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Synthesis and applications of fluorinated, polyfluoroalkyl- and polyfluoroaryl-substituted 1,2,3-triazoles

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1,2,3-Triazoles and organofluorine substitutents are both important structural and functional motifs used in a range of applications. This review summarises the confluence of these two important moities and provides a comprehensive account of the methods for synthesising and applying fluorine-, polyfluoroalkyl- and polyfluoroaryl-substituted 1,2,3-triazoles. Focus has been devoted to recent examples and applications where the properties of both the 1,2,3-triazole and organofluorine substituent are proposed to be important in enhancing the compound's functionality.

1. Introduction

1,2,3-Triazoles are incredibly important motifs used in a range of fields due to their high thermal, chemical and biological stability. They possess two lone pairs available for bonding and have a relatively high dipole moment of >4 D,[1] leading to triazoles being both good hydrogen bond acceptors/transition metal ligands and good hydrogen bond donors. Based on these various properties, 1,2,3-triazole derivatives have found applications in drug discovery,[2] bioconjugation,[2a,3] carbohydrate,[4] peptide,[5] and DNA chemistry,[6] supramolecular chemistry,[7] polymer science[8] and sensing applications,[9] amongst others.[10]

The widespread application of 1,2,3-triazoles is also due to their ease of synthesis. The thermal azide–alkyne cycloaddition (AAC), originally reported by Michael[11] and later formalised and popularised by Huisgen,[12] provides simple access to 1,2,3-triazoles, however often as a mixture of regioisomers (Scheme 1A). In 2002, the groups of Meldal and Sharpless independently reported the use of a copper(I) catalyst that promotes the AAC reaction between azides and terminal alkynes at room temperature, and provides only the 1,4-regioisomer of

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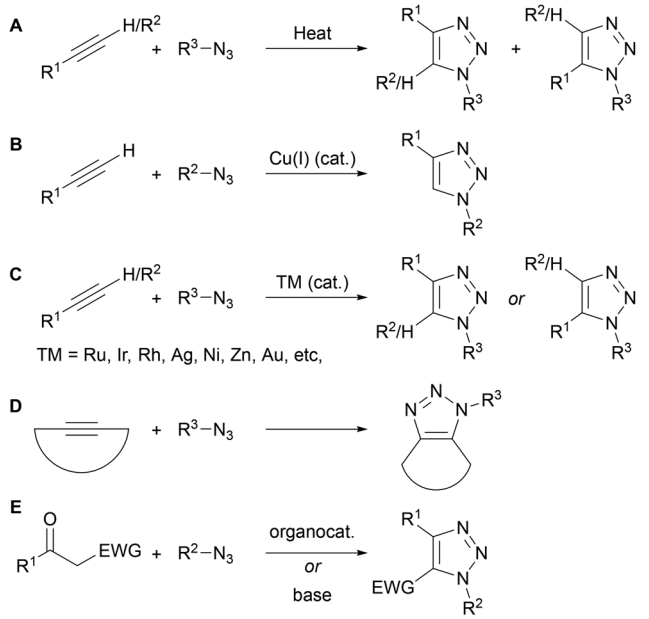
Jason L. Westwood

Jason L. Westwood was born in Birmingham and studied chemistry at the University of Warwick, obtaining a Bachelor of Science degree in 2022. He then completed a Master of Science by Research at the same institution, under the supervision of Dr Mark Greenhalgh. Currently, he is continuing his research for a PhD in organic chemistry in Dr Mark Greenhalgh's group at the University of Warwick.



Scheme 1 Synthetic approaches to 1,2,3-triazoles.

triazole product (Scheme 1B).[13] Following this seminal work, a wide range of transition metal catalysts (Ru, Ir, Rh, Ag, Ni, Zn, Au) have been reported for AAC reactions.[14] Depending on the catalyst, selective access to either the 1,4- or 1,5-regioisomer of triazole is now possible with both terminal and internal alkynes (Scheme 1C). The use of strained alkynes has also been used to accelerate the metal-free AAC reaction through strain release,[3b,c] with this approach particularly suited to bioconjugation strategies (Scheme 1D). Beyond AAC reactions, organocatalytic and base-mediated approaches to 1,2,3-triazoles have been reported from ketones and azides

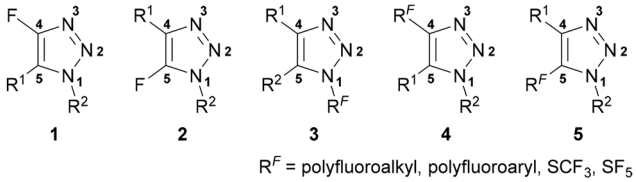


Fig. 1 Fluorinated triazole structures covered in this review.

(Scheme 1E).[14e,15] Finally, a range of azide-free approaches have been developed, which typically use hydrazine, hydrazone or diazo derivatives as the nitrogen-rich substrate.[14e,15b,c,16]

Organofluorine compounds have also attracted significant interest in a range of fields due to their unique physicochemical, electrochemical and biological properties, which are often distinct from their non-fluorinated analogues.[17] Many of these differences originate from the high electronegativity of fluorine which results in high dipole moments, low polarisability, small size and strong C–F bonds.[18] The main area of application is within medicinal chemistry,[19] where the introduction of fluorine impacts various pharmacological properties of the drug candidate, including membrane permeability, metabolic stability, lipophilicity, and binding affinity. Beyond medicinal chemistry, the unique properties of organofluorine compounds have also resulted in their application in agrochemicals[20] and functional materials.[17,21]

Combining the unique structural, chemical and biological properties of 1,2,3-triazoles and fluorine therefore provides great potential for applications across a range of fields.

Fluorine may be incorporated directly on the triazole ring at the C(4) (**1**) or C(5) (**2**) position, or alternatively polyfluoroakyl/aryl substituents may be incorporated at the N(1) (**3**), C(4) (**4**) or C(5) (**5**) position (Fig. 1). This review will provide a thorough summary of recent advances in the synthesis of these classes

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Henry Stone is originally from Oxfordshire and obtained an integrated MChem degree from the University of Warwick in 2022. Henry completed his final year Masters research project under the supervision of Dr Stefan Roesner and Prof. Mike Shipman on the stereoselective synthesis of 1,2-diazetidine-3-carboxylic acid derivatives for use in peptidomimetics. Currently, Henry is working as a PhD student in the Greenhalgh group on a project sponsored by GoldenKeys® High-tech Materials Co., Ltd.

Yingjian Xu

Prof. Dr Yingjian Xu CCHEM FRSC is the CEO of GoldenKeys® High-tech Materials Co., Ltd, and an Honorary Professor at the University of Warwick. After his BSc degree at Huaqiao University, he obtained a PhD in organic chemistry at University of Warwick under the supervision of Prof. Martin Wills, during which he developed of a series of patented XuPHOS catalysts. After a postdoctoral position with Prof. John Brown FRS (Oxford), he joined PhosphonicS. In late 2016, he started his own company, which specialises in organometallic catalysts, metal-ligating functionalised materials and molecular purification technologies for pharmaceutical and fine chemical industries.

of triazoles, in addition to an overview of their applications. Focus has been devoted to applications where the properties of both the 1,2,3-triazole and organofluorine substituent are proposed to play essential roles in the compound's functionality. Several specialised reviews have been released on aspects of the synthesis or applications of fluorinated triazoles,[22–24] however to the best of our knowledge no comprehensive review on the subject currently exists.

2. Synthesis of C(4) and C(5) fluorinated 1,2,3-triazoles

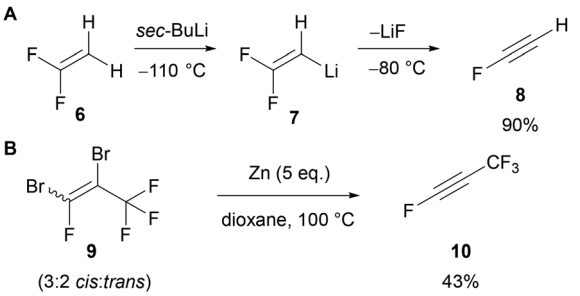
2.1. Introduction

The introduction of fluorine at the C(4) or C(5) position of a 1,2,3-triazole would ideally be achieved using a fluoroalkyne, however, these substrates are relatively difficult to synthesise and are typically unstable.[25] The earliest preparation of fluoroacetylene **8** was reported by Middleton and Sharkey in 1959 through the pyrolysis of monofluoro-maleic anhydride at high temperature (650 °C) and low pressure (5–7 mmHg).[26] In 1982, Sauvêtre reported that lithiation of 1,1-difluoroethylene **6** and subsequent β-elimination of LiF gave fluoroacetylene **8** (Scheme 2A). However, both fluoroacetylene **6** and the lithiated intermediate **7** are unstable and explosive.[26,27] In the same year Taylor[28] synthesised perfluoropropyne **10** through the debromination of dibromotetrafluoropropene **9** (Scheme 2B). Perfluoropropyne **10** was obtained by condensation at −196 °C. Due to the challenges of synthesising and handling fluoroalkynes, approaches to access 4- and 5-fluorotriazoles that avoid the use of a fluoroalkyne have been pursued.

Some traction has been gained in the use of fluoroalkyne surrogates to circumvent the use of unstable fluoroalkynes.[29] In general, these 'surrogates' are fluoroalkenes bearing an electron-withdrawing substituent which serves two purposes; (i) as an activating group to promote the initial reaction with an azide, and (ii) as a leaving group to provide the triazole in the final step (Scheme 3).

