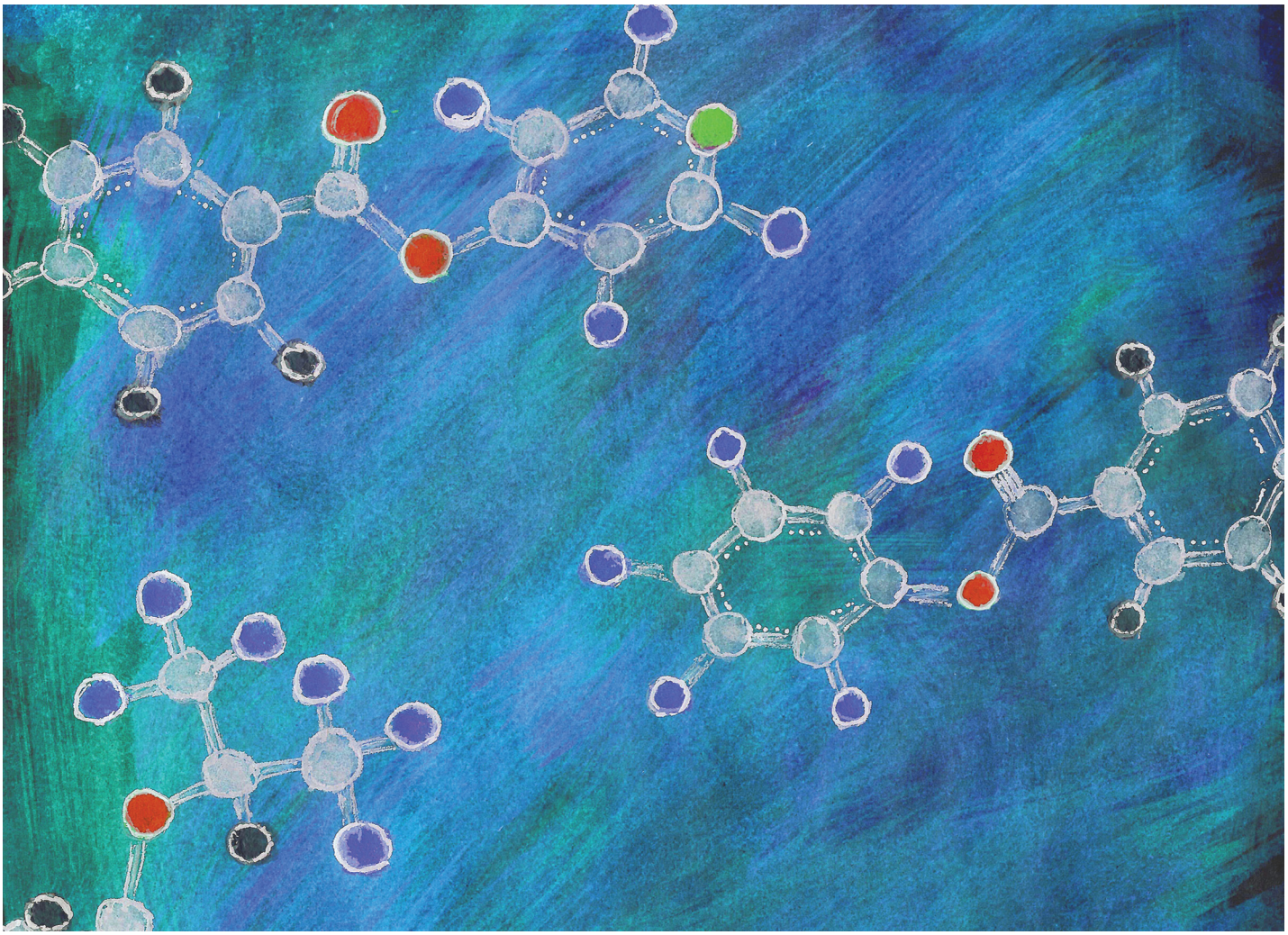

A highlight of recent advances in fluorinated reactive intermediates by Bonn and Brittain, Department of Chemistry, Durham University, Durham, United Kingdom.

Recent developments in the use of fluorinated esters as activated intermediates in organic synthesis

This review highlights recent advances in the use of fluorinated reactive intermediates as an activation mode of carboxylic acids within synthetic organic chemistry. A range of their transformations are discussed.

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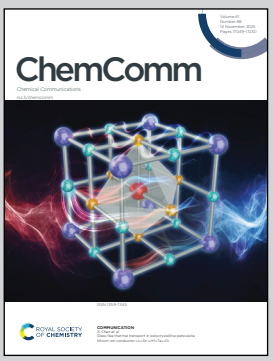

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Recent developments in the use of fluorinated esters as activated intermediates in organic synthesis

Daniel E. Bonn and William D. G. Brittain *

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Carboxylic acids are versatile synthetic building blocks; however, they often require activation in order to partake in a range of transformations. Activation through the formation of esters gives a characteristically less reactive intermediate in subsequent reactions compared to other related functionalities (*e.g.* acyl chlorides). Fluorinated ester functional groups offer the ability to significantly modulate the electronics of the system to allow for reactions to occur under mild conditions and hence offer new activation modes starting directly from carboxylic acids. This review highlights examples of this class of esters as promising synthetic handles and their use in further procedures from isolated forms or through *in situ* generation.

1. Introduction

Carboxylic acids are important and ubiquitous functional groups within organic synthesis, where they lend themselves to useful transformations into other functional groups through various reactions. Some of the most common reaction classes applied to carboxylic acids are nucleophilic addition–eliminations. This typically involves conversion of a carboxylic acid to a more reactive intermediate that allows coupling with a nucleophile through the formal substitution of an OH group. Common examples of these types of activated intermediates include acyl chlorides, acyl fluorides, aldehydes, anhydrides, and Weinreb amides, to name but a few;[1–3] hence a large catalogue of activated intermediates exists. However, synthesis of these activated functionalities is normally performed *in situ* on account of convenience and potential instabilities arising from unwanted reactions with water or air. The ability to form isolatable, bench-stable activated carboxylic acid derivatives provides flexibility and control in synthetic routes, allowing for the removal of potential substituents not compatible with further reactions with the intended nucleophile. Ester functional groups are a textbook example of an activated acid equivalent and lend themselves to this concept due to their typical stabilities; for example, hydrolysis of esters classically requires heat in the presence of an acid or base.[3] Additionally, methyl and *tert*-butyl esters are regularly used as carboxylic acid protecting groups due to their favourable stability profiles,[4–7] with well-established reactions from their parent substrates. However this stability can create problems in that their further

Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, UK.
E-mail: william.d.brittain@durham.ac.uk

Daniel E. Bonn

Dan completed an MChem degree in 2023 before beginning his PhD studies under the supervision of Dr William D. G. Brittain at Durham University. His research mainly focuses on the development of new methodologies utilising organofluorine based reagents as well as the development of routes to metal chelating natural products, along with the precursors involved in their biosynthetic pathways.

William D. G. Brittain

Will conducted his PhD studies at the University of Birmingham under the supervision of Prof. John Fossey and Prof. Ben Buckley. He moved to Durham University in 2017 to take up a PDRA position with Prof. Steven Cobb before being awarded a Leverhulme ECF in 2020. He is currently an Associate Professor of Organic Chemistry at Durham, where his research group focuses on synthetic chemistry, in particular the preparation and use of organofluorine compounds.

reaction in addition–elimination reactions may require harsh conditions, strong nucleophiles and/or metal-based reagents that need to be employed on account of the typical poor leaving group ability of methoxides and *tert*-butoxides (high pK_a of the associated conjugate acid).[8] In order to overcome this limitation, the leaving ability of the alkoxide can be enhanced through tuning of its electronic or steric properties.

