ L water	0 %	9 %	6 %
21	0.6 mmol scale, 1.5 mL / 1.5 mL Water / PhCN	0 %	29 %	12 %

Table 3: Optimisation table for reaction shown in scheme 19. Conditions: compound **66** (0.2 mmol, 66 mg); water (0.5 mmol, 9 μ L); TFA (0.02 mmol, 2.3 mg); benzonitrile (1 mL); 3.5 hours and 60 °C. Yields determined by quantitative ^{19}F NMR—standard 4,4-difluorobenzophenone or trifluoroethanol.

From this table it can be seen that the mass balance is off, by up to 98 % in entries 9 and 10. The explanation for that is theorised to be due to fluoroform evolution and the following escape of the reaction vessel based on Togni *et al*'s work.⁶⁶ The mechanism for the formation of fluoroform is unexplained in the literature. However, hypervalent iodine reagents can often partake in radical reactions thus this could be a potential reason for fluoroform formation.⁶⁴ One potential source of a trifluoromethyl radical that could in turn form fluoroform is shown in scheme 22:



Scheme 22: Potential route for radical generation through dimethyl benziiodoxole **66** decomposition.

The standard conditions resulted in a quantitative ^{19}F NMR yield of 16 % of benzamide **91** along with 22 % of ester **89**, similar to results from the previous Ritter reactions undertaken. Entry 2 was carried out to determine the effect of doubling the dilution of water in benzonitrile and the result corroborated the relationship between decreasing concentration of water in solvent and decreased reactivity due to greatly decreased yield and a large amount of unreacted starting material remaining.

Entry 3 used half the volume of benzonitrile, effectively doubling the concentration of water, however, yield of product benzamide **91** greatly reduced to 3 %. This could be due to there being insufficient solvent for the reaction materials to be sufficiently solvated or reduced solvent favouring fluoroform evolution given the very poor mass balance with 95 % of fluorine missing in the ^{19}F NMR.

To aid in isolation of benzamide **91** given benzonitrile's inability to be rotary evaporated, in entry 4-6 DCE was added as an increasingly high-volume co-solvent with a corresponding decrease in benzonitrile volume to maintain an overall volume of 1 mL due to DCE's higher volatility. DCE was the co-solvent chosen owing to its use by Togni *et al* in a direct trifluoromethylation reaction under similar conditions.⁶⁶ However, these entries' yields, within experimental error of each other (2-6 %), cannot compare to standard conditions. There is a trend from entry 4-6 of increasing synthesis of ester **89**, although it is unclear what causes this, as there is no trend observed with increasing or decreasing benzonitrile volume in entries 1-3, just a large decline when changing from 1 mL.

To investigate the effect of changing the volume of the nucleophile, water, entries 7-10 vary the volume between 50 μL to 500 μL . A large volume of water compared to standard

conditions as a starting point was considered due to the potential for overcoming water's poor nucleophilicity via mere volume.⁷⁴ Entries 7 and 8 show comparable yields to standard conditions despite the large excess of water, along with a lower yield of ester **86**. However, entries 9 and 10 show a yield of only 1 % despite full conversion of dimethyl benziodoxole **63** into iodo alcohol **80** potentially demonstrating that at higher concentrations of water, fluoroform synthesis is greatly more favoured. It is also worth noting reactions involving dimethyl benziodoxole **66** are mostly carried out under anhydrous conditions due to moisture sensitivity and hygroscopicity.^{55-58, 60, 63, 65-66, 67}

The chosen temperature of 60 °C was replicated from the Togni Ritter type reaction. A decrease in temperature to 40 °C was attempted in entry 11. This reaction had a very low yield of 1 % of benzamide **91** alongside a high yield of ester **89**, 32 %. Moreover, 78 % of dimethyl benziodoxole **66** remained unreacted implying a higher temperature is needed to provide sufficient activation enthalpy for product formation. Curiously, the mass balance of the reaction was over 100 % based on moles of dimethyl benziodoxole **66** used, but this is likely due to an erroneous internal standard measurement. An increase in temperature to 80 °C in entry 12 resulted in a similar yield, 13 %, to that of the standard, however, it also led to the formation of multiple side products unable to be identified in the ¹⁹F NMR yield or isolated. This implies 80 °C is too hot for dimethyl benziodoxole **66** to function without reagent degradation or that another element in the reaction degrades such as ester **89** given the lowered yield, 14 %.

Reaction time was altered in entries 13-15 although these reactions yielded yields within experimental error of each other and the standard (11-15 %). This does potentially mean the reaction could be shortened to 2 hours given the full conversion of dimethyl

benziodoxole **66** to iodo alcohol **80**, however, to ensure consistency with previous entries, 3.5 hours was maintained throughout future reactions despite the potential for energy waste.