Mark Greenhalgh

Mark completed his Undergraduate degree at the University of Sheffield before moving to Bristol, and then Edinburgh, to complete a PhD with Stephen Thomas on iron-catalysed hydrofunctionalisation of alkenes and alkynes. Mark then moved to the University of St Andrews to conduct postdoctoral work with Andrew Smith on the development and mechanistic understanding of organocatalytic enantioselective methodologies. In April 2020, Mark moved to the University of Warwick as an Assistant Professor to start his independent research group and was promoted to Associate Professor in 2024. His group work on utilising unconventional non-covalent interactions for catalysis and drug discovery.

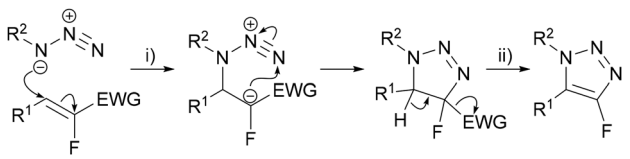


Scheme 2 Preparation of fluoroalkynes.

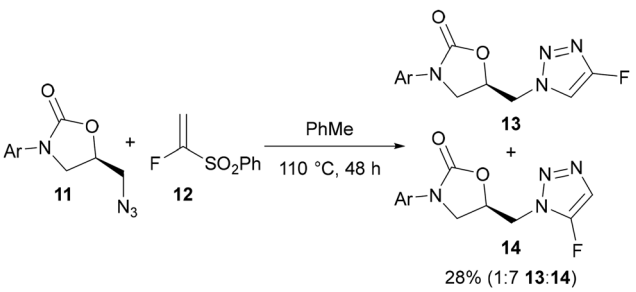
The first example of this 'surrogate' approach was reported by Reck in 2005,[29a] using α-fluorovinylsulfone **12** (Scheme 4). A thermal AAC reaction with oxazolidinone-functionalised azide **11** at 110 °C gave a 1 : 7 mixture of the 1,4- and 1,5-regioisomers **13** and **14** in a combined yield of 28%.

2.2. 4-Fluoro-1,2,3-triazoles

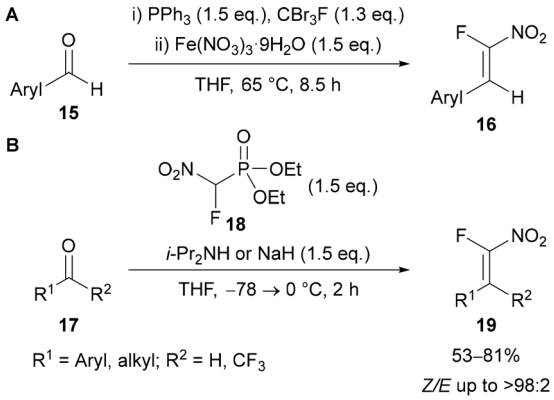
Building on Reck's initial work, Roy[29b] and Nenajdenko[29c] showed the efficiency and regioselectivity of these reactions can be improved by using an α-fluoronitroalkene **16** as a fluoroalkyne surrogate in combination with a Brønsted acid catalyst (Schemes 6 and 7). The preparation of α-fluoronitroalkenes **16** was achieved in a 'one-pot' process from a benzaldehyde derivative **15** *via* an α-fluorobromoalkene intermediate (Scheme 5A).[29b,30] It is worth noting that this procedure is only applicable for the synthesis of β-aryl α-fluoronitroalkenes **16** as



Scheme 3 Fluoroalkyne 'surrogate' approach.



Scheme 4 Cycloaddition-elimination using α-fluorovinylsulfone fluoroalkyne surrogate **12**.[29a]

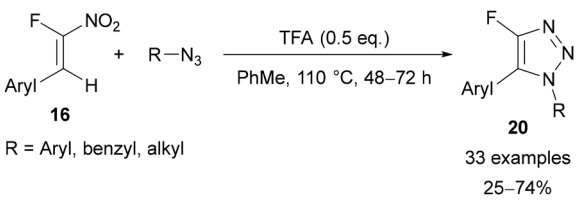


Scheme 5 Preparation of α-fluoronitroalkenes (A) *via* an α-fluorobromoalkene intermediate; (B) through a Horner–Wadsworth–Emmons approach.

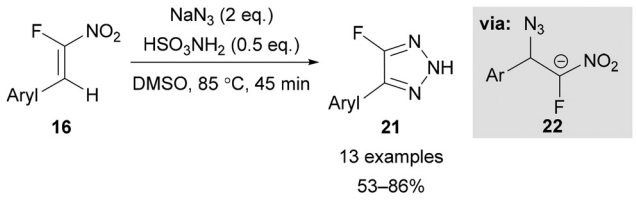
conversion of the α-fluorobromoalkene intermediate to the final nitroalkene product requires stabilisation of a radical intermediate by the aryl substituent. However, Beier has reported an alternative Horner–Wadsworth–Emmons approach using diethyl fluoronitromethylphosphonate **18** (Scheme 5B), which allows access to both β-alkyl- and β-aryl α-fluoronitroalkenes.[31] However, to the best of our knowledge these β-alkyl α-fluoronitroalkenes have not yet been applied for triazole synthesis.

Roy utilised β-aryl α-fluoronitroalkenes **16** for the regioselective preparation of 1,5-disubstituted-4-fluoro-1,2,3-triazoles **20** in good yields (Scheme 6).[29b] Through screening a range of Lewis and Brønsted acids, it was shown that regioselectivity and yield was significantly enhanced by using trifluoroacetic acid (TFA). This can be explained by the mechanism given in Scheme 3, where protonation of the electron-withdrawing nitro group can further promote regioselective product formation. A range of aryl- and alkyl-substituted azides were tolerated, however aryl azides bearing electron-withdrawing groups gave lower yields.[29b] α-Fluoronitroalkenes bearing β-aryl groups with *para*- or *meta*-substitution were tolerated, with those bearing electron-donating groups providing the highest yields.

Nenadjenko showed the addition of sodium azide to β-aryl α-fluoronitroalkene **16** in the presence of sulfamic acid led to the formation of 4-fluoro-1,2,3-N*H*-triazoles **21** (Scheme 7).[29c] Low nitroalkene concentration was necessary for a successful



Scheme 6 Synthesis of 1,5-disubstituted-4-fluoro-triazoles **20** from α-fluoronitroalkenes **16**.

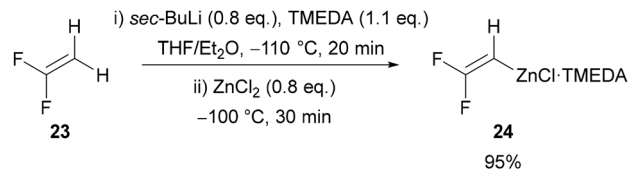


Scheme 7 Synthesis of 4-fluoro-N*H*-1,2,3-triazoles **21**.[29c]

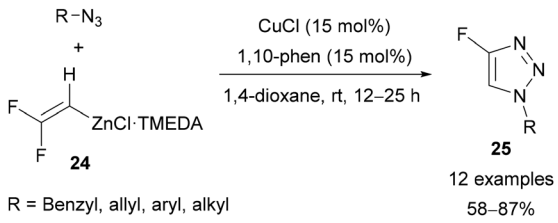
reaction, with this requirement suggested to minimise the polymerisation of proposed intermediate **22** (Scheme 7). In addition to activating the α-fluoronitroalkene to nucleophilic addition, sulfamic acid was also suggested to promote protonation of intermediate **22** to favour triazole formation over polymerisation. The N*H*-triazoles were isolated in good yields, and the reaction is tolerant of a variety of aryl substituents, except for those bearing electron-withdrawing groups, which were liable to undergo competitive anionic polymerisation.

Inspired by the work of Sauvêtre (Scheme 2A),[27] Ichikawa reported difluorovinylzinc *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) complex **24** as a thermally stable fluoroacetylene equivalent (Scheme 8).[32] Lithiation of 1,1-difluoroethylene **23**, followed by addition of zinc chloride and TMEDA gives difluorovinylzinc TMEDA complex **24** in excellent yield. The reagent was reported to be thermally stable, allowing it to be stored and used as a solution in THF/Et_2O. Ichikawa initially used this reagent in palladium-[32] and copper-catalysed[32,33] cross-coupling reactions with aryl, alkenyl, alkynyl, allyl, and benzyl coupling partners, before applying it in the formation of 4-fluoro-1,2,3-triazoles in 2020.[34]

In the presence of CuCl and 1,10-phenanthraline, Ichikawa demonstrated that difluorovinylzinc TMEDA complex **24** could be applied in the copper-catalysed synthesis of a variety of 4-fluoro-triazoles **25** in good yields (Scheme 9).[34] A range of substituted benzylic azides were tolerated; however, the appli-



Scheme 8 Preparation of difluorovinylzinc complex **24**.

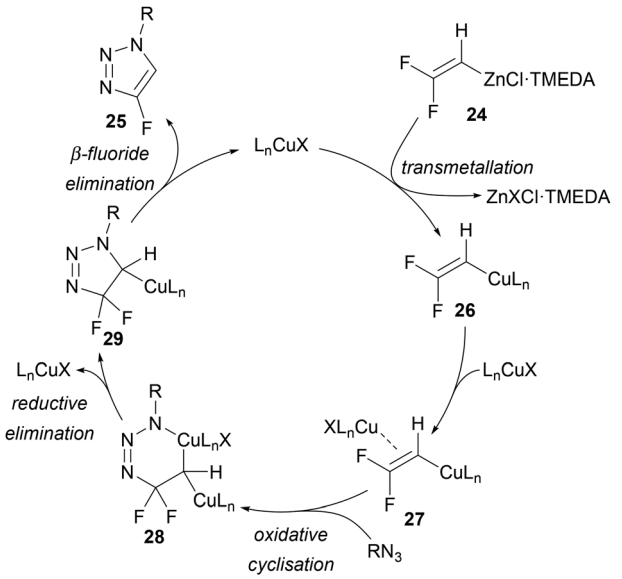


Scheme 9 Copper-catalysed synthesis of 4-fluoro-1,2,3-triazoles **25** from difluorovinylzinc TMEDA complex **24**.