To generate activated intermediates with increased leaving group ability, carbodiimide-based reagents such as EDC, DIC and DCC have been developed, which can readily activate carboxylic acids for addition–elimination reactions. They are commonly used as economical and commercially available coupling agents for the synthesis of amides, esters, and thioesters, sometimes being paired with *N*-hydroxy based additives such as HOBt to improve the reaction efficiency.[9,10] Other conventional reagents include HATU, HBTU and CDI, which result in an increased leaving group ability. To increase the reactivity further, introduction of electron-deficient substituents within the leaving group has been studied. The incorporation of fluorine atoms is one approach that has been gaining much attention in this area. Whilst fluorine is the most electronegative element, its large C_{sp^3}–F bond energy of 456 kJ mol^{-1} (in CF_4) also makes it the strongest single bond to carbon within organic chemistry with a dipole moment of 1.86 D (in CH_3F).[11,12] Additionally, fluorine atoms share a comparable van der Waals radius with hydrogen (1.47 Å and 1.20 Å, respectively), hence showing similar steric behaviour when replaced in an analogue.[13] Fluorinated intermediates have been previously used to influence the reactivity and stability of other activated intermediates such as ylides and thianthrenium salts.[14,15] Additionally, donor–acceptor carbenes bearing a CF_3 substituent have been shown to be useful reagents for both nucleophilic and electrophilic-type reactions.[16–18] Similarly, fluorinated ester substrates offer more potential synthetic value for reactions carried out under mild conditions or with weaker nucleophiles than non-fluorinated esters on account of their improved leaving group ability and increased electrophilicity of the carbonyl C_{sp^2} centre. Within our own research group, we have standing interest in the development of methodology within organofluorine chemistry,[19,20] and thus we aspired to highlight the recent advances in the generation of highly reactive fluorinated ester intermediates. Outlined within this highlight, we examine approaches for the generation of activated, ester-based intermediates containing fluorine substituents starting from carboxylic acids, reactions which proceed through these intermediates to generate other species capable of undergoing addition–elimination reactions, and how they are compatible with a selection of subsequent reactions with a variety of different nucleophiles.

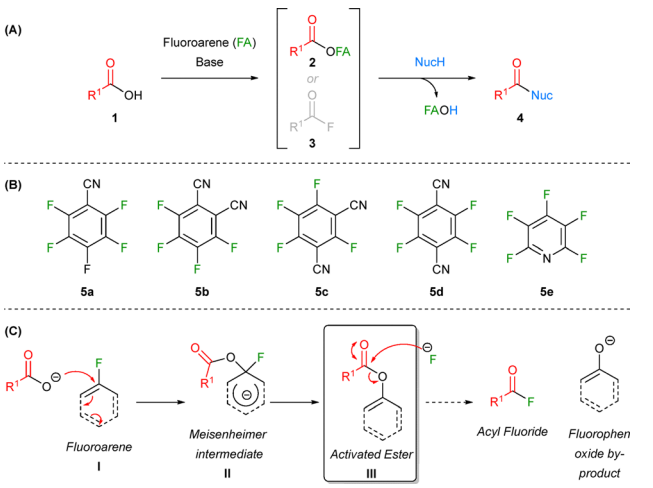
2. *In situ* activation of carboxylic acids *via* fluorinated esters

One way in which the reactivity of fluorinated esters can be harnessed is through their *in situ* generation from carboxylic acids. This allows for highly reactive species to be created and consumed without the requirement for isolation. This is a particularly attractive proposition as employment of ^{19}F NMR techniques allows for the direct monitoring of intermediate formation and subsequent consumption. Highlighted here are aromatic, heteroaromatic, silicon and sulphur-based examples, which utilise an *in situ* generation approach.

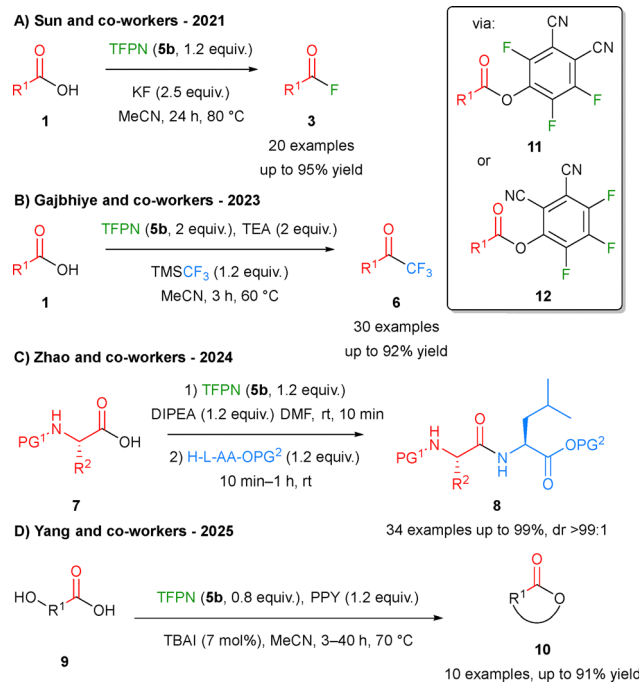
2.1 Perfluoro-aromatic and heteroaromatic esters

A class of compounds that are ideally set up for the formation of activated esters are perfluoroaromatics (Scheme 1(B)). In contrast to their hydrocarbon equivalents, perfluoroaryls act as electrophiles capable of readily undergoing S_NAr reactions with a range of nucleophiles.[21–26] Perfluoro-aromatic or fluoroarene based electrophiles are much more electron deficient than other EWG containing phenyl derivatives and are hence substantially more susceptible to S_NAr especially with weak carboxylate nucleophiles.[27] When a perfluoroaryl undergoes S_NAr, nucleophiles attack a C_{sp^2}–F bond releasing a fluoride ion following the collapse of the associated Meisenheimer intermediate (Scheme 1(C)).[28,29] In the case of a carboxylate anion, this results in the formation of an activated ester bearing the highly fluorinated aromatic substituent (Scheme 1(C), **III**).[30–32] Depending on how well the subsequently released fluoride ion is sequestered, this can undergo further reaction to form an acyl fluoride alongside a fluorophenoxide by-product.[33]

Cyano-based fluoroarenes **5a–5d** have been under recent investigation. In 2021, Sun and co-workers (Scheme 2(A)) showed that carboxylic acids can be converted to the corresponding acyl fluorides using tetrafluorophthalonitrile (TFPN, **5b**) in the presence of KF *via* activated esters (**11** & **12**).[31] Within this study, they also investigated pentafluorobenzonitrile (PFBN, **5a**), *meta*-tetrafluorophthalonitrile (TFPN, **5c**), *para*-tetrafluorophthalonitrile (*para*-TFPN, **5d**) and pentafluoropyridine (PFP, **5e**), which all showed >57% conversion to the acyl fluoride. Hexafluorobenzene (HFB) was also studied but gave no conversion. The reaction was hence optimised for TFPN and a substrate scope of 20 examples gave isolated yields of up to 95% for the acyl fluoride. The regiochemistry of intermediate



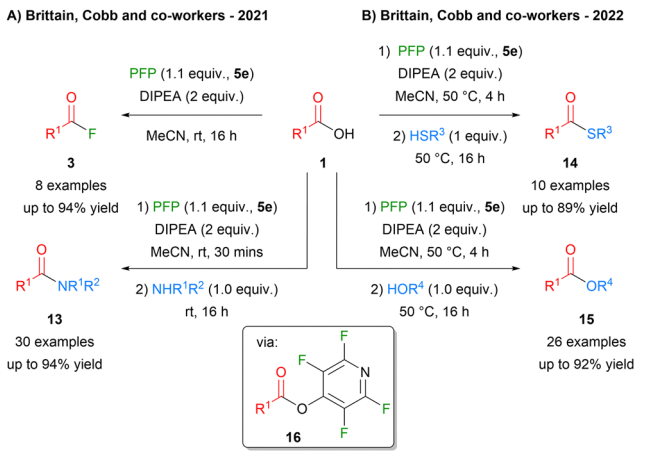
Scheme 1 (A) A nucleophilic substitution from a carboxylic acid mediated by a fluorinated arene based ester with (B) selected examples of compatible fluoroarenes and (C) a general mechanism.



Scheme 2 Examples of reactions using perfluorophthalonitrile esters to make (A) acyl fluorides, (B) trifluoromethyl ketones, (C) peptides and (D) macrolactones.