The role of the acid catalyst is shown in scheme 14, that of activating dimethyl benziodoxole **66** to facilitate nitrile ligand coordination. To demonstrate the importance of this activation step, the reaction was carried out without TFA in entry 16 which left dimethyl benziodoxole **66** untouched as predicted. As an alternative to TFA as an Bronsted acid catalyst, two Lewis acid catalysts were trialled in entries 17 and 18, scandium triflate and copper triflate respectively. Both yields of benzamide **91** were comparable at 5 and 4 % respectively albeit less than under standard conditions: copper triflate left 69 % of dimethyl benziodoxole **66** unconverted implying it is more effective than scandium triflate given it yielded a similar result with only 31 % of the amount of dimethyl benziodoxole **66** provided. Of further note is the absence of ester **89** being synthesised implying TFA is crucial for synthesis of ester **89** providing further evidence for the structure theorised.

Entries 19 and 20 utilised scaled up conditions, from 0.2 mmol of dimethyl benziodoxole **66** to 0.4 mmol with a corresponding doubling of other reactant quantities. Entry 19 showed a minorly improved yield from standard conditions—16 % yield to 21 % yield of compound **63** alongside a reduced yield of benzamide **91**, implying this reaction benefits from larger quantities. This could potentially be down to an overall error reduction. One observation during experiments was condensation inside the reaction vessel owing to water evaporating and condensing out of the reaction mixture, reducing the volume available for reacting. With a larger volume of reaction mixture, such

evaporation would proportionally be smaller. Entry 20 was the same scale as entry 19 but with 200 μ L of water based on doubling the volume of entry 9 to see if varying the water at higher scale had an effect. While the yield of benzamide **91**, 9 %, was within experimental error of entry 9, 13 %, it was half that of entry 19 although synthesis of ester **89** was reduced.

Entry 21 was an extra increase of 0.2 mmol dimethyl benzamide **66** with a corresponding proportional increase in other reagents with the caveat of using a mixture of 1.5 mL of water and 1.5 mL of benzonitrile as the solvent. These conditions resulting in the highest yield achieved of benzamide **91** of 29 % with a 'low relative to benzamide **91**' yield of 12 % of ester **89**. This continued the trend of increased scale benefitting yield of benzamide **91** although it is currently unknown why such a large increase in volume of water helped to increase yield when the same was not true for entries 9, 10 and 20. However, it does continue the trend between entry 1 and 19 of increased scale increasing yield of compound whilst also decreasing yield of dimethyl benziodoxole **89**.

Isolation of benzamide **91** proved elusive throughout the project despite the HRMS mass matching benzamide **91** being identified through analysis of crude samples prepared from the experiments carried out. A colleague also attempting synthesis of benzamide **91** similarly failed isolation after multiple attempts despite the correct signals being identified in both HRMS and ^{19}F NMR. First, isolation was attempted through column chromatography using a variety of ratios of pentane and ethyl acetate. These attempts were unsuccessful with the most clear problem being due to the benzonitrile being hard to separate out. In an effort to ease separation, prep TLC were carried out to positive effect *vis-à-vis* separation of compounds, but it revealed a new problem, one potentially

masked by the benzonitrile in the results of the column chromatography attempts carried out previously. This was that benzamide **91** appears to be unstable on silica—¹H NMR of the prep TLC fraction identified as belonging to the product revealed the compound as benzamide, with the trifluoromethyl group having eliminated. An acid-base extraction was also attempted but likewise was unsuccessful. The potential instability of benzamide **91** was known as similar compounds are prone to hydro-defluorination, yet it has been synthesised according to a different method, thus the instability was expected but believed not be the critical issue it turned out to be.^{33-35, 75}

Adapting the Method with an Alternative Nitrile—4-Phenylbenzonitrile

While efforts into using benzonitrile as the nitrile in the Ritter type reaction were ongoing, the use of a solid nitrile was trialled. Benzonitrile is a liquid at room temperature and thus able to be used as the reaction solvent, but in an attempt to broaden the reaction scope to nitriles unable to act as solvents, biaryl **94**, 4-phenylbenzonitrile was used as an exemplar solid nitrile. The reaction solvent chosen was DCE owing to its use by Togni *et al* in a direct trifluoromethylation reaction under similar conditions.⁶⁶