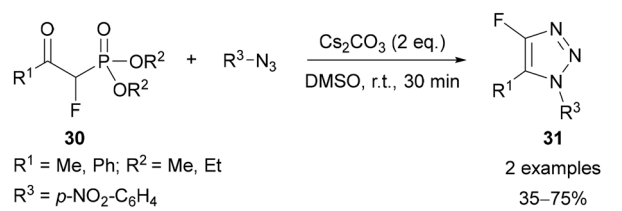
cation of aryl and allylic azides required the use of 2.5 eq. of **24** to achieve good yields.

A mechanism for this reaction was proposed to begin with transmetallation of **24** to give Cu–fluoroalkene **26**, followed by co-ordination of CuCl (Scheme 10). This allows for oxidative cyclisation to 6-membered metallocycle **28** followed by reductive elimination and β-fluoride elimination to give the triazole product **25**. The proposal of one σ-bonded Cu and one π-complexed Cu is in line with the mechanism described by Fokin for copper-catalysed alkyne–azide cycloadditions.[35] An alternative pathway through initial β-fluoride elimination to give *in situ* fluoroacetylene was considered but discounted through preliminary mechanistic experiments.[34]

Building on previous work on the reaction of β-ketophosphonates and azides to give 1,5-disubstituted triazoles,[36] Chou demonstrated that a range of 1,4,5-trisubstituted triazoles could be produced in the base-mediated reaction of α-substituted-β-ketophosphonates and azides.[37] Of the 35 examples reported, two demonstrated the introduction of a fluorine at the C(4) position of the triazole **31**, by using the appropriate α-fluoro-β-ketophosphonate **30** (Scheme 11).



Scheme 10 Ichikawa's proposed mechanism for the copper-catalysed synthesis of 4-fluoro-1,2,3-triazoles **25** from difluorovinylzinc TMEDA complex **24**.



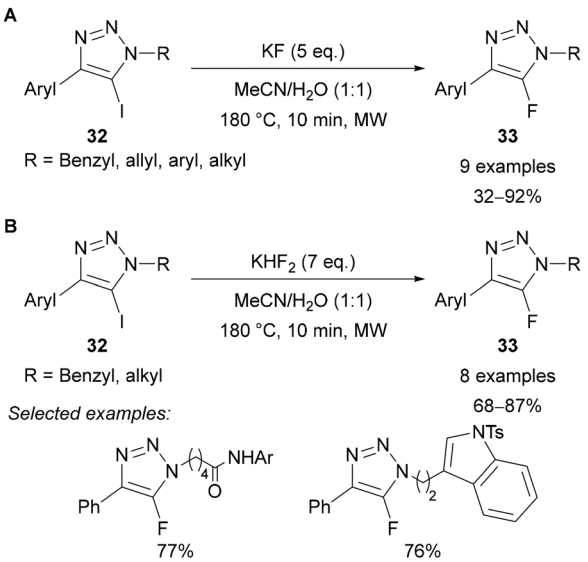
Scheme 11 Base-mediated synthesis of 4-fluoro-1,2,3-triazoles **31** from α-fluoro-β-ketophosphonates **30** and azides.

2.3. 5-Fluoro-1,2,3-triazoles

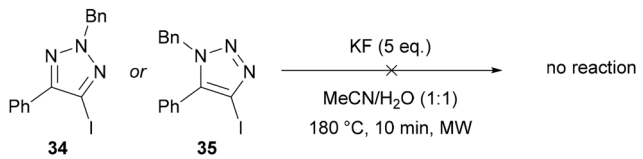
The synthesis of 5-fluoro-1,2,3-triazoles **33** has been exclusively achieved from 5-iodo-1,2,3-triazoles **32** through a so-called "halogen exchange" (Halex) reaction.[38] This approach was first reported by Fokin in 2012 using KF at 180 °C under microwave irradiation (Scheme 12A).[38] The reaction is tolerant of various functional groups in both the N(1) and C(4) positions, except for alkyl chains at C(4), which led to a complex mixture of products. Additionally, the high temperature required for this reaction led to decomposition over long reaction times. The work was extended to include amide, ketone, nitrile and *N*-*p*-toluenesulfonyl functional groups by using the acidic KHF_2 reagent in place of KF (Scheme 12B).[38]

Neither of the other regioisomers of iodotriazole (**34** or **35**) could be applied in this methodology, with >98% of the starting iodotriazole recovered in each case (Scheme 13).[38]

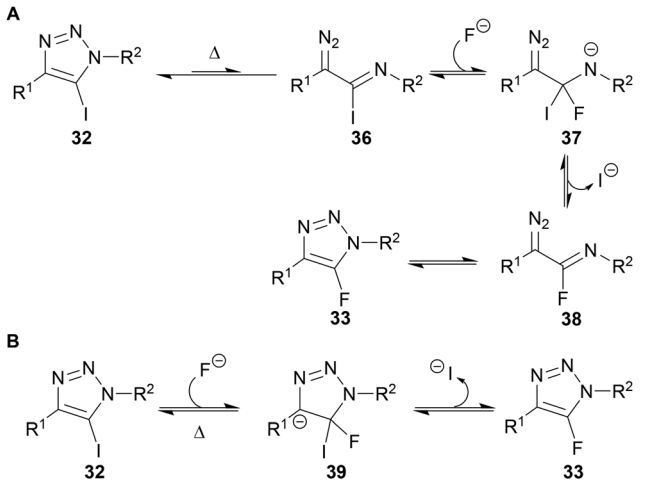
Since 5-iodotriazole **32** can undergo a Dimroth-like fragmentation through ring-chain isomerisation,[39] it was proposed the reaction may proceed *via* imidoyl iodide **36**, which could undergo iodide–fluoride exchange and ring-chain isomerisation to give 5-fluorotriazole **33** (Scheme 14A). This proposal is consistent with neither of the other regioisomers of iodotriazole being applicable in this reaction (Scheme 13) and is supported by the known reaction of imidoyl halides to give fluoride analogues under similar conditions.[40] Although this



Scheme 12 Halex reaction reported by Fokin[38] using (A) KF; (B) KHF_2.



Scheme 13 Alternative iodotriazole regioisomers unreactive under Halex reaction conditions.



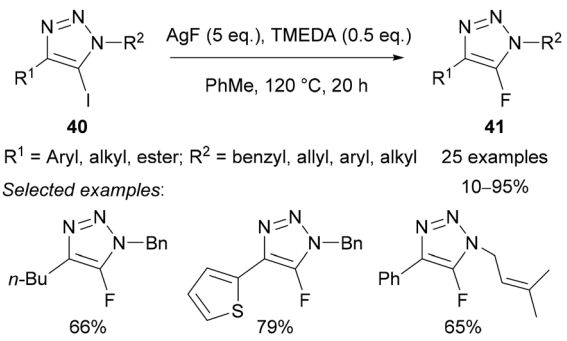
Scheme 14 (A) Fokin's proposed mechanism for Halex reaction; (B) alternative S_NAr mechanism.[38]

mechanism was favoured by the authors, they could not rule out the possibility of an S_NAr-type pathway (Scheme 14B).

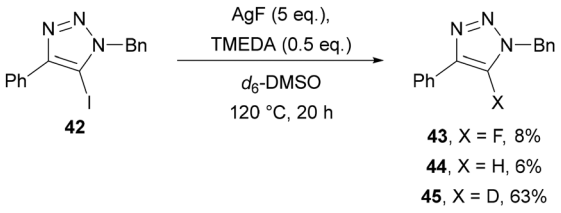
In 2015, Chu further developed the Halex reaction by demonstrating that AgF could be used as the fluoride source in the presence of TMEDA as a solubilising agent in toluene at reflux (Scheme 15).[41] This method was applicable to a wider substrate scope, in particular triazoles bearing C(4) alkyl substituents, which were not tolerated in Fokin's method using KF.[38]

Protodehalogenated triazole side-products were also observed, which prompted mechanistic studies using deuterated solvents. Using d_6-DMSO as solvent provided 63% of the deuterodehalogenated triazole **45** (Scheme 16), whilst the use of D_2O in DMF or MeCN led to 32% and 25% of triazole **45**, respectively. These studies indicated that the protodehalogenated side-product may form by intercepting an organometallic intermediate, hence, the need for strict exclusion of water in this transformation.

Replacing AgF with KF or CsF provided no conversion, indicating that silver is essential for this reaction. It was therefore proposed that, in contrast to Fokin's method using KF, AgF is



Scheme 15 Alternative Halex reaction conditions reported by Chu using silver fluoride.



Scheme 16 Deuteration studies.

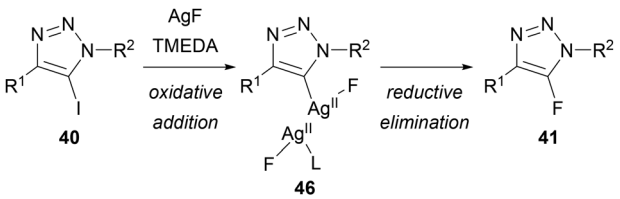
not simply providing a nucleophilic source of fluoride. Based on a related mechanism proposed by Ritter for the fluorination of stannanes,[42] Chu suggested that oxidative addition of silver into the carbon–iodine bond of **40** gives a bimetallic silver(II) fluoride intermediate **46**, which undergoes reductive elimination to give the triazole product **41** (Scheme 17).