11 was predicted to be favoured based on previous studies by Chambers *et al.*, which suggested that the nucleophile tends to attack a carbon site that maximises the number of adjacent *ortho* and *meta* fluorines.[34] The findings were also consistent with previous reports in which *para*-cyano groups were found to enable conjugate stabilisation of the Meisenheimer intermediate.[35] However, Sun and co-workers suggested that both activated esters **11** & **12** formed, where the latter was the major intermediate, supported by NMR evidence. Gajbhiye and co-workers applied the TFPN methodology to the synthesis of trifluoromethyl ketones (**6**) in 2023 (Scheme 2(B)).[32] Within their study, similar optimisation was performed using TFPN, PFBN, PFP and HFB, whereby a carboxylic acid was mixed with a chosen fluoroarene, base and trifluoromethyltrimethylsilane ($TMSCF_3$). In this case, the addition–elimination reaction was believed to proceed *via* the activated ester rather than the acyl fluoride as the fluoride ion released during S_NAr was believed to be sequestered through reaction with the $TMSCF_3$ present, given the high strength of Si–F bonds (BDE = 540 kJ mol^{-1}).[36] This subsequently released a trifluoromethyl anion into solution that could undergo addition–elimination with the activated ester. Again, TFPN was shown as the optimal perfluoroaryl and hence was applied to 30 examples to generate trifluoromethyl ketones, giving yields of up to 92%. During the optimisation, several conditions tested appeared to stall at the activated ester, namely at lower temperatures or when using inorganic bases such as K_2CO_3 or Cs_2CO_3, whereby reaction with the weak nucleophile CF_3^- was prevented. Whilst an *in situ* reaction was favoured in this case, insight into possible conditions whereby the activated esters could be isolated was investigated. Furthermore in 2024, Zhao and co-workers expanded the scope of TFPN to the rapid synthesis of peptides *via* acyl fluorides generated from the activated esters, without racemisation and with reaction times between 10 min and 1 h (Scheme 2(C)).[37] Within the substrate scope, 10 amides and 34 peptides were synthesised with yields up to 99%. As with the other studies outlined here, TFPN was shown to be the best fluoroarene reagent. Interestingly, use of Na_2CO_3 or K_2CO_3 in MeCN at rt without any additives resulted in >90% isolated yield of the activated ester with only trace amounts of the corresponding acyl fluoride detected. Likewise, use of DIPEA in toluene gave the same result but in 81% yield. Hence, when reaction conditions are varied specifically, these reactions can be tuned to either proceed through an acyl fluoride or allow for the preparation of isolated activated fluoroarene esters selectively. Recently, TFPN has also been used to mediate intramolecular esterification reactions. As part of a wider investigation into the synthesis of esters and thioesters, Yang and co-workers applied their procedure to the synthesis of macrolactones (Scheme 2(D)).[38] Despite the possibility of dimerization through intermolecular reactions, their standard conditions successfully produced the desired cyclised products in isolated yields between 47 and 91% for a range of aliphatic and phenolic alcohols.

Brittain, Cobb and co-workers have focussed on the utility of PFP to carry out one-pot reactions in a similar fashion to TFPN. After investigating PFP as a reagent for phenol protection, work was carried out in 2021 to optimise a deoxyfluorination process of carboxylic acids that proceeds *via* a tetrafluoropyridyl (TFP) activated ester, **16** (Scheme 3(A)).[30,39,40] Using an equivalent ratio of carboxylic acid, PFP and DIPEA, acyl fluorides were successfully synthesised in up to 94% isolated yield. The subsequently generated acyl fluorides resulting from addition–elimination of the fluoride towards the activated ester were used as part of one-pot amide bond formation. A selection of 30 amides were generated with varying functionality to give isolated yields of up to 94%. Furthermore, in a follow-up study, the same methodology was applied to the synthesis of esters and thioesters (Scheme 3(B)). A total of 36 examples in up to 92% isolated yields demonstrated a good substrate tolerance for the PFP methodology.[41] Limitations

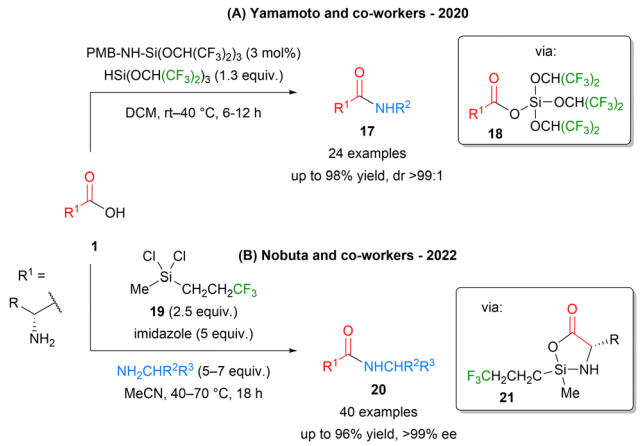


Scheme 3 A selection of transformations using tetrafluoropyridyl esters to synthesise (A) acyl fluorides and amides as well as (B) thioesters and esters.

in the rate of formation of the acyl fluorides were attributed to the electronics of the carboxylic acid starting material. A ^{19}F NMR reaction monitoring study between 4-methoxybenzoic acid and 4-nitrobenzoic acid revealed significantly lower conversion to the acyl fluoride at 50 °C for nitro-containing acids pointing to the nucleophilicity of the carboxylate as being the driving factor in the reaction rate. Furthermore, addition of the nucleophile to be coupled in the presence of unreacted PFP was shown to result in unwanted S_NAr between the pair, limiting subsequent formation of the target product through the formation of unwanted substituted TFP containing side-products. In contrast whilst PFP is reactive enough to partake in S_NAr, pentafluorophenyl esters and less fluorinated aryl analogues are rarely derived from S_NAr reactions due to the decreased electrophilicity of HFB. More typically, they are generated from esterification of a fluorinated phenol with the carboxylic acid mediated by a coupling agent such as EDC, DIC or DCC.[42–50] Although this removes the convenience of *in situ* formation of an activated intermediate, their utility arises in their ability to be readily isolated, allowing for flexibility in further reactions (see Section 3.1).

2.2 Silyl esters

The use of silicon-based esters as reactive intermediates has been explored as early as 1969 when Chan and Wong showed the possibility of amide coupling using $SiCl_4$, albeit with a large excess of base employed to quench/limit the emission of HCl gas.[51] Due to the great stability of Si–F bonds and the inherent toxicity of SiF_4, it is no surprise that the use of this reagent would be impractical, potentially requiring elevated temperatures as well as gas handling procedures due to the risk of producing gaseous HF. Hence, many examples of orthosilicate and chlorosilane reagents have since been developed for the synthesis of amides and peptides.[52] The use of silicon-based reagents offers some advantages over more traditional amide coupling approaches including environmental benefits due to the large relative abundance of silicon in the Earth's crust.[53] The first example of a class of fluorine-containing silyl esters for amidation was that of the tetrakis(perfluoroalkoxy)-silanes, particularly those generated from $Si[OCH(CF_3)_2]_4$.[54] In an attempt to increase reactivity, Mukaiyama and co-workers investigated the effect of fluoro-substituted alkoxy groups over non-substituted tetraalkoxysilanes, showing an enhanced yield in most cases with fluorinated reagents. Due to the high electronegativity of fluorine it would be expected that, similar to the fluoroarenes (Section 2.1), the silicon centre would be made more electrophilic for reaction with weaker carboxylate nucleophiles. Consequently, Yamamoto and co-workers in 2020 expanded to tris(perfluoro-alkoxy)silanes, specifically $HSi(OCH(CF_3)_2)_3$, for the synthesis of peptides (Scheme 4(A)).[55] An initial range of substrates were evaluated to assess amine protecting group tolerance and racemisation giving yields between 57 and 99% with exceptional stereoselectivity in 45 examples following optimisation of the silane reagent. Through mechanistic studies for the generation of the associated silyl ester intermediate, it was found that introduction of a catalytic amount of $BnHNSi(OCH(CF_3)_2)_3$ showed >99% conversion after 30 min compared to 72% after 1 h for Boc-Ala-OH without the addition of the catalyst



Scheme 4 Amide/peptide forming reactions using (A) a tris(perfluoroalkoxy)silane or (B) $MTFPSCl_2$.

(92% conversion after 6 h). Hence, following optimisation of reaction conditions and the aminosilane/orthosilicate catalyst, an extensive substrate scope was explored using $PMBNHSi(OCH(CF_3)_2)_3$ at 3 mol% loading. For the 21 peptides made using this procedure, the yield was shown to increase by an average of 17% compared to that without the addition of the catalyst, while maintaining the high stereoselectivity of >99 : 1 dr or er.