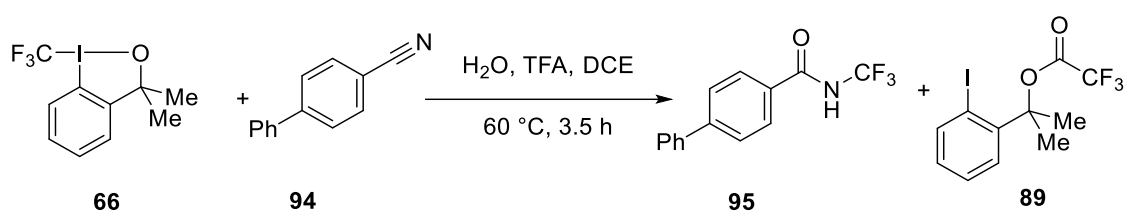
DCE was chosen as a solvent due to its use by Togni *et al* in their direct trifluoromethylation of benzotriazole—it tolerated working with dimethyl benziodoxole **66** and the same reaction conditions. The amount of biaryl **94** used was initially chosen as 2 mmol (10 equivalents) alongside the standard 0.2 mmol dimethyl benziodoxole **66**, 0.5

mmol water, 0.02 mmol TFA. This is due to unsurety of how much would be needed going from a truly large excess of benzonitrile due to its use as a solvent.

These conditions resulted in a <1 % yield based on ^{19}F NMR and poor conversion of dimethyl benziiodoxole **66** into iodo alcohol **80** implying poor coordination of biaryl **94**.

Moreover, ester **89** was also still produced with a yield of 5 %.

Further conditions were then attempted as shown in table 4:



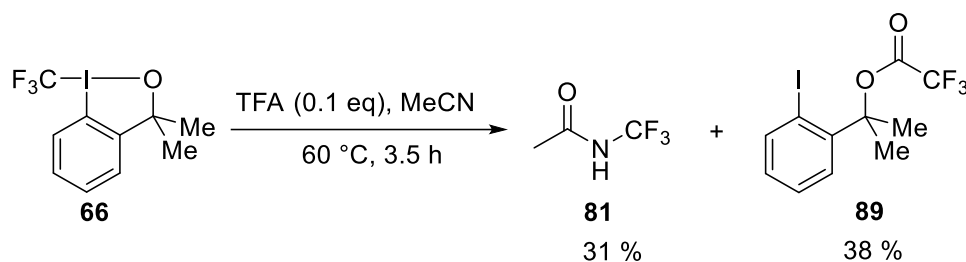
Entry	Conditions	Dimethyl Benziiodoxole 66	Biaryl Amide 95	Ester 89
1	Standard	41 %	<1 %	5 %
2	70 °C	0 %	2 %	8 %
3	5 h	0 %	2 %	11 %
4	2 h	76 %	<1 %	2 %

Table 4: Optimisation table for synthesis of biaryl amide **95**. Conditions: dimethyl benziiodoxole **66** (0.2 mmol); biaryl **94** (10 mmol); water (0.5 mmol); TFA (0.02 mmol) and DCE (2mL). Yields determined by quantitative ^{19}F NMR using 4,4-difluorobenzophenone as a standard.

Further conditions were not attempted due to poor results. What these results do show is that more work is needed to progress this project beyond using liquid nitriles. A further reason for the poor results outside of the phase change from liquid to solid nitrile, could be due to, following the trend of benzonitrile being less basic than acetonitrile, with 4-phenylbenzonitrile being even less basic, 4-phenylbenzonitrile being largely unable to coordinate to dimethyl benziodoxole **66**. Between entry 1 and entry 3, reaction time is increased by 1.5 hours and yield of biaryl amide **95** does increase but the yields are low enough to be within experimental error of each other.

Revisiting the Original Method with New Improvements

Entry 21, table 3 (0.6 mmol, water : benzonitrile in a 1.5 ml : 1.5 ml) had the best NMR yield of benzamide **91** at 29 %. This led to some introspection and thoughts as to what could be changed. At the same time, elucidation as to the identify of ester **89** was ongoing and an attempt was made to carry out a Ritter-style reaction without a nucleophile, seeing as this product forms independent of the nucleophile used. Furthermore, acetonitrile was used as it can be simply removed through rotary evaporation under vacuum unlike benzonitrile. Also, due to the product's seeming association with TFA, stoichiometric quantities of TFA were used. This resulted in reaction scheme 23:

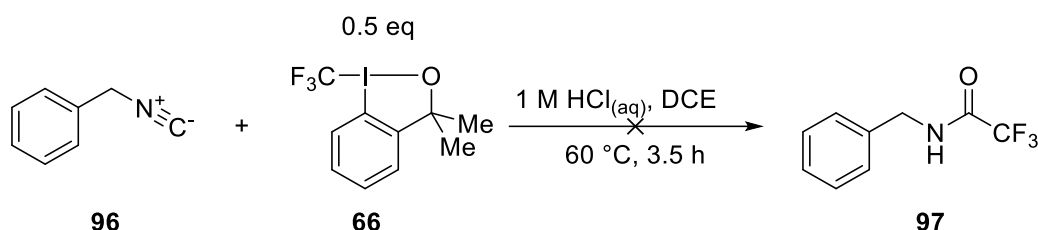


Scheme 23: Reaction scheme for the attempt to isolate ester **89** for structure elucidation utilising a Ritter type reaction without an explicit nucleophile added.