3. Synthesis of C(4) and C(5) polyfluoroalkyl- and polyfluoroaryl-1,2,3-triazoles

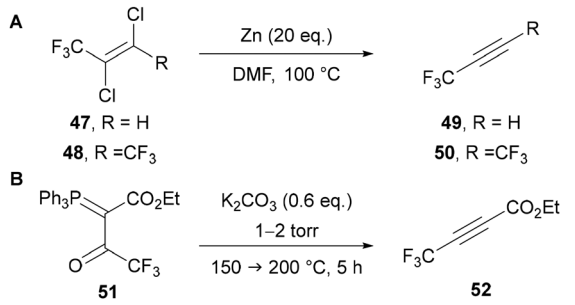
3.1. Introduction

The preparation of C(4) and C(5)polyfluoroalkyl-1,2,3-triazoles would be most easily attempted through the use of polyfluoroalkyl-substituted alkynes, however simple analogues are gaseous and potentially unstable species. In the 1960s, Norris[43] and then Moore[44] used the zinc mediated reduction of dichloroalkenes **47** and **48** for the preparation of 3,3,3-trifluoropropyne **49** and hexafluorobut-2-yne **50**, respectively (Scheme 18A). Hamper[45] also showed it was possible to prepare α-acetylenic esters through the vacuum pyrolysis of α-acylmethylenephosphorane **51** at 150–200 °C and 1–2 torr (Scheme 18B). This procedure specified the need for slow heating to ensure the unstable alkyne product **52** is not formed too quickly. The issues of thermal instability and difficult handling due to their gaseous nature are akin to those encountered with fluoroacetylene derivatives. Despite the challenges, Hamper's method is still used for the preparation of perfluoroalkyl-substituted α-acetylenic esters.[46]

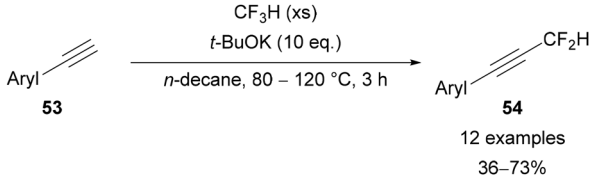
Shibata has reported the use of fluoroform as a source of difluorocarbene for the preparation of difluoromethyl-substituted alkynes **54** from phenylacetylene derivatives **53** (Scheme 19).[47] Under basic reaction conditions, fluoroform can be used as a source of the $^-CF_3$ carbanion, or as the more



Scheme 17 Mechanistic proposal for Chu's Halex reaction.[41]



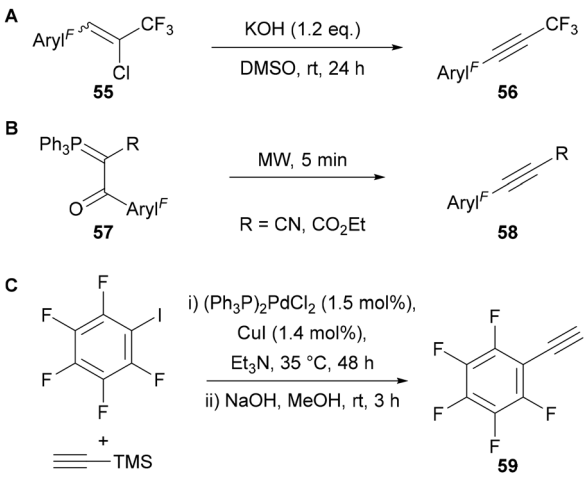
Scheme 18 Preparation of perfluoroalkyl-alkynes.



Scheme 19 Synthesis of CF_2H-substituted phenylacetylene derivatives.

stable difluorocarbene and a fluoride anion.[48] A range of difluoromethyl-alkynes can be synthesised by this method, including those bearing electron-rich and -poor arenes and heteroarenes.

In contrast to polyfluoroalkyl-substituted alkynes, polyfluoroaryl-alkynes are generally more stable and easier to prepare and handle, thus simplifying the synthesis of the corresponding polyfluoroaryl-1,2,3-triazoles. In 1991, Zanardi[49] showed that polyfluoroaryl-alkynes bearing a CF_3-substituent **56** could be synthesised by base-mediated elimination of HCl from the corresponding chloroalkene **55** (Scheme 20A). Adopting a similar approach to Hamper, Rao showed that β-oxo-alkylidenetriphenylphosphoranes **57** could be transformed to the corresponding polyfluoroaryl-alkynes **58** following just 5 minutes of microwave irradiation (Scheme 20B).[50] Finally, polyfluoroaryl-substituted alkynes, such as **59**, can be prepared from the corresponding polyfluoroaryliodide through a Sonogashira cross-coupling reaction (Scheme 20C).[51]



Scheme 20 Preparation of polyfluoroaryl-alkynes. $Aryl^F$ = polyfluoroaryl.

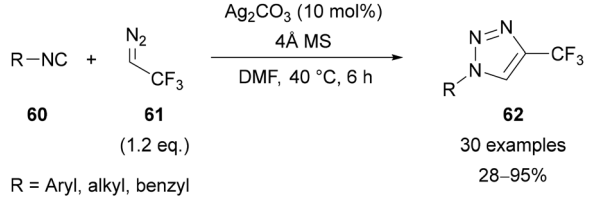
Due to the relative ease with which polyfluoroaryl-substituted alkynes can be accessed, the corresponding triazoles are generally synthesised using well-established metal-catalysed azide–alkyne cycloaddition reactions. As such, these synthetic methods have not been explicitly discussed in this review and the following sections will focus on the synthesis of polyfluoroalkyl-substituted triazoles. Examples of thermal AAC reactions have been reported for the synthesis of polyfluoroalkyl-substituted triazoles,[23a,b,44,46b,49,52] often giving mixtures of regioisomers. The following sections will therefore focus on a diverse range of specialised approaches that selectively provide access to a single regioisomer of triazole product.

3.2. 4-Polyfluoroalkyl-1,2,3-triazoles

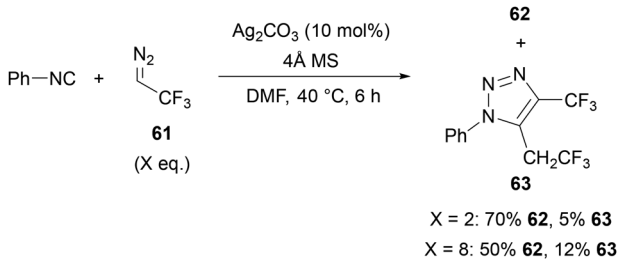
In 2015, Ma reported the silver-catalysed synthesis of 4-CF_3-1,2,3-triazoles **62** from isocyanides **60** and 2,2,2-trifluorodiazoethane **61** (Scheme 21).[52,53] It should be noted that low molecular weight diazo compounds are potentially explosive,[54] and previous explosions have been reported with 2,2,2-trifluorodiazoethane.[55] The approach proved to be regioselective and applicable to a variety of aryl isocyanides, bearing electron-donating and -withdrawing substituents in the *ortho*-, *meta*-, and *para*-positions. Adamantyl isocyanide was also tolerated, although cyclohexyl and *t*-butyl isocyanides gave only modest conversion to the triazole products.

Interestingly, it was reported that if two or more equivalents of the diazo reagent were used, 1,4,5-trisubstituted triazole **63** was isolated in up to 12% yield (Scheme 22). Treatment of the triazole product **62** with 2,2,2-trifluorodiazoethane **61** under the reaction conditions did not lead to the formation of 1,4,5-trisubstituted triazole **63**, indicating that this side-product is most likely formed prior to the formation of triazole **62**. Based on *in situ* ^{13}C NMR and IR monitoring, it was suggested that the isocyanide co-ordinates to the silver catalyst to give a silver (I) isocyanide complex,[56] which undergoes cycloaddition with 2,2,2-trifluorodiazoethane **61**. This provides a Ag-intermediate, which following protonation gives the product **62**. Alternatively, reaction of this Ag-intermediate with 2,2,2-trifluorodiazoethane **61** gives side-product **63**.

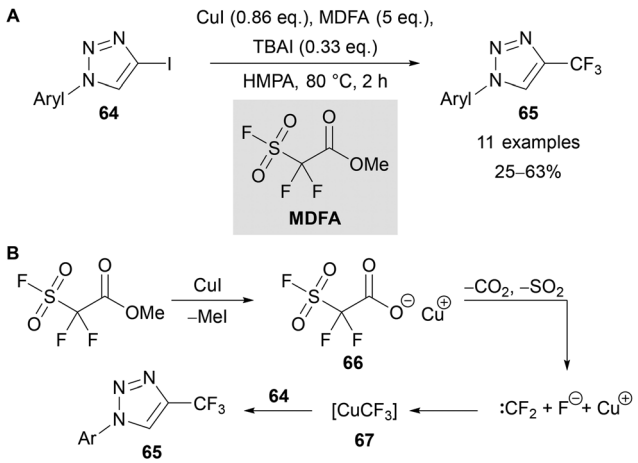
In 2020, Panja reported an alternative approach to prepare 4-trifluoromethyl-triazoles **65** through the copper-mediated



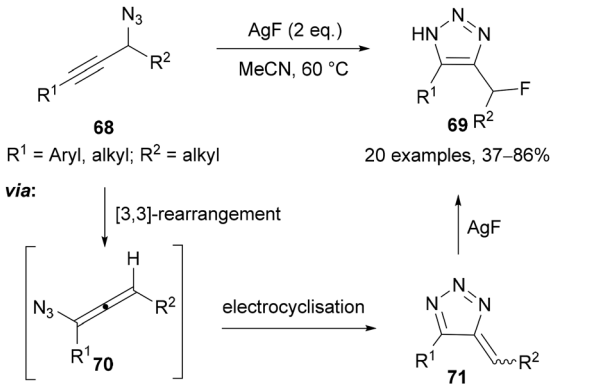
Scheme 21 Synthesis of 4-trifluoromethyl-triazoles from isocyanides and 2,2,2-trifluorodiazoethane.