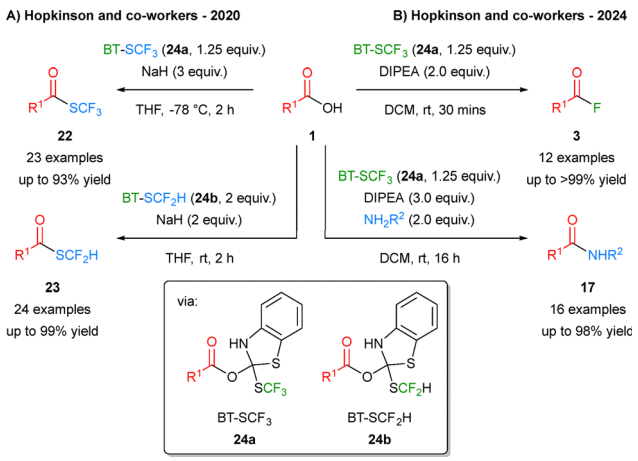
Typically, one of the main challenges associated with the amidation of amino acids is that they require the use of protecting groups on the α-amine to prevent unwanted dipeptide formation through a self-reaction. Various attempts have been made to address this issue, for example, the use of synergistic reagents that can both activate the carboxylic acid whilst protecting the α-amine but these typically involve compounds with high toxicity and the potential for polymerisation.[56,57] Accordingly, Liskamp and co-workers first made their contribution to the challenge through the proposed use of cyclic oxazasilolidines – an activated ester intermediate formed through reaction of an α-amino acid with dichlorodimethyl silane.[58] Although their procedure showed good conversion and omission of metal-based reagents, limitations were in the incompatibility of the approach with bulky amines introduced after formation of the intermediate. Nobuta and co-workers in 2022 improved upon this prior work by applying their procedure to more sterically hindered amines (Scheme 4(B)).[59] Their use of dichloro(methyl)(3,3,3-trifluoro-propyl)silane ($MTFPSCl_2$, **19**) followed by careful optimisation highlighted that enhancement of the reagent electrophilicity, as per the properties of fluorine, improved reaction of oxazasilolidine (**21**) with a large range of amines bearing bulky substituents. Their scope of 17 amides from α-amino acids and amines, including cyclohexylamine, cyclooctylamine and *tert*-butylamine, showed good yields of up to 84%. Furthermore, with good tolerance in stereochemical conservation (up to >99% ee), effective reaction with bulky amines was proved. Additionally, a selection of 23 anilides was reported showing up to 96% yield from various aniline derivatives. Reactions with L-arginine, L-asparagine and L-glutamine were found to be unsuccessful with no further explanation. An example starting from an unprotected L-serine successfully generated the product, albeit in moderate

yield (42%), demonstrating a lack of nucleophilic interference of the hydroxyl group with the silane.

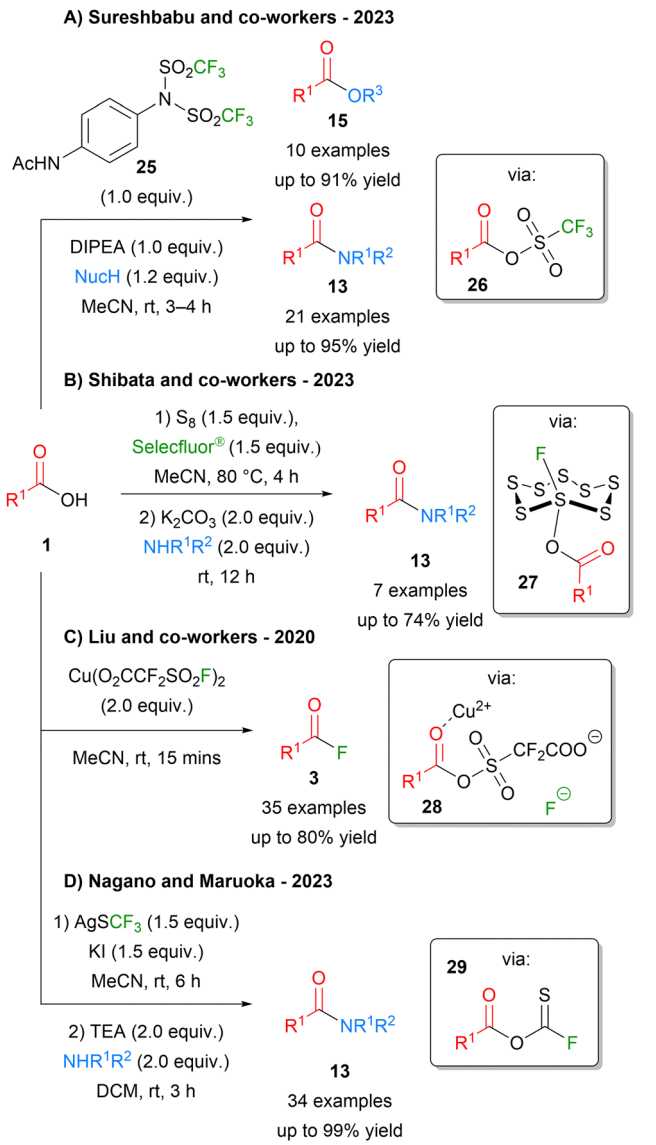
2.3 Sulphur-containing esters

An array of deoxyfluorination reagents have been developed over the years for the conversion of a hydroxyl group to a fluorine. Many typically contain an electrophilic sulphur site that mediates the cleavage of an S–F bond to introduce fluoride into a reaction. Notable examples include DAST, Deoxo-Fluor®, XtalFluor-E® and Pyfluor.[60–63] Consequently, when such reagents are subjected to a carboxylate nucleophile, the deoxyfluorination reaction proceeds *via* a fluorinated ester intermediate typically collapsing to form an acyl fluoride. The Hopkinson group developed trifluoromethylthio-containing benzothiazolium salt reagents (BT-reagents, **24**) as a means for the formation of amides and fluorinated-thioesters.[64,65] In 2020, Hopkinson and co-workers reported formation of tri- and di-fluoromethylthioesters (Scheme 5(A)).[64] Following formation of the intermediate (**24a** or **24b**), thioesters can be generated *via* a four-membered transition state arising from intramolecular addition–elimination of the intermediate. A total of 47 examples of fluorinated thioesters were synthesised with yields of up to 99%. The mechanistic pathway was shown to be concerted and never formally gave SCF_3^- or SCF_2H^-, which, in the case of the latter, avoids the generation of an unstable anion that favours decomposition to a thiocarbonyl following liberation of a fluoride. Further investigation using these reagents (in this case $BTSCF_3$) for deoxyfluorination exploited this concept (Scheme 5(B)).[65] The released fluoride can undergo reaction with the thioester formed *via* intermediate **24a** to form an acyl fluoride. This report also included a scope of amide bond formation that follows the same reaction pathway, giving 16 examples in up to 98% yield.

In 2023, Sureshbabu and co-workers reported the development of a new amide, ester and peptide coupling agent, which showed promise as a bench stable, crystalline solid with high thermal stability (decomposition temperature >159 °C).[66] A handful of triflate surrogates were screened in a peptide forming reaction between Fmoc-Val-OH and H-Phe-OMe. This showed that 4-acetamidophenyl triflimide gave the highest conversion when employed with MeCN and DIPEA as the solvent and base system with a short activation time of only 20 min. The *meta*- and *ortho*-fluorinated analogues, with respect to NTf_2, provided decreased yields respectively under the same conditions, rationalised by the electronic repulsion between the fluorine substituent and the triflyl group. A literature adapted protocol was employed for the synthesis of the triflimide from the parent acetyl-protected aniline. The proposed mechanism highlights the deoxygenative process carried out from the fluorinated ester (**26**) following reaction with the reagent. The deprotonated carboxylic acid attacks the sulfonyl centre of the triflimide resulting in the formation of the acyl trifluoromethanesulfonic anhydride (**26**) highlighted in Scheme 6(A). Subsequent addition–elimination with the chosen nucleophile results



Scheme 5 The utility of BT-reagents developed by the Hopkinson group to synthesise (A) tri- and di-fluoromethylthioesters as well as (B) acyl fluorides and amides.