One difference in this reaction compared to previous ones is that the acetonitrile was sourced from a Winchester i.e. not dried on alumina column acetonitrile, and no attempt was made to thoroughly dry the apparatus. This is due to what prompted the project in the first place, the accidental formation of an amide through insufficiently anhydrous conditions. As it turned out, this was the correct choice, a fair yield, 38 %, of ester **80** was seen in the NMR alongside a yield of 31 % for amide **81**. Explicitly adding water appears to be worse than using solvent with premixed water potentially due to the water sensitivity of dimethyl benzamide **66**. One theory is that water and benzonitrile/acetonitrile are immiscible thus when added into a reaction, despite stirring, the mixture is biphasic whereas non-anhydrous solvents are monophasic with the water completely dissolved, potentially aiding its availability and thus reactivity comparatively.

Testing the Use of an Isocyanide as the Nitrile Source

Another reaction, based off the Ritter-type reaction and attempting to make a trifluoromethylated amide was attempted based on the use of an isocyanide. However, it is important to note that this would provide a C-CF₃ amide as opposed to an N-CF₃ amide such as benzamide **91**, the type of trifluoromethylated amide this project was focused on. Isocyanide **96**, benzyl isocyanide was the isocyanide chosen due to its structural and electronic similarity to benzonitrile compared with the alternative isocyanides available, none of which possessed a phenyl ring and were markedly different in electron richness, a key factor in the ability to coordinate to dimethyl benziodoxole **66**. The reaction conditions were as laid out in scheme 24:



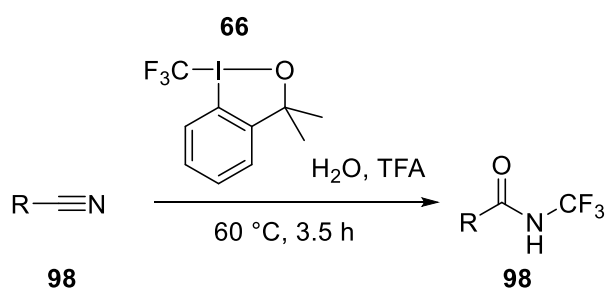
Scheme 24: Reaction scheme for attempted synthesis of isocyanide derived **97** using isocyanide **96** with 1 M HCl as an acid catalyst in place of TFA.

Due to potential issues of isocyanide insertion arising from use of a Bronsted acid such as TFA,⁷⁶ aqueous HCl was chosen as the catalytic activator for dimethyl benziodoxole **66** activation. However, unfortunately, aqueous HCl is known to decompose isocyanides into formamide and this was seen in ¹H NMR.⁷⁷

The reaction was unsuccessful, with nothing showing on ^{19}F NMR aside from a tiny peak at -150 ppm. Although this does mean full conversion of dimethyl benziodoxole **66** into iodo alcohol **80**, the fluorine ‘lost’ is likely due to the evolution of fluoroform as seen in many of the other reactions. Failure was also likely because of reagent decomposition from the aqueous HCl instead of coordinating to dimethyl benziodoxole **66**. Moreover, due to the prohibitively malodorous benzyl isocyanide it made unpleasant working conditions for everyone in the laboratory despite stringent precautions undertaken to attempt to minimise exposure.

Conclusion + future work

This project aimed to introduce a novel method of $N\text{-CF}_3$ amide synthesis, providing an alternate approach to the more standard existing methods, shown in general terms in scheme 25:



Scheme 25: General reaction scheme for this project's $N\text{-CF}_3$ amide synthesis route.

The method proposed utilised both a green and simple approach using mild reagents in a one-pot reaction. The novelty in the approach was based on fusing and expanding upon

two existing synthetic procedures, both based on a 'Ritter style' reaction, that is, amide synthesis through addition of water to a nitrilium ion and trifluoromethylation of nitriles via hypervalent iodine. Drawing these two methods into one established a new foray into *N*-CF₃ amide synthesis, but one based on proven chemistry.