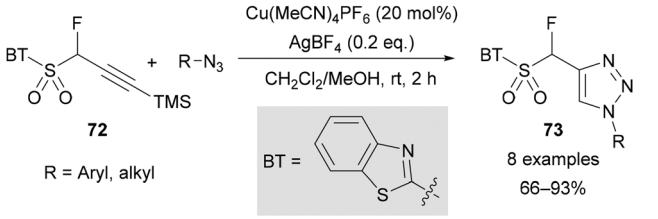
Scheme 22 Formation of side-product **63** in the presence of excess 2,2,2-trifluorodiazoethane **61**.



Scheme 23 Synthesis and proposed mechanism for the copper-mediated formation of 4-trifluoromethyltriazoles **65**.



Scheme 24 Banert cascade approach to α-fluoro-N*H*-1,2,3-triazoles **69**.



Scheme 25 Copper-catalysed synthesis of α-fluoro-benzothiazole sulfone-substituted triazoles.

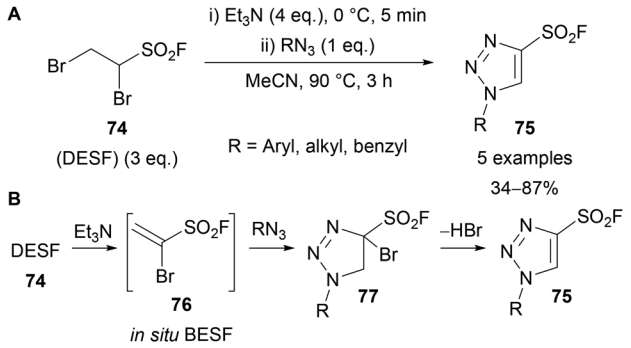
trifluoromethylation of 4-iodotriazoles **64** (Scheme 23A).[57] The use of CuI, methyl-2,2-difluoro-2-(fluorosulfonyl) acetate (MDFA, also known as Chen's reagent),[58] and tetrabutylammonium iodide (TBAI) gave the desired trifluoromethyl triazole products **65** in moderate yields. The reaction was proposed to proceed through demethylation of MDFA by iodide to give copper carboxylate complex **66** (Scheme 23B). Decarboxylation results in the loss of CO_2 and SO_2 to give difluorocarbene[59] and a fluoride ion, which can combine to form Cu–CF_3 intermediate **67**. Finally, this intermediate mediates the cross-coupling with iodotriazole **64** to give the trifluoromethylated triazole product **65**.[58,60]

Topczewski reported an interrupted Banert cascade reaction[61] for the preparation of α-fluoro-N*H*-1,2,3-triazoles **69** (Scheme 24).[62] Heating propargylic azide **68** at 60 °C was proposed to promote a [3 + 3]-sigmatropic rearrangement to give allene intermediate **70**, which undergoes electrocyclisation to triazafulvene **71**. Finally, nucleophilic addition of fluoride provides the α-fluoro-N*H*-1,2,3-triazole product **69** (Scheme 24).[62,63]

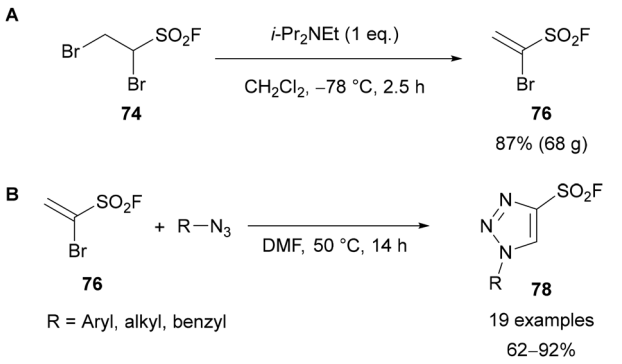
Zajc reported the synthesis of fluorinated 1,4-disubtituted-1,2,3-triazoles **73** from novel fluorinated benzothiazole sulfones **72** (Scheme 25).[64] This transformation involves silyl-deprotection followed by a copper-catalysed AAC reaction with aryl or alkyl azides. The benzothiazole sulfone-substituted triazoles **73** were subsequently applied in Julia–Kocienski olefination reactions (see section 6.2).[64]

In 2018, both Moses[65a] and Fokin[65b] used 1-bromoethenesulfonyl fluoride **76** (known as BESF or Br–ESF) as a synthetic equivalent for acetylenesulfonyl fluoride for the preparation of 4-sulfonyl fluoride-substituted 1,2,3-triazoles **75**. Sulfonyl fluorides are commonly applied reagents in SuFEx click reactions, used in a variety of fields and notably as biological probes.[66] Moses showed this reagent could be formed *in situ* by reacting 1,2-dibromoethane-1-sulfonyl fluoride **74** (DESF) with Et_3N for 5 minutes. Addition of an azide and heating to 90 °C, in the absence of any catalyst, provides the 4-sulfonyl fluoride-substituted triazole product **75** as a single regioisomer (Scheme 26A).[65a] Aryl azides bearing electron-donating and withdrawing groups were tolerated, however, no examples using alkyl azides were demonstrated. It was proposed that following *in situ* formation of BESF **76**, [3 + 2]-cycloaddition of the azide provides triazoline **77**, which following elimination of HBr gives triazole **75** (Scheme 26B). Moses also demonstrated the use of *in situ* generated BESF for the synthesis of isoxazoles and β-sulfams.

Fokin showed it was possible to synthesise and isolate BESF **76** on a 68 g scale by elimination of HBr from 1,2-dibromoethane-1-sulfonyl fluoride at −78 °C (Scheme 27A).[65a,67] In the absence of a catalyst, the reaction of BESF **76** with both aryl and alkyl azides gave a wide range of 4-sulfonyl fluoride-substituted 1,2,3-triazoles **78** in good yields (Scheme 27B).



Scheme 26 Preparation and proposed mechanism for the formation of 4-sulfonyl fluoride-substituted 1,2,3-triazoles.

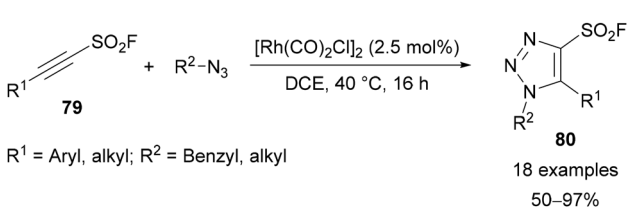


Scheme 27 (A) Large-scale synthesis and isolation of BESF **76**; (B) preparation of 4-sulfonyl fluoride-substituted triazoles **78** using BESF **76**.

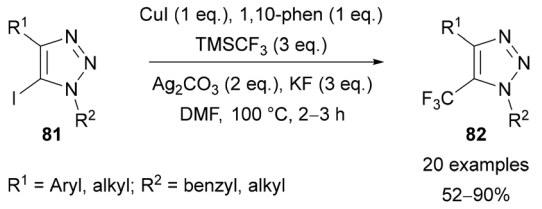
In 2020, Moses extended and improved on this approach with the development of alkynyl sulfonyl fluoride reagents **79** that were applied for the synthesis of 12 different classes of heterocycle.[68] Within this broad scope, the synthesis of 4-sulfonyl fluoride-substituted triazoles **80** was demonstrated through a Rh-catalysed AAC reaction (Scheme 28).

3.3. 5-Polyfluoroalkyl-1,2,3-triazoles

Beyond the use of thermal AAC reactions, efforts have been made to selectively install trifluoromethyl groups in the C(5) position of 1,2,3-triazoles, resulting in various methods published in recent years. An approach that is comparable to Panja's work[57] above was reported by Cao in 2013.[69] The



Scheme 28 Synthesis of alkynyl sulfonyl fluoride reagents **79** and application for synthesis of 4-sulfonyl fluoride-substituted triazoles **80**.

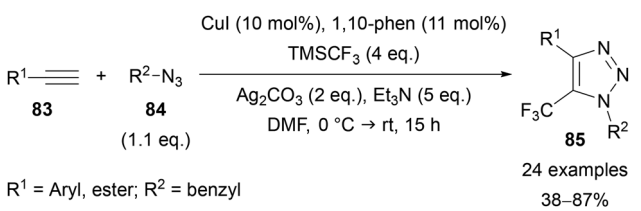


Scheme 29 Copper-mediated synthesis of 5-trifluoromethyl-substituted 1,2,3-triazoles **82**.

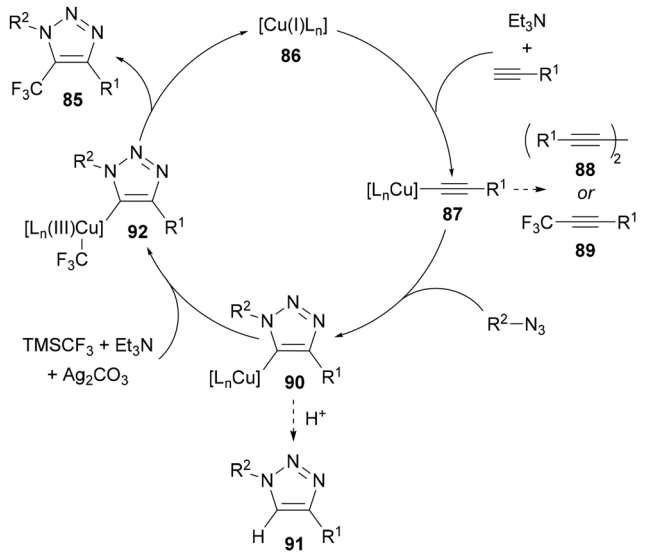
copper-mediated transformation of 1,4-diaryl-5-iodo-1,2,3-triazole derivatives **81** to the trifluoromethylated analogue **82** was achieved using $TMSCF_3$ (Ruppert–Prakash reagent)[70] as the trifluoromethyl source (Scheme 29). The method provides triazoles **82** in good yields and was demonstrated with both electron-neutral and -rich aromatics at the C(4) position and a range of *N*-benzylic and *N*-alkyl substituents.