Scheme 6 Transformations of carboxylic acids *via* sulphur-containing fluorinated esters using (A) a 4-acetamidophenyl triflimide reagent, (B) Selectfluor® and elemental sulphur, (C) a copper salt and (D) a silver salt.

in the removal of a triflate anion and in-turn generation of the target amide, ester or peptide. As such, the reaction showed excellent substrate tolerance with yields up to 95% for esters, amides and dipeptides. Additionally, a successful gram-scale synthesis of Z-L-Phe-Ala-OMe was performed with 85% yield.

The electrophilic fluorination reagent Selectfluor® has been under recent investigation for its potential applications in the generation of acyl fluorides from carboxylic acids (Scheme 6(B)). The work carried out by Shibata and co-workers highlighted the formation of acyl fluorides *via* sulphur-containing fluorinated-ester intermediates using elemental sulphur, S_8.[67] The proposed mechanism, supported by ^{19}F NMR and DFT, began with the S_8 abstraction of fluoride from Selectfluor®, where the remaining DABCO derivative acts as a base to deprotonate the carboxylic acid. The carboxylate subsequently attacks the S^+–F sulphur centre to form the activated ester (**27**) before intramolecular attack of the S–F bond into the ester carbonyl. Displacement then leads to deoxyfluorination forming an acyl fluoride and leaving the remaining oxidised sulphur species. This methodology was applied to a one-pot amidation procedure showing its utility for the generation of secondary and tertiary amides.

Liu and co-workers discovered the rapid and versatile synthesis of acyl fluorides using copper(II) trifluoromethylsulfonyltrifluoroacetate [$Cu(O_2CCF_2SO_2F)_2$] (Scheme 6(C)).[68] They initially studied the synthesis of difluoromethyl ketones based on previous work indicating a similar transformation from the acid analogue of the ligand within this copper complex.[69,70] Previously, this reagent had been employed as a trifluoromethylation agent for various aryl and heteroaryl iodides as well as benzyl bromides.[71] However, when it was exposed to carboxylic acids without the presence of a base, rapid deoxyfluorination was found to occur. Optimised conditions for 4-methoxybenzoic acid afforded the corresponding acyl fluoride in a yield of 84% within 15 min in MeCN. Longer reaction times led to very little deviation in conversion whereas alternative solvents such as DMF, THF and DCM led to diminished yields. The proposed mechanistic pathway demonstrated the formation of the activated ester intermediate (**28**) with the coordination of the copper ion to the carbonyl oxygen. Following this, the free F^- performs an addition–elimination reaction to furnish the acyl fluoride. Interestingly, during the optimisation the introduction of a base had very little effect on the overall yield, albeit with a slight reduction. This may be due to the lessened influence of the copper complex when under basic conditions. Further transformations of the acyl fluorides were explored namely in the formation of amides, ketones, thioesters and esters.

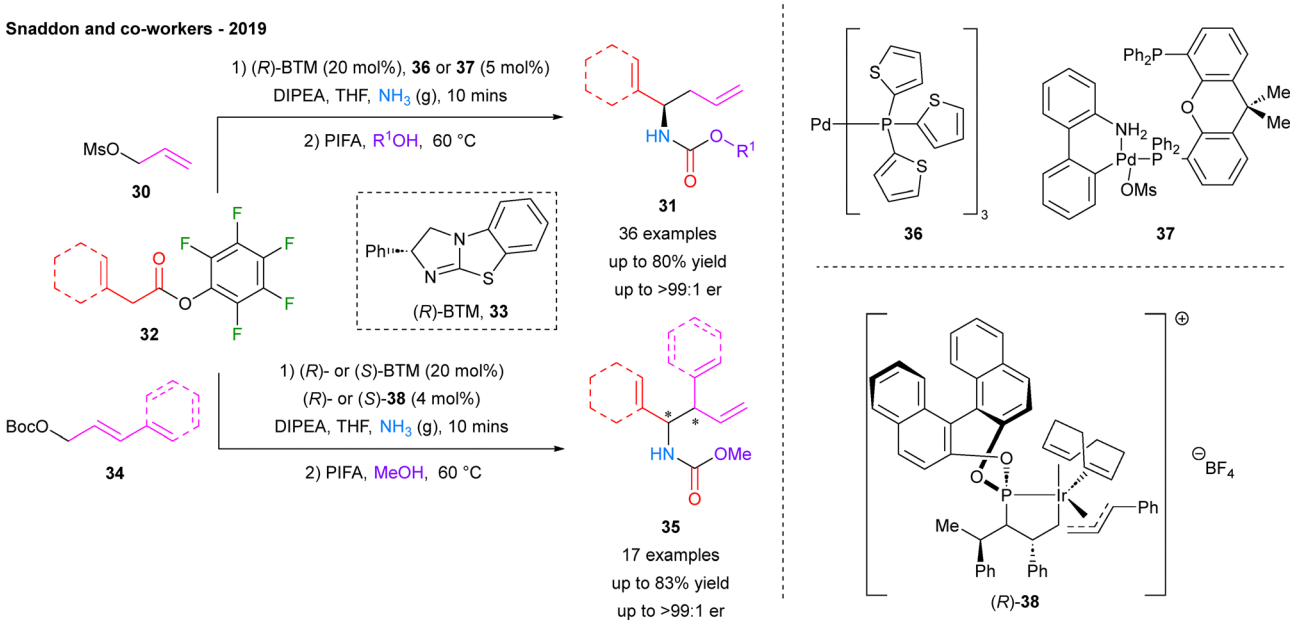
Similarly, Nagano and Maruoka studied the use of another group 11 transition metal in the synthesis of acyl fluorides *via* an *in situ* activated sulphur containing ester (Scheme 6(D)). Using commercially available potassium iodide and silver(I) trifluoromethanethiolate they explored a range of transformations from carboxylic acids with a focus on the synthesis of peptides from sterically hindered amino acids.[72] The silver species and potassium iodide initially react to give a K[Ag(SCF_3)I] complex, which breaks down into silver(I) iodide and $KSCF_3$ on account of the high affinity of silver for iodine atoms. As seen previously, SCF_3^- anions are very unstable and so the potassium salt collapses into KF and carbonothioic difluoride (SCF_2). This leads to the formation of the activated ester intermediate (**29**) following the reaction of SCF_2 with an equivalent of carboxylic acid in the presence of KF. A second equivalent of acid then reacts with the thiocarbonyl fluoride of the intermediate before collapsing to form the target acyl fluoride. Following filtration through silica, the crude material was concentrated and used without purification in further reactions. An extensive substrate scope study was performed for the synthesis of amides and dipeptides showing yields of up to 99% and 91% respectively. Other transformations successfully demonstrated included Suzuki–Miyaura cross-couplings, Friedel–Crafts reactions and esterification.

3. Reactions of isolated fluorinated esters

The isolation of activated carboxylic acid equivalents can provide flexibility in synthesis through the removal of unwanted side-products and unreacted reagents that may cause complications downstream. Being able to access bench stable but reactive species can be challenging. However, the use of fluorinated esters has shown much promise. There are several well-established moieties including PFPh, HFIP and alkyl-based esters. In this section the synthetic utility of these species is presented.