This project has shown the potential for synthesising *N*-CF₃ amides from simple reagents but isolation of these compounds remained elusive, with even a more senior colleague being unable. A qNMR yield of 29 % at best is encouraging in that it proves there is potential in this method, but as it stands currently this result fails to satisfy the aim of providing a useful alternative to existing procedures. Moreover, it was only with a single nitrile, benzonitrile, that these results were able to be achieved. To be industrially relevant, the reaction should be more tolerable of the nitrile used. Attempting the use of isocyanates was discontinued after one reaction, in part due to poor results but mainly due to prohibitively unpleasant odours, that despite use in a fumehood, disrupted work for everyone proximate to the experiment. Likewise, multiple attempts at using a bulkier, more electron deficient nitrile, 4-cyanobiphenyl, showed that more electron rich nitriles are necessary for the *N*-CF₃ amide to form.

Of interest was the remarkably low mass balance of the reaction compared to what would be expected given total conversion of starting material. One potential explanation for this could be fluoroform evolution as previously proposed by Togni *et al*,⁶⁶ however the mechanism of its formation is at present unclear. It could be hypothesised that a potential radical pathway could be responsible, especially given the nature of hypervalent iodine and its potential for radical mechanisms as previously proposed by

Mace *et al*,⁶⁴ and that the reaction was carried out in a brightly lit fumehood. It should be noted that this is conjecture pending further work.

One large aspect of this project was the great deal of time spent trying to overcome challenges in yield and purification, many times without success. A better carried out project would more quickly move on from failed methods instead of attempting to persevere through, and in the process, wasting time.

One result of no relevance to the aim of the project, but more so correcting a flaw in previous literature, was the discovery of the 'Ritter style' reaction Togni reagent byproduct with spectroscopic data that conflicts with the commonly thought byproduct compound structure. However, definitive proof of the identity of this side-product was not found, only that it couldn't be what was previously theorised.

The overall implications of this work are that a basic framework has been created for the synthesis of *N*-CF₃ amides, but that more research and optimisation is required.

As it stands, this current work lacks credibility due to the lack of isolation of the key compound the project aimed to make. Therefore, future work must include at minimum a full characterisation of benzamide **91**.

Research is ongoing into the use of premixed solvent-water mixtures in place of explicitly adding water to the reaction mixture contemporaneously with solvent. This is based on the interesting results obtained when acetonitrile from an opened bottle was used as the nitrile and no water was added to the reaction, yet the *N*-CF₃ amide was still produced in a better yield than when water wasn't premixed.

Of interest also would be an investigation into the potential radical fluoroform evolution pathway as this would provide an answer to the high conversion, low recovered mass conundrum. A further benefit to this would be that it could lead to a method that inhibits fluoroform generation allowing conservation of the -CF_3 moiety and ultimately a higher $N\text{-CF}_3$ amide yield.

Experimental Section

General Experimental Information

Unless stated otherwise, all reactions were carried out in standard glassware under an inert atmosphere of argon. All reagents were purchased from commercial suppliers and used without further purification. All water used was deionised before use and solvents were dried on a column of alumina prior to use.

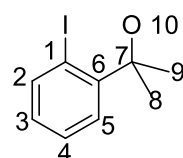
TLC (Thin layer chromatography) was performed on Merck aluminium backed silica gel 60 F254 plates that were visualised under ultraviolet radiation (254 nm) and stained using KMnO_4 solution when necessary. Mass spectroscopy was done using the high-resolution ESI (electron spray ionisation) mass spectrometer Bruker micrOTOF II.

^1H , ^{13}C and ^{19}F NMR spectra were recorded on either Bruker AV(III)400HD or Bruker AV(III)500HD in deuterated solvent and their chemical shifts (δ) given in parts per million (ppm) and are internally referenced to residual solvent signals (CDCl_3 is referenced at δ 7.26 and 77.16 for ^1H and ^{13}C NMR respectively). For ^1H and ^{13}C NMR spectra tetramethylsilane ($\text{Si}(\text{CH}_3)_4$) is used as an external standard and attributed a chemical shift of 0 ppm. For ^{19}F NMR spectra trichlorofluoromethane (CFCl_3) is used as an external standard and attributed a chemical shift of 0 ppm. All coupling constants (J) are given in

Hz. ^1H NMR multiplicities are designated using the abbreviations: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, p = pentet, m = multiplet. The ^1H NMR and ^{19}F NMR coupling constants (J) are quoted to the nearest 0.1 Hz while ^{13}C NMR coupling constants (J) are quoted to the nearest 1 Hz.

Experimental methods and analytical data

2-(2-Iodophenyl)propan-2-ol (**80**)



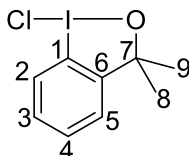
Iodo alcohol **80** was synthesised following a literature procedure:⁶⁷ Methyl iodide (0.65 mL, 10.50 mmol) in dry diethyl ether (7 mL) was added dropwise to a solution of magnesium turnings (383 mg, 15.75 mmol) in dry diethyl ether (7 mL) and heated to reflux. Stirring was maintained for 90 minutes upon which the reaction vessel was cooled to 0 °C in a salted ice bath. Next, methyl 2-iodobenzoate (0.46 mL, 3.00 mmol) was added with dry diethyl ether (7 mL) in a dropwise fashion and the vessel was then left warm up to rt and to stir for 5 hours.