Tsui published a related interrupted copper-catalysed AAC reaction to prepare 5-trifluoromethyl-1,2,3-triazoles **85** (Scheme 30).[71a] The cycloaddition of a range of alkynes with azides was achieved using a combination of CuI, 1,10-phenanthroline, $TMSCF_3$, Ag_2CO_3, and Et_3N. Alkynes bearing a range of aryl and ester substituents were tolerated, however only the use of benzylic azides was demonstrated. Improved yields were obtained when $TMSCF_3$ was added at 0 °C before warming the reaction to room temperature, with this approach proposed to slow down the decomposition of the reagent.

A catalytic cycle was proposed based on literature[72] with control reactions showing that formation of a CF_3-substituted internal alkyne **89** or the protonated triazole **91** prior to CF_3 substitution were not relevant for the productive catalytic cycle (Scheme 31). Following formation of copper acetylide **87**, in the absence of azide, formation of both diyne **88** and CF_3-alkyne **89** can occur. However, when an azide is present, cycloaddition with the copper acetylide gives cuprated triazole **90**, which can be protonated by water or protic solvent to form protonated triazole **91** as a side-product. Alternatively, reaction of cuprated triazole intermediate **90** with $TMSCF_3$ in combination with Ag_2CO_3-mediated oxidation, gives proposed copper(III) intermediate **92**. This copper(III) species can undergo reductive elimination to form the product and regenerate catalyst **86**.[71a] Zhu and Li reported a related process, where the silver oxidant used by Tsui was omitted, and the reaction was simply run in the presence of air.[71b] Of note, a specific glycinamide bis-tri-



Scheme 30 Interrupted copper-catalysed azide–alkyne cycloaddition for the synthesis of 5-trifluoromethyl-substituted 1,2,3-triazoles **85**.



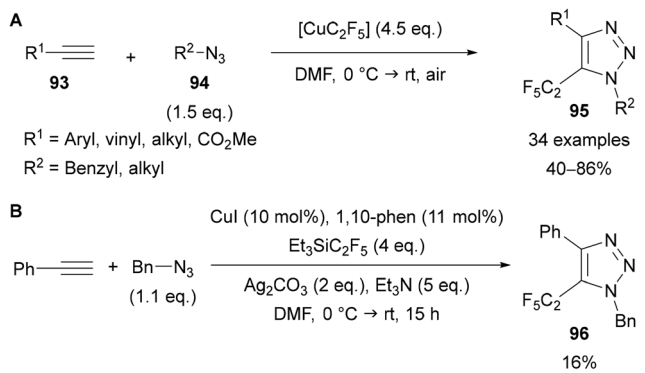
Scheme 31 Proposed catalytic cycle of interrupted CuAAC reaction.

azole ligand was required to obtain good selectivity for the trifluoromethylated triazole product over the protonated triazole side-product. The method was also demonstrated with longer chain perfluoroalkylsilanes and applied to a wider range of azides and alkynes than reported by Tsui.

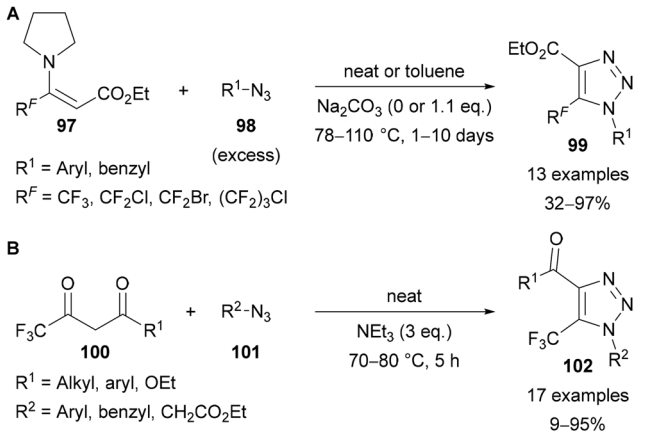
Building on their previous work,[71a] Tsui published an interrupted copper-mediated AAC reaction for the preparation of 5-C_2F_5-substituted triazoles **95** (Scheme 32A).[71c] This method requires the preparation of $[CuC_2F_5]$ from gaseous HCF_2CF_3, CuCl, *t*-BuOK and $Et_3N{\cdot}HF$ in a glovebox, however once the fluorinating agent has been prepared it can be used under aerobic conditions. Following a series of control experiments, it was proposed that the reaction proceeds in a similar manner to other interrupted copper-catalysed AAC reactions through formation of a 5-cuprated-triazole intermediate, which undergoes reductive elimination to install the C_2F_5 group. Interestingly, applying $Et_3SiC_2F_5$ under the conditions reported in their previous methodology for the synthesis of 5-trifluoromethyl-substituted 1,2,3-triazoles (see Scheme 30)[71a] led to only 16% yield of the C_2F_5-substituted triazole **96,** demonstrating the advantage of using CuC_2F_5 in this approach (Scheme 32B).

Beyond the use of copper-mediated couplings and cycloadditions, Zhu reported the formal [3 + 2] cycloaddition between tertiary enamines **97** and azides **98**[15] to give 5-polyfluoroalkyl substituted triazoles **99** (Scheme 33A).[73a] High temperatures and long reaction times were required, and the reactions were generally performed neat, with an excess of azide used as solvent. When benzyl azides were used the addition of sodium carbonate was also required. In a related base-mediated approach,[15] Bakulev showed that a range of 5-trifluoromethyl substituted triazoles **102** could be access from trifluoromethyl 1,3-diketones and β-ketoesters **100** in the presence of triethylamine as a Brønsted base (Scheme 33B).[73b] A range of 1,3-dicarbonyls were applicable, however only azides bearing electron-withdrawing groups gave good yields (for example *p*-$MeOC_6H_4N_3$: 12%; BnN_3: 9%).

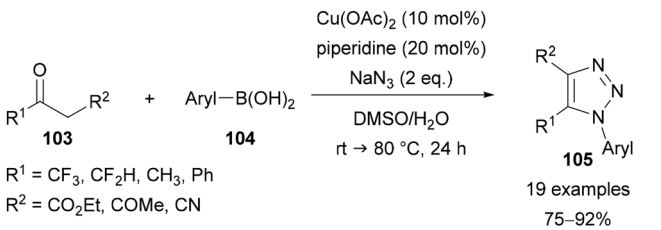
In 2013, Cao reported a combined copper- and piperidine-catalysed reaction of (hetero)aryl boronic acids **104**, ketones **103** and sodium azide for the preparation of 1,4,5-trisubstituted-1,2,3-triazoles **105** (Scheme 34).[73c] In this method, the aryl boronic acids **102** are converted to the corresponding aryl azides *in situ via* a copper-catalysed Chan–Lam coupling with sodium azide. Triazole synthesis can then take place through



Scheme 32 Copper-mediated synthesis of 5-C_2F_5-substituted triazoles **95**.



Scheme 33 Enamine and base-mediated synthesis of C(5)-polyfluoroalkyl-substituted triazoles.

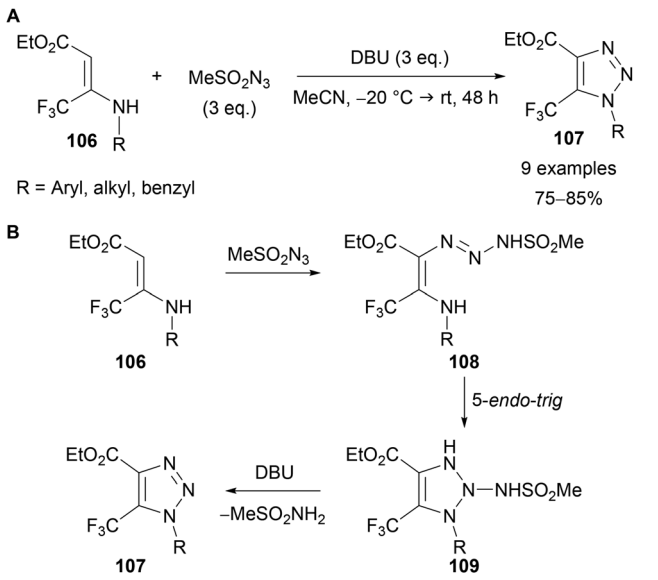


Scheme 34 Copper- and piperidine-catalysed synthesis of triazoles, through Chan–Lam coupling followed by CuAAC.

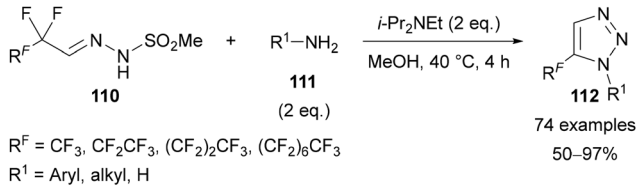
enamine catalysis.[15,74] The ketones used all required an anion-stabilising substituent in the β-position, such as another ketone, an ester or a nitrile. Of relevance to this review, trifluoromethyl and difluoromethyl ketones were applied to give CF_3 and CF_2H substituents in the C(5) position, in addition to fluorinated aryl N(1) substituents.[73c]

Tverdekhlebov has also demonstrated the preparation of 1-alkyl-5-trifluoromethyl-1,2,3-triazoles **107** through the reaction of secondary enamines **106** with mesyl azide in the presence of DBU (Scheme 35A).[75] Calculation of frontier orbital energies by Kascheres in 1993,[76] coupled with experimental data led to the following proposed mechanism (Scheme 35B). The nucleophilic enamine **106** reacts with electrophilic mesyl azide, which, following tautomerisation, gives intermediate triazine **108**. The electron-withdrawing methanesulfonyl group is necessary to lower the LUMO of the azide and promote this initial reaction.[76] An 'anti-Baldwin' 5-*endo-trig* cyclisation of the enamine nitrogen onto the triazine gives intermediate **109**, which following DBU-mediated elimination of methanesulfonamide provides triazole product **107**.