3.1 Pentafluorophenyl (PFPh) esters

PFPh esters are commercially available reactive intermediates typically appended to amino acids for pre-installed activation for reaction with nucleophiles. PFPh esters are rarely synthesised from hexafluorobenzene on account of sluggish S_NAr reactions observed with many nucleophiles. This is due to the presence of deactivating *para*-fluorine substituents, destabilising the eventual Meisenheimer intermediate as all starting C–F bonds are equivalent. Hence, a coupling procedure of the carboxylic acid and pentafluorophenol has become a common approach, allowing for isolation of the fluorinated ester (see the end of Section 2.1). Not only does the introduction of the pentafluorophenyl group lead to possible reaction at the C_{sp^2} of the ester, but the acidity of any α-protons is greatly influenced by the nearby electron-poor fluorophenyl ring, guiding possible α-alkylation, α-allylation and α-benzylation procedures. This area has been extensively explored by the Snaddon group, optimising many enantioselective and asymmetric procedures.[73–80] This highlights the distinctive role that activated esters can have, whereby "off-site" reactivity can take place whilst the reactive acid equivalent stays intact. The synthesis of linear or branched homoallylic amines from acyclic PFPh esters and allylic sulfonates/carbonates utilised both the enhanced acidity of the α-position and also the possible nucleophilic addition–elimination at the carbonyl that the fluorinated ester mediates (Scheme 7).[81] In 2019, Snaddon and co-workers outlined a procedure which employs cooperative catalysis of a Lewis base and transition metal to induce high regio- and enantio-control with high levels of diastereoselectivity. Through switching between palladium and iridium-based transition metal

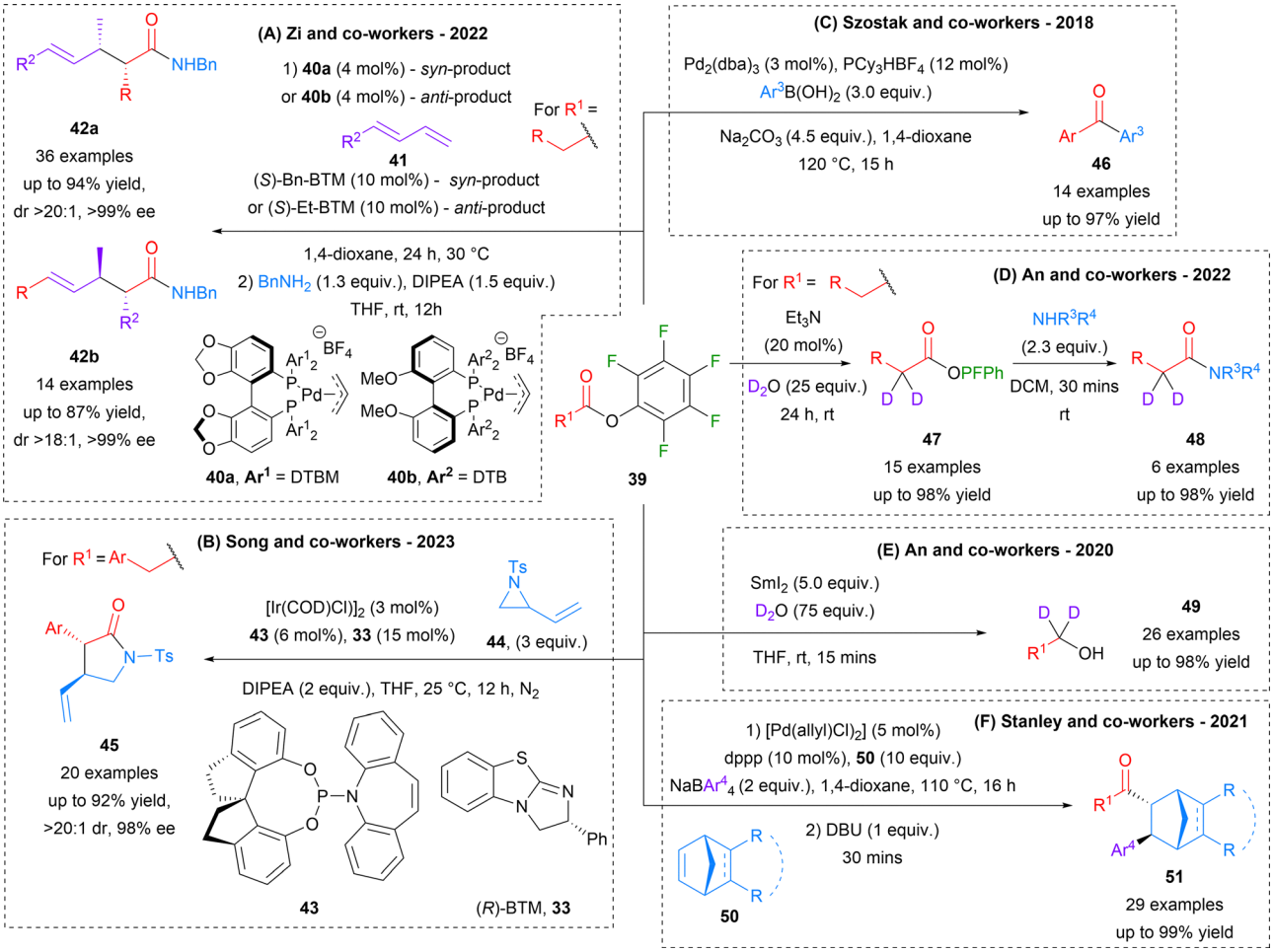


Scheme 7 The synthesis of linear and branched *N*-substituted homoallylic amines from PFPh esters.

complexes, enolate attack can be directed to occur at each position of the allyl component, giving either linear or branched regioisomers, respectively. The now formed intermediate amide then underwent a Hofmann rearrangement in which the isocyanate intermediate was transformed into a carbamate in the presence of a chosen alcohol preventing any subsequent decarboxylation. Overall, high stereoselectivity of >99 : 1 er was shown for 36 examples of linear *N*-substituted homoallylic amines in yields of up to 80% as well as 17 examples of the branched analogues in up to 83% yield.

Several other reports demonstrate the synergic effect of enhanced α-acidity and acyl donor ability of PFPh esters. In 2022, Zi and co-workers developed a methodology for the stereodivergent coupling of 1,3-dienes and enolisable PFPh esters whereby the stereoselectivity was controlled through the chirality of the palladium complex and the Lewis base used to mediate the reaction (Scheme 8(A)).[82] Extensive optimisation and substrate scope studies were performed, showing that **40a** in combination with (*S*)-Bn-BTM or **40b** paired with (*S*)-Et-BTM gave preference for the *syn*- and *anti*-products, respectively. Interestingly, it was shown that when the phosphine ligands within the palladium complex and Lewis base had opposite absolute stereochemistry, *syn*-selective products were observed. Coincidentally, matching absolute configuration resulted in *anti*-selective products, with very little deviation in dr, ee and yield in either case. This indicated that the stereochemistry was set through the interaction of the palladium complex and benzotetramisole (BTM) species. Using mild reaction conditions, 36 examples of the *syn*- and 14 of the *anti*-products were assessed giving up to 94% yield, >20 : 1 dr, >99% ee and 87% yield, >18 : 1 dr, >99% ee, respectively. In another study, Song and co-workers implemented a new method for the synthesis of chiral γ-lactam structures (Scheme 8(B)).[83] Using a dual catalyst system of isothiourea and an iridium complex, a [3+2] asymmetric annulation occurred between a PFPh ester and a vinyl aziridine. The proposed mechanism highlighted the initial addition–elimination of the isothiourea into the acyl donor which in turn formed the ammonium enolate that then reacted with the η^3-allyl iridium species to form the target chiral γ-lactam ring. A large range of vinyl aziridines as well as aryl groups within the PFPh esters were evaluated generally showing a large tolerance across examples with stereoselectivity of >20 : 1 dr and 98% ee with yields of up to 92%. During the reaction optimisation, 2,3,5,6-tetrafluorophenyl, 4-nitrotetrafluorophenyl, 3,5-trifluoromethylphenyl and 2,4,6-trichlorophenyl esters were considered as alternative reaction partners. All analogues gave consistent dr ratios of >20 : 1, whilst 2,4,6-trichlorophenyl esters afforded the greatest ee of 95% but conversely affording the lowest yield of 16%. The entries for 4-nitrotetrafluorophenyl and 3,5-trifluoromethylphenyl showed indifferent results of ~80% ee and ~25% yield. Although the PFPh esters accomplished the most promising outcomes, the 2,3,5,6-tetrafluorophenyl derivative differed by only 1–2% in both ee and yield, showing its potential presumably due to a similar reactivity profile.