The resultant mixture was then treated with ammonium chloride (4.5 mL) and subsequently water (10 mL). After, the mixture was filtered over celite and the organic phase separated and then solvent was removed under reduced pressure leaving a yellow-

brownish oil that was used in the next step without further purification (346 mg, 1.32 mmol, 44%).

¹H NMR (400 MHz, CDCl₃) δ 7.97 (dd, *J* = 7.81, 1.38 Hz, 1H, H²), 7.63 (dd, *J* = 7.97, 1.72 Hz, 1H, H⁵), 7.34-7.36 (m, 1H, H³), 6.90 (td, *J* = 7.97, 1.38 Hz, 1H, H⁴), 2.51 (s, 1H, H¹⁰), 1.76 (s, 6H, H⁸⁻⁹); **¹³C NMR** (101 MHz, CDCl₃) δ 148.5, 142.7, 128.6, 128.1, 126.8, 93.2, 73.6, 29.8 (2C); **HRMS** (ESI): calc. (C₉H₁₁INO): [M+Na]⁺ 284.9747, found 284.9744. Data matches literature.⁶⁷

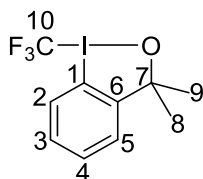
1-Chloro-1,1-dihydro-3,3-dimethyl-1,2-benziodoxole (84)



Chloro benziodoxole **81** was synthesised following a literature procedure:⁶⁸ Crude 2-(2-iodophenyl)propan-2-ol (487 mg, 1.86 mmol) dissolved in anhydrous acetonitrile (5 mL) was heated to 75 °C upon which time trichloroisocyanuric acid TCCA (120 mg, 0.62 mmol) dissolved in dry acetonitrile (3 mL) was added and the resultant mixture was kept at reflux for 6 minutes. The mixture was then filtered hot over celite to remove the white precipitate of isocyanuric acid. The filtrate was concentrated and after an acetonitrile recrystallisation, yellow crystals were afforded. Two further concentrations and recrystallisations were carried out leading to a crop of yellow crystals (297 mg, 1.06 mmol, 57 %).

¹H NMR (400 MHz, CDCl₃): δ 8.02 (d, J = 8.11 Hz, 1H, H²), 7.50-7.59 (m, 2H, H^{3,4}) 7.17 (dd J = 7.36, 1.89 Hz, 1H, H⁵), 1.55 (s, 6H, H^{8/9}); **¹³C NMR** (101 MHz, CDCl₃) δ 149.5, 130.9, 130.5, 128.4, 126.1, 114.6, 85.1, 29.2 (2C); **HRMS** (ESI): calc. (C₉H₁₀ClOI): [M+H]⁺ 296.9533, found 296.9538. Data matches literature.⁶⁷

3,3-Dimethyl-1-(trifluoromethyl)-1,2-benziodoxole, Togni reagent I (**66**)



Dimethyl benziodoxole **66** was synthesised following a literature procedure:⁶⁸ anhydrous KF (20 mg, 0.34 mmol), 1-chloro-1,1-dihydro-3,3-dimethyl-1,2-benziodoxole (50 mg, 0.17 mmol) and dry acetonitrile (3 mL) were stirred overnight at rt then placed in a salted ice bath at which point trifluoromethyltrimethylsilane (26 mg, 0.19 mmol) was introduced leading to a period of vigorous stirring with contemporaneous warming to r.t. Subsequently, the mixture was filtered over celite and the resultant filtrate concentrated to dryness under vacuum then extracted with pentane (8 mL) then, in a cool water bath (15 °C), concentrated to dryness to impart the white crystalline product (18 mg, 0.05 mmol, 32%).