In 2021, Bi reported an alternative route to 5-polyfluoroalkyl triazoles **112** through the reaction of perfluoroalkyl *N*-mesylhydrazones **110** with amines **111** (Scheme 36).[77] This reaction was proposed to proceed by defluorinative condensation of the amine **111** with the perfluoroalkyl *N*-mesylhydrazone **110**, followed by cyclisation and elimination of methanesulfinic acid. A very large scope was reported, with triazoles **112** generally obtained in excellent yields. In addition to simple aryl and alkyl amines, complex natural products and bioactive molecules containing primary amines were also applied. The perfluoroalkyl *N*-mesylhydrazone substrates **110** were reported to be bench-stable solids that can be synthesised through the condensation of methanesulfonohydrazide and perfluoroalkyl aldehyde hydrates.



Scheme 35 Use of enamines **106** and mesyl azide for triazole synthesis (A) and proposed mechanism (B).

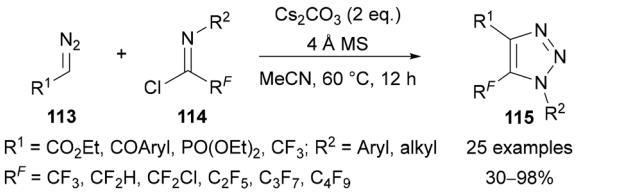


Scheme 36 Defluorinative [4 + 1] annulation of perfluoroalkyl *N*-mesylhydrazones **110** with primary amines **111**.

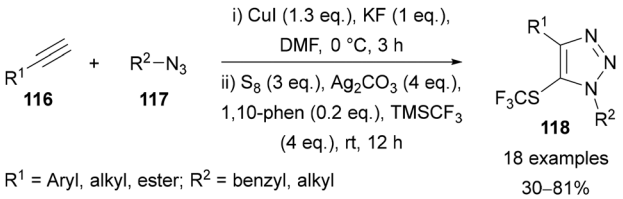
Wu has also reported an alternative approach to C(5)-polyfluoroalkylated triazoles **115** using diazo compounds **113** and polyfluoroalkyl-imidoyl chlorides **114** (Scheme 37).[78] A wide range of different polyfluoroalkyl substituents on the imidoyl chloride were demonstrated. While the *N*-substituent was generally aromatic, an example of an *N*-alkyl-substituted imidoyl chloride was also successfully applied. Ethyl diazoacetate was generally used, however other stabilised diazo compounds were demonstrated, including those bearing aryl ketones, phosphonates and a trifluoromethyl group. Although some diazo compounds are relatively unstable, this method provides access to triazoles that would be difficult to access through other routes, such as the example with CF_3 groups in both the C(4) and C(5) positions.

Interrupted copper-mediated AAC reactions have also been used for the synthesis of (5)-SCF_3-substituted triazoles **118** (Scheme 38).[79] A combination of Cu(I) iodide, elemental sulfur, $AgCO_3$ and $TMSCF_3$ was proposed to generate a $CuSCF_3$ reagent *in situ*, which can intercept the copper–triazole intermediate formed through the CuAAC reaction. The use of a range of both aryl and alkyl azides and alkynes was demonstrated to provide triazoles **118** in good yields.

Xu reported an interrupted CuAAC that allowed for the isolation of stable 5-stannyl-1,2,3-triazoles **119**, which could be reacted with a range of electrophiles and applied in cross-



Scheme 37 Synthesis of C(5)-polyfluoroalkylated triazoles **115** from diazo compounds **113** and polyfluoroalkyl-imidoyl chlorides **114**.



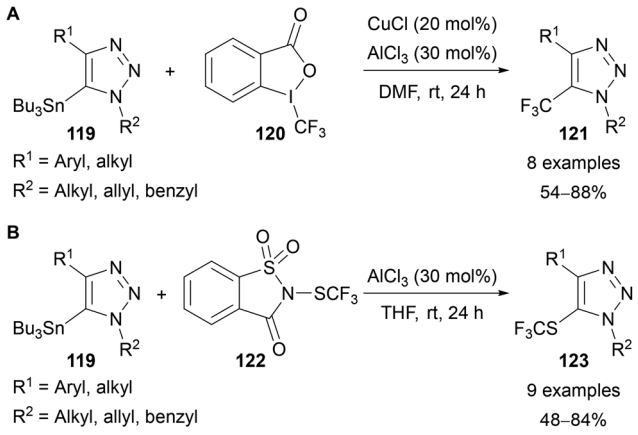
Scheme 38 Copper-mediated synthesis of 5-SCF_3-1,2,3-triazoles **118**.

coupling reactions.[80] The reaction of these 5-stannyl-1,2,3-triazoles **119** with Togni reagent II **120** or *N*-trifluoromethylthiosaccharin **122** provided access to a range of 5-CF_3 and 5-SCF_3 triazoles **121** and **122**, respectively (Scheme 39).[80]

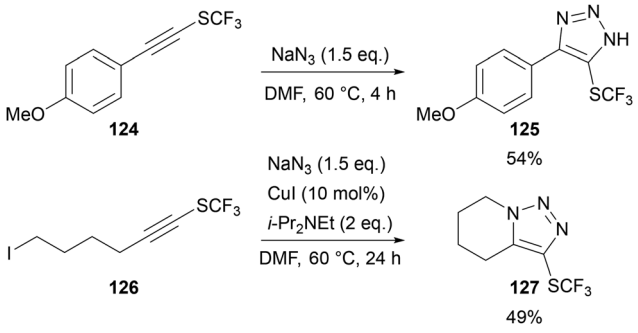
Billard reported an alternative approach to the synthesis of 5-SCF_3-triazoles **125** through the direct reaction of NaN_3 with a SCF_3-substituted alkyne **124** (Scheme 40).[81] A one-pot two-step cycloaddition–alkylation process was also demonstrated to give ring-fused triazole **127**.

More general access to 5-SCF_3-triazoles from SCF_3-substituted alkynes has been reported by Guo and Song using ruthenium and rhodium catalysis, respectively (Scheme 41).[82] Guo reported the use of both trifluoroethyl- and (trifluoromethyl) thiosubstituted alkynes (**128** and **129**) for the synthesis of 1,2,3-triazoles bearing a CH_2CF_3 or SCF_3 substituent in the C(5) position (Scheme 41A).[82a] The majority of examples focused on the use of trifluoroethyl-substituted alkynes **128**, with a range of both aryl and alkyl azides and aryl alkynes demonstrated. A significantly lower yield was obtained using an enyne substrate and no examples of alkyl-substituted alkynes were reported. Three examples of 5-SCF_3-triazoles **132** were also synthesised under analogous conditions with good yields obtained. The regioselectivity of the 5-CF_3CH_2-triazoles **131** was confirmed for several products by X-ray crystallography.

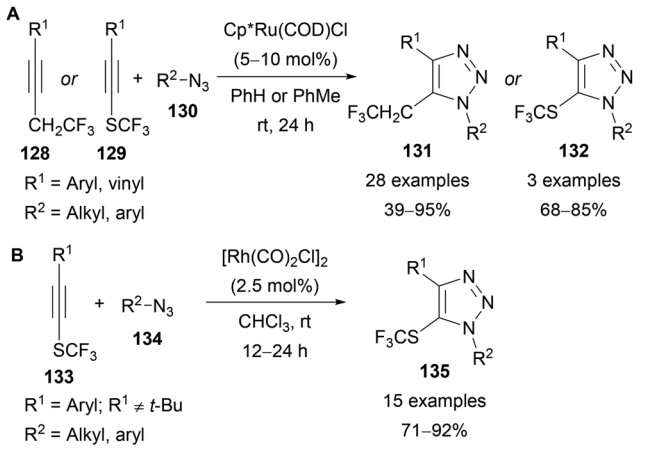
Song reported a complementary rhodium-catalysed AAC reaction of SCF_3-substituted alkynes **133**, where once again a range of alkyl and aryl azides were utilised, but only aryl-substituted alkynes were demonstrated (Scheme 41B).[82b] The only alkyl-substituted alkyne attempted (R^1 = *t*-Bu) gave no reaction, however Song also reported an extended scope of thio- and seleno-alkynes bearing alkyl and aryl substituents (*i.e.* not CF_3) where examples of alkynes bearing linear alkyl chains were also successfully demonstrated.



Scheme 39 Electrophilic fluorination of 5-stannyl-triazoles **119** with (A) Togni reagent II **120**; (B) *N*-trifluoromethylthiosaccharin **122**.



Scheme 40 Synthesis of 5-SCF_3-triazoles utilising NaN_3.



Scheme 41 Preparation of 5-CH_2CF_3 and 5-SCF_3-1,2,3-triazoles.

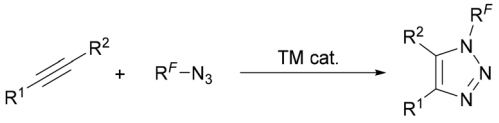
4. Synthesis of *N*-polyfluoroalkyl- and -aryl-1,2,3-triazoles

4.1. Introduction

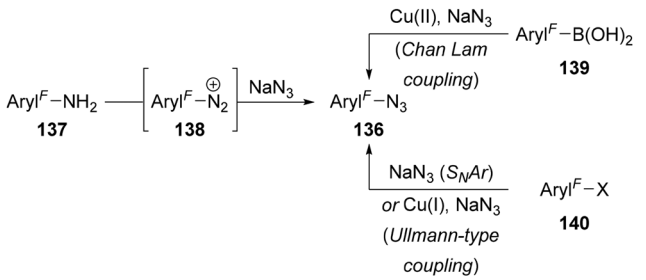
Whilst *N*-fluorinated 1,2,3-triazoles are known, their low stability means few syntheses or applications have been reported.[23a] The synthesis of *N*-polyfluoroalkyl- and aryl triazoles is much more common and is usually achieved through transition metal-catalysed AAC reactions (Scheme 42),[13,14] however other methods will also be discussed in this section. The main challenge therefore often lies in the synthesis of the polyfluoroalkyl- and aryl azides required for use in these AAC reactions.