Deuteration of organic compounds has been shown to be a valuable tool for assessing various properties through spectroscopic analysis such as in NMR spectroscopy, where deuterated substrates are routinely employed in labelling studies.[84,85] Additionally, implementing the heavy isotope of hydrogen has the possibility of positively influencing pharmacokinetic profiles of drug candidates.[86] In 2020, An and co-workers demonstrated the incorporation of deuterium through the reduction of PFPh esters using an *in situ* generated SmI_2–D_2O complex (Scheme 8(E)).[87] A series of alternative esters were evaluated, namely phenyl, thioethyl and ethyl, in which yields of <5–65% were obtained relative to the typical >95% yield of the PFPh



Scheme 8 A selection of transformations from PFPh esters. (A) 1,3-Diene and PFPh ester coupling, (B) γ-lactam synthesis, (C) non-decarbonylative Suzuki-Miyaura cross coupling, (D) α-deuteration, (E) reductive deuteration and (F) synthesis of bicyclic ketones.

esters. A scope of 26 examples showed high yields of up to 98% as well as compatibility with further derivatisation including Dess–Martin oxidation, Williamson ether synthesis and deoxychlorination reactions, giving 81–90% yields. Further work in 2022 established a mild procedure for the deuteration at the α-position within PFPh esters using a catalytic amount of TEA with high regioselectivity (Scheme 8(D)).[88] Subsequent further reaction with a range of nucleophiles allowed for the synthesis of α-deuterio amides, esters and carboxylic acids. This process was driven by the enhanced acidity that PFPh groups can induce as illustrated during optimisation of the reaction revealing 96% H/D exchange. Interestingly, 4-trifluoromethylphenyl and phenyl esters shared similar H/D exchange values albeit being almost half that of the PFPh esters. Additionally, DFT calculations further supported the observation determining an aqueous pK_a difference of 7.5 in favour of the PFPh esters (computed pK_a value for pentafluorophenyl 2-phenyl acetate of 9.9). In total, 15 examples of α-deuterio PFPh esters (**47**) were synthesised in a range of yields between 90 and 98% in 24 h at rt. It was found that if the amount of TEA was increased to 2.5 equiv. from 20 mol%, the resulting product ended up as the corresponding carboxylic acid. Further reaction of the esters with primary or secondary amines showed conversion to the associated amides (**48**) in 30 min with 6 examples displaying up to 98% isolated yield. Finally, the previous reductive–deuteration process highlighted from 2020 was applied in one pot.[87] α-Deuteration followed by introduction of the SmI_2–D_2O methodology produced deuterated alcohols in moderate to good yields.

Suzuki–Miyaura cross coupling reactions have become a well-established cornerstone in chemical synthesis, typically involving the formation of a biaryl from an arylboronic acid and an aryl halide catalysed by a palladium complex. Pseudohalides such as triflates, acyl chlorides or acyl fluorides have been investigated as alternative coupling partners whereas esters are normally deemed too unreactive;[89–92] although, there are some limited examples of decarbonylative Suzuki–Miyaura cross coupling reactions present within the literature from non-activated ethyl and phenyl esters,[93–96] as well as non-decarbonylative cases from 2-pyridyl or phenyl esters.[97,98] Szostak and co-workers implemented a methodology where PFPh esters were used as sufficiently activated acyl donors for non-decarbonylative Suzuki–Miyaura coupling to take place (Scheme 8(C)).[99] Using palladium catalysis at elevated temperature, 14 aryl ketones were synthesised in up to 97% yield, showing high conversion from the activated esters.

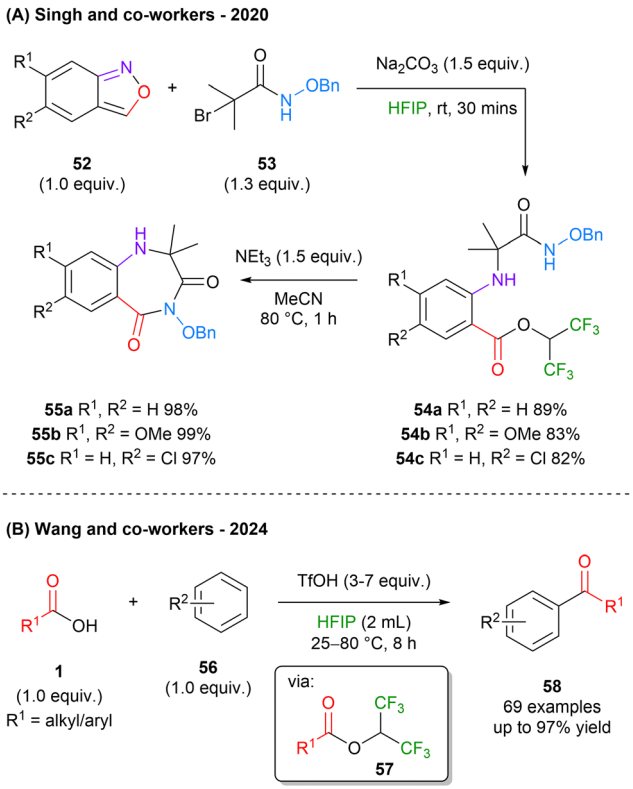
Another example of the synthetic flexibility of PFPh esters is observed in the palladium catalysed carboacylation synthesis of ketones.[100] The work carried out by Stanley and co-workers in 2021 illustrated the diastereoselective formation of an elaborate bicyclic ketone structure **51** starting from a PFPh ester (Scheme 8(F)). Careful optimisation of the pre-catalyst and ligand showed a high dr of >20 : 1 in favour of the *trans*-product when employing [Pd(allyl)Cl_2] and 1,3-bis(diphenylphosphino) propane (dppp) as the catalyst system. The stereoselectivity was believed to arise on account of the induced epimerisation that can occur between the *cis*- and *trans*-isomers with the sodium pentafluorophenoxide and/or triarylborane by-products. A total of 29 examples were synthesised in yields of up to 99%. Although styrene, a series of cycloalkenes and vinyltrimethylsilane alkene substrates failed to undergo conversion to the ketone product, a notable example starting from methyl (1*S*,2*R*,4*S*)-bicyclo[2.2.1]hept-5-ene-2-carboxylate gave a moderate yield of 53% as a mixture of diastereomers in a 1 : 1.2 ratio.

3.2 Hexafluoroisopropyl (HFIP) esters

HFIP's main use in synthetic chemistry has been overwhelming as a solvent with a high hydrogen bonding donor ability and large dielectric constant (16.7).[101] These favourable characteristics aid its ability to solubilise and stabilise a large range of species including those which are highly charged.[102] One of the earliest examples of HFIP ester formation was in investigations into alternative intermediates for peptide synthesis. As the fluorinated alcohols act as weak nucleophiles, Kopple and co-workers in 1979 investigated HFIP esters as activated intermediates generated under mild conditions, simultaneously removing the need for unaccommodating solvents despite their slower reaction times.[103] Typically, higher boiling point solvents such as DMF or DMSO are used but they make purification difficult due to their high boiling points. From carboxylic acids, the synthesis of HFIP esters follows standard esterification procedures.[104–107] Subsequent reports have shown the benefit of utilising the deoxyfluorination reagent XtalFluor-E® to give easy-to-remove water-soluble side products.[108] Meanwhile, HFIP esters have been utilised in a range of methodologies; Hojo and co-workers in 2024 revealed that a solid-phase synthesised peptide containing a dipicolylamino leaving group could be converted to an HFIP ester which then mediated the ligation of a second peptide in solution.[109]

Additionally, as part of a multistep total synthesis of furanocembranoids molestin E, *ent*-sinulacembranolide A and *ent*-sinumaximol A, Donohoe and co-workers used the HFIP acrylate to achieve a high level of stereocontrol for generation of the corresponding alcohol giving >98 : 2 dr.[110] The HFIP intermediate was then subjected to *trans*-esterification to form the TMSE protected carboxylic acid. Other examples of HFIP ester transformations include its use in the synthesis of 3-amino-1,5-benzodiazepine-2-one derivatives as well as gold-catalysed cycloisomerizations.[104,111]

In a recent study, Singh and co-workers established an amination strategy using highly functionalised alkyl bromides under mild and metal-free conditions (Scheme 9(A)).[112] As alluded to in their work, very few literature procedures exist