¹H NMR (400 MHz, CDCl₃): δ 7.52-7.55 (m, 2H, H^{2,5}), 7.38-7.45 (m, 2H, H^{3,4}), 1.48 (s, 6H);

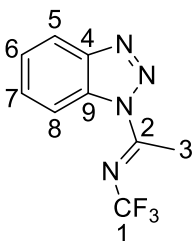
¹³C NMR (101 MHz, CDCl₃) δ 149.37, 130.77, 129.98, 127.98, 127.49, 110.61, 110.42;

Signals believed missing due to low intensity—7, 8/9 **¹⁹F NMR** (376 MHz CDCl₃): δ -40.2

HRMS (ESI): calc. (C₁₀H₁₁F₃IO): [M+H]⁺ 330.9801, found 330.9800. Data matches literature.⁶⁷

Compounds **79** and **87** was synthesised following a literature procedure:⁶⁶ Togni reagent I (66 mg, 0.20 mmol) and benzotriazole (36 mg, 0.30 mmol) with acetonitrile (2 mL) and trifluoroacetic acid (2.5 mg, 0.02 mmol) were stirred at 60 °C for 3.5 hours. The reaction mixture was cooled and then sodium bicarbonate solution was added to the mixture and stirred. The resulting suspension was filtered, and the organic and aqueous phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 8 mL). The combined organic phases were dried over magnesium sulfate after which the solution was filtered. The mixture was then concentrated under reduced pressure to remove solvent.

(*E*)-*N*-(1-(1H-Benzo[d][1,2,3]triazol-1-yl)ethylidene)-trifluoromethanamine (79)

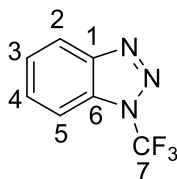


The resulting crude material was purified by column chromatography (pentane: DCM in a 5:1 ratio). The resultant solution was evaporated under reduced pressure to yield white crystals: 11 mg, 0.05 mmol, 24 %.

¹H NMR (400 MHz, CDCl₃) δ 8.43 (*d*, *J* = 8.41 Hz, 1H, H⁵), 8.14 (*d*, *J* = 8.41 Hz, 1H, H⁸), 7.68 (*td*, *J* = 1.15, 7.10 Hz, 1H, H⁶), 7.54 (*td*, *J* = 1.15, 7.18 Hz, 1H, H⁷), 3.11 ((appears *d* likely stemming from *E/Z* isomers), *J* = 1.36 Hz, 3H, H³); **¹⁹F NMR** (376 MHz, CDCl₃): δ -53.5;

HRMS (ESI): calc. (C₉H₈F₃N₄): [M+H]⁺ 229.0696, found 229.0698. Data matches literature.⁶⁶

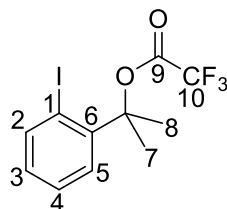
1-(Trifluoromethyl)-1*H*-benzo-1,2,3-triazole (87)



Isolation from the resulting crude material was attempted through multiple column chromatography attempts using a variety of pentane: ethyl acetate ratios and pentane : DCM (9:1, 8.5:1 and 8:1) but no product was isolated. ¹⁹F NMR yield of 2 % was determined through use of internal standard 2,2,2-trifluoroethanol.

¹⁹F NMR (376 MHz CDCl₃): δ -57.8. **HRMS** (ESI): calc. C₇H₄F₃N₃: [M]⁺ 187.0352, not detected. Data matches literature.⁶⁶

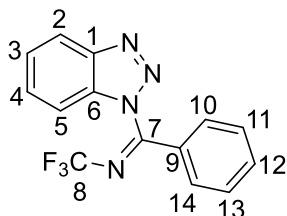
2-(2-iodophenyl)propan-2-yl 2,2,2-trifluoroacetate(89)



Acetonitrile (1.00 mL), Togni reagent I (66 mg, 0.20 mmol) and TFA (23 mg, 0.20 mmol) were stirred at 60 °C for 3.5 hours. Sodium bicarbonate solution was added to the mixture and stirred. The resulting suspension was filtered, and the organic and aqueous phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 8 mL). The combined organic phases were dried over magnesium sulfate after which the solution was filtered. The mixture was then concentrated under reduced pressure. The resulting crude material was purified by column chromatography (pentane: ethyl acetate in a 9:1 ratio), yielding white crystals 6 mg, 0.02 mmol, 8 %.

¹H NMR (400 MHz, CDCl₃): δ 8.00 (*dd*, *J*¹ 1.46 Hz, *J*² 7.80 Hz, 1H, H²), 7.45 (*dd*, *J*¹ 1.75 Hz, *J*² 7.90 Hz, 1H, H⁴), 7.37 (*td*, *J*¹ 1.44 Hz, *J*² 7.28 Hz, 1H, H⁵), 6.97 (*td*, *J*¹ 1.73 Hz, *J*² 7.28 Hz, 1H, H³), 2.00 (*s*, 6H, H^{6,7}) **¹³C NMR** (101 Mhz, CDCl₃): δ 155.94, 143.52, 142.96, 129.77, 128.39, 127.14, 113.16, 91.78, 87.23, 27.28.). **¹⁹F NMR** (376 MHz CDCl₃): δ -74.3. **HRMS (ESI)**: calc. C₁₁H₁₀F₃I₁O₂: [M]⁺ 357.9677, not detected. Previously unreported compound.

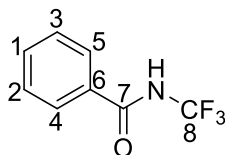
(Z)-1-(1*H*-benzo-1,2,3-triazol-1-yl)-1-phenyl-*N*-(trifluoromethyl)methanimine (90)



Togni reagent I (66 mg, 0.20 mmol) and benzotriazole (36 mg, 0.30 mmol) with acetonitrile (2 mL) and trifluoroacetic acid (2.5 mg, 0.02 mmol) were stirred at 60 °C for 3.5 hours. Sodium bicarbonate solution was added to the mixture and stirred. The resulting suspension was filtered, and the organic and aqueous phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 8 mL). The combined organic phases were dried over magnesium sulfate after which the solution was filtered. The mixture was then concentrated under reduced pressure to remove solvent. The resulting crude material was purified by column chromatography (pentane: DCM in a 5:1 ratio) but no product was isolated. ¹⁹F NMR yield of 9 % was determined through use of internal standard 2,2,2-trifluoroethanol.

¹⁹F NMR (376 MHz CDCl₃): δ -56.1. **HRMS (ESI)**: calc. C₁₄H₉F₃N₄: [M]⁺ 290.0779, not detected. Previously unreported compound.

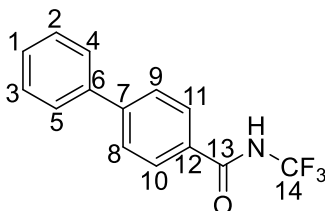
***N*-(trifluoromethyl)benzamide (91)**



Benzonitrile (1.50 mL), Togni reagent I (198 mg, 0.60 mmol), water (1.5 mL) and TFA (7 mg, 0.06 mmol) were stirred at 60 °C for 3.5 hours. Sodium bicarbonate solution was added to the mixture and stirred. The resulting suspension was filtered, and the organic and aqueous phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 8 mL). The combined organic phases were dried over magnesium sulfate after which the solution was filtered. The mixture was then concentrated under reduced pressure to remove solvent. Isolation was attempted through multiple column chromatography attempts using a variety of pentane: ethyl acetate ratios (9:1, 8.5:1 and 8:1) but no product was isolated. ^{19}F NMR yield of 29 % was determined through use of internal standard 2,2,2-trifluoroethanol.

^{19}F NMR (376 MHz CDCl_3): δ -57.1 **HRMS** (ESI): calc. ($\text{C}_8\text{H}_6\text{F}_3\text{NNaO}$): $[\text{M}+\text{Na}]^+$ 212.0294, found 212.0288. Product known but no ^{19}F NMR reported.⁷⁵

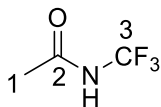
***N*-(trifluoromethyl)4-carboxamide biphenyl (95)**



4-cyanobiphenyl (358 mg, 2.0 mmol), 1-trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benzodioxole (66 mg, 0.20 mmol), water (9.00 μ L, 0.50 mmol), TFA (2.28 mg, 0.02 mmol) and DCE (1.5 mL) were stirred at 60 $^{\circ}$ C for 5 hours. The resulting mixture was concentrated under reduced pressure to yield white crystals of 4-cyanobiphenyl and a brown oil. Isolation was attempted through multiple column chromatography attempts using a variety of pentane: ethyl acetate ratios (9:1, 8.5:1 and 8:1) but no product was isolated. ^{19}F NMR yield of 2 % was determined through use of internal standard 2,2,2-trifluoroethanol.

^{19}F NMR (376 MHz CDCl_3): δ -56.7, **HRMS** (ESI): calc. $\text{C}_{14}\text{H}_{10}\text{F}_3\text{NO}$: $[\text{M}]^+$ 265.0714, not detected. Product known but no spectroscopic data published.

***N*-(trifluoromethyl)acetamide (81)**



Togni reagent I (66 mg, 0.20 mmol), TFA (2 mg, 0.02 mmol) and acetonitrile (1 mL) were stirred at 60 °C for 3.5 hours. The resulting mixture was concentrated under reduced pressure to remove solvent. Isolation was attempted through multiple column chromatography attempts using a variety of pentane: ethyl acetate ratios (9:1, 8.5:1 and 8:1) but no product was isolated. ^{19}F NMR yield of 31 % was determined through use of internal standard 2,2,2-trifluoroethanol.

^{19}F NMR (376 MHz CDCl_3): δ -56.4. **HRMS**(ESI): calc. $\text{C}_3\text{H}_4\text{F}_3\text{NO}$: $[\text{M}]^+$ 127.0244, not detected.

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