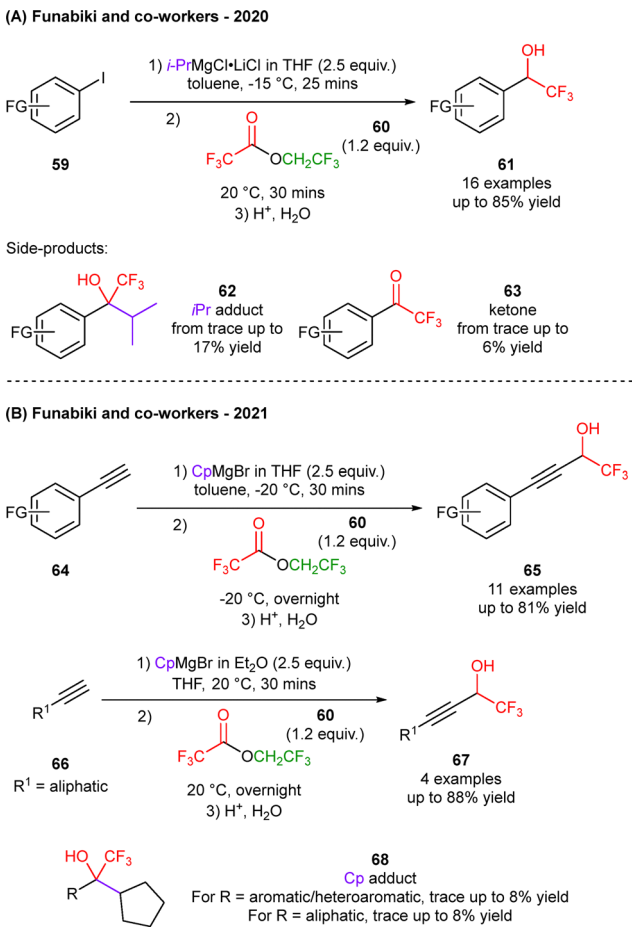
Scheme 9 HFIP esters as reactive intermediates in (A) 1,4-benzodiazepine-3,5-dione synthesis and (B) Friedel–Crafts acylation reactions.

for the synthesis of pharmaceutically relevant 1,4-benzodiazepine-3,5-dione scaffolds (**55**). Using their developed conditions, substrate **54** could be accessed. However, subsequent intramolecular condensation of the weakly nucleophilic amide was only successful through improvement of the ester electrophilicity – now possible with the HFIP ester **54** over the ethyl alternative. Another recent application of HFIP esters was in Friedel–Crafts acylation reactions using TfOH over other traditional Lewis acids such as $AlCl_3$ (Scheme 9(B)). Wang and co-workers demonstrated the direct formation of HFIP esters from parent carboxylic acids in the presence of TfOH which could then undergo intermolecular or intramolecular acylation with a range of phenyl derivatives in high regioselectivity.[113] An extensive substrate scope of 69 examples highlighted an excellent tolerance of varying arene and carboxylic acid substrates. Investigation of the mechanism and kinetics confirmed the predicted pathway and established a normal kinetic isotope effect. The underlying benefit here was the elimination of the need to produce an acyl chloride from the corresponding acid, typically needed for this well-established procedure through the use of a solvent to generate another equally useful activated intermediate.

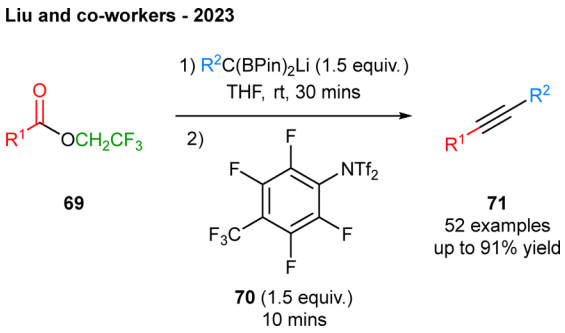
3.3 Fluoroalkyl esters

Alkyl esters are typically seen as fairly unreactive analogues of carboxylic acids normally requiring harsh conditions to undergo reaction. As discussed previously (Section 3.1), it is possible for alkyl esters such as those with ethyl substituents to undergo

cross coupling reactions, albeit often requiring elevated temperatures and the presence of transition metal complexes. Additionally, esters tend to serve as substrates for reactions with organometallic reagents such as Grignard, which subsequently give the corresponding tertiary alcohol following acidic workup. Consequently, Funabiki and co-workers have investigated the installation of the α-trifluoromethyl alcohol motif into a range of substrates (Scheme 10). These substrates were found to be susceptible to reaction with the "turbo" Grignard reagent ^{i}PrMgCl·LiCl which can typically act as a carbon nucleophile, reducing agent or as a base; it was intended to utilise a combination of these in a one-pot procedure of successive reactions.[114] The initial study in 2020 was carried out using iodoarenes or iodoheteroarenes (**59**) with trifluoroethyl trifluoroacetate (**60**) to furnish α-aryl or α-heteroaryl-α-trifluoromethyl alcohols (Scheme 10(A)). The proposed mechanism first suggested an iodine–magnesium exchange on the iodoarene which subsequently underwent nucleophilic addition with the trifluoroethyl trifluoroacetate to afford a magnesium alkoxide in equilibrium with the corresponding CF_3 ketone. ^{i}PrMgCl·LiCl then partakes in a second reactivity mode to reduce the ketone to the eventual α-aryl-α-trifluoromethyl alcohol following an acidic workup. Comparisons of the trifluoroethyl and methyl trifluoroacetates showed that slightly elevated temperatures were compatible with the former. This allowed for faster nucleophilic addition and reduction steps which in turn gave an overall improvement in the yield. Hence, a total of 16 compounds were synthesised according to the optimised conditions in up to 85% yield, despite the formation of the ^{i}Pr adduct and any of the unreacted CF_3 ketone. Later, Funabiki and co-workers explored the synthesis of 1-trifluoromethylated propargyl alcohols using a similar reagent but instead utilised their proton abstraction ability (Scheme 10(B)).[115] In this case, the need for harsh bases like ^{n}BuLi for alkyne deprotonation was eliminated. Optimisation highlighted that CpMgBr was a superior Grignard reagent over the previously used ^{i}PrMgCl·LiCl. The bulkiness of the Cp group was proposed to enhance the yield through improvement of the final reduction step as well as limiting the formation of the unwanted alkylated adduct. Consequently, a range of aryl and alkyl containing terminal alkynes were utilised as starting substrates, giving the corresponding 1-trifluoromethylated propargyl alcohols in yields of up to 92%.



Scheme 10 The application of turbo Grignard reagents with fluoroalkyl esters to form (A) α-aryl-α-trifluoromethyl alcohols and (B) 1-trifluoromethylated propargyl alcohols.



Scheme 11 The conversion of a fluoroalkyl ester to an alkyne.

Furthermore, Liu and co-workers displayed the conversion of a fluorinated alkyl ester into an internal alkene through coupling of a fluoroalkyl ester with a *gem*-diborylalkane (Scheme 11).[116] The reaction has been shown to be facilitated by electrophilic enolate-O trapping followed by a deborylative elimination to furnish the desired alkyne (**71**). The fluorinated alkyl ester (**69**) was shown to be far more reactive than the corresponding Me and ^{t}Bu esters, giving almost quantitative yield at −50 °C. The perfluorinated aryl triflimide (**70**) served as the trapping reagent. In addition to the scope showing good substrate tolerance, the procedure allowed access to isotopically labelled ^{13}C-alkyne species.

4. Conclusions

The formation of fluorinated ester intermediates from carboxylic acids has seen a huge surge in development over recent years. Whilst these substrates offer an alternative to traditional carboxylic acid activation methods, they also present new utility as a spectroscopic handle during a reaction in the form of techniques such as ^{19}F NMR. In particular, the perfluoroaromatic and heteroaromatic reagents such as PFP and TFPN have been shown to exhibit good reactivity with weakly nucleophilic carboxylate

anions to allow for *in situ* reaction with a range of nucleophiles. Furthermore, whilst known transformations of carboxylic acids like amides and thioesters have been explored, fluorinated esters have also been used to develop reactions to access alkynes, CF_3 ketones and SCF_3 ketones to name a few. However, the further development of stable but more importantly, isolatable fluorinated esters is an area that requires further exploration to give more flexibility to the synthetic chemist's toolbox which already includes highly useful PFPh and HFIP analogues. Therefore, there is much scope for the generation of novel fluorinated reactive materials which are bench stable and can be added directly into reactions to give high coupling efficiency.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this highlight.

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