4.2. Synthesis of polyfluoroaryl and -alkyl azides

Polyfluoroaryl azides **136** are readily accessed in several ways,[83] including from polyfluoroaryl amines **137** (*via* the diazonium salt **138**),[84] boronic acids **139** (through Cu(II)-catalysed Chan



Scheme 42 Common approach to synthesise *N*-polyfluoroalkyl- and aryl-substituted 1,2,3-triazoles. TM = transition metal.

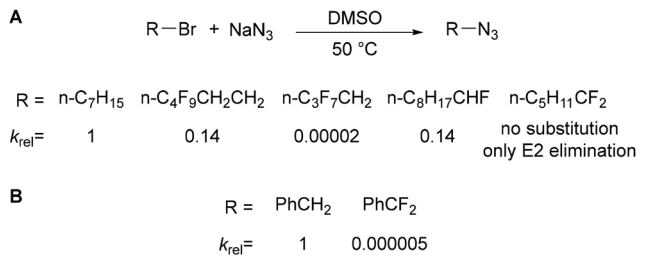


Scheme 43 General procedure for synthesis of polyfluoroaryl ($Aryl^F$) azides **136**.

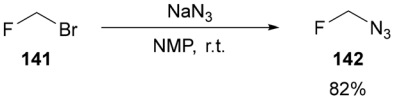
Lam coupling)[85] and halides **140** (through either S_NAr[86] or Cu (I)-catalysed Ullmann-type coupling)[87] (Scheme 43).

The synthesis of polyfluoroalkyl azides is significantly more challenging.[88] Alkyl azides are most conveniently synthesised by S_N2 substitution of a (pseudo)halide leaving group by azide,[83,89] however introduction of fluorine substituents on the alkyl chain severely inhibits nucleophilic substitution. Dolbier Jr has studied in detail the effect of fluorine substitution on the nucleophilic substitution of alkyl halides by sodium azide (Scheme 44A).[90] Comparing a simple alkyl bromide to γ- and β-fluorinated alkyl bromides revealed a significant deceleration in S_N2 rate upon introduction of fluorine close to the reaction centre [relative rates: *n*-$C_7H_{15}Br$ (1); *n*-$R^FCH_2CH_2Br$ (0.14); *n*-R^FCH_2Br (0.00002)]. Whilst introduction of single α-fluorine substituent on an alkyl chain is tolerated [relative rates: *n*-$C_7H_{15}Br$ (1); *n*-$C_8H_{17}CHFBr$ (0.14)], α,α-difluorinated substrates do not undergo substitution in MeOH and only undergo E2 elimination in DMSO. The reduction in the rate of substitution was proposed to originate from two main effects: (1) the inductive electron-withdrawing effect of fluorine destabilising the developing partial positive charge in the S_N2 transition state; and (2) electrostatic repulsion of the approaching nucleophile due to the lone pairs/electron density on fluorine.

In line with Dolbier Jr's kinetic studies, the synthesis of monofluoromethyl azide **142** is relatively simple to achieve from bromofluoromethane **141** and sodium azide in NMP at room temperature (Scheme 45).[91] The azide was obtained in quantitative yields and could be isolated by co-distillation with THF in 82%.



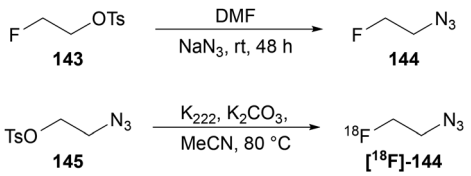
Scheme 44 Kinetic studies on the nucleophilic substitution of fluorinated alkyl bromides by azide.



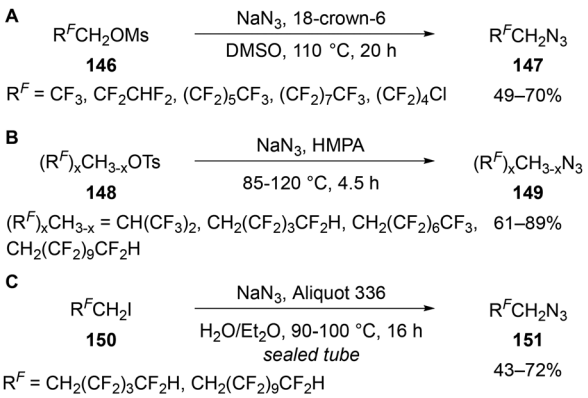
Scheme 45 Synthesis of monofluoromethyl azide **142**.

The preparation of 2-fluoroethyl azide **144** is also relatively simple through displacement of the respective tosylate **143** with sodium azide (Scheme 46).[92] Alternatively these azides can be accessed through displacement of a β-tosylated azide **145** by fluoride. This approach has been widely exploited for the synthesis of ^{18}F-labelled azide [^{18}**F**]-**144** using ^{18}F isotopically enriched KF (Scheme 46).[92,93]

As shown in Dolbier Jr's kinetic studies, the synthesis of β,β-difluorinated alkyl azides is considerably more difficult, with high temperatures and long reaction times often required. Wu and Chen have shown the synthesis of long chain polyfluoroalkyl azides **147** can be synthesised from the reaction of the corresponding alkyl mesylate **146** and sodium azide for 20 h at 110 °C in the presence of 18-crown-6 (Scheme 47A).[94] Koroniak-Szejn subsequently investigated the use of both alkyl mesylates and tosylates **148**, with the latter providing higher yields (Scheme 47B).[95] Shorter reaction times and reaction temperatures of 85 or 120 °C were achieved by using sodium azide in HMPA. Notably, the tosylate of hexafluoroisopropanol (HFIP) was applicable under these conditions to give a secondary alkyl azide. Koroniak-Szejn also reported a smaller range of alkyl iodides **150** were applicable when using sodium azide and Aliquot 336 (phase transfer



Scheme 46 Synthesis of isotopic 2-fluoroethyl azide.



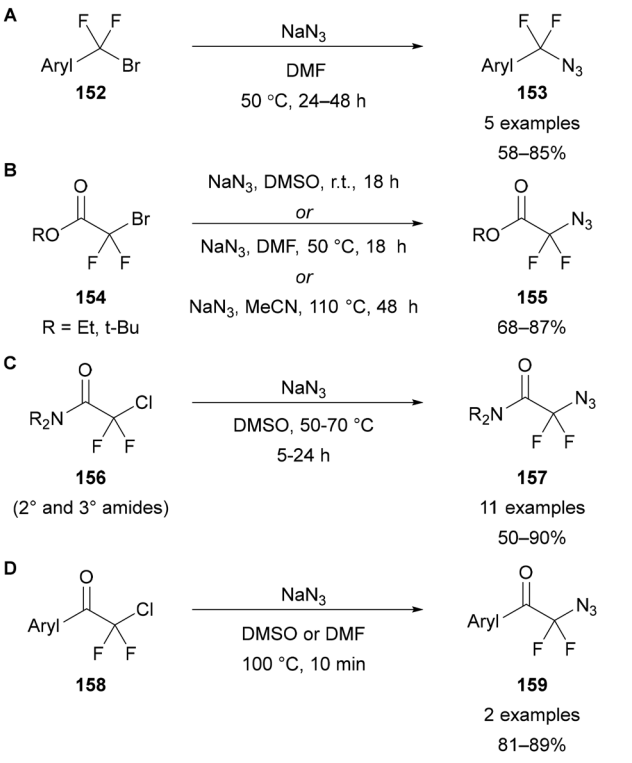
Scheme 47 General procedure for synthesis of 1,1-dihydro-fluroalkyl azides.

catalyst) in a water/Et_2O mixture in a sealed tube at 90–100 °C (Scheme 47C).[95] The yields obtained were generally lower, suggesting the methods from mesylate of tosylate substrates are the best option for the synthesis of these polyfluorinated azides.

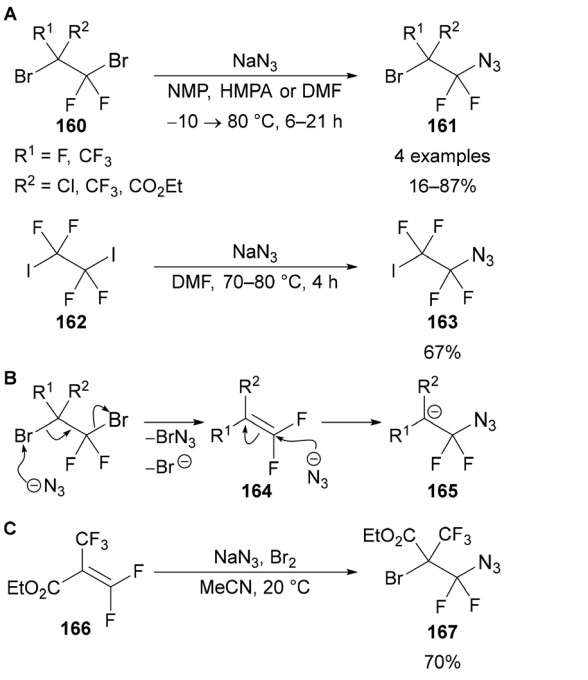
The only examples of α,α-difluorinated azides that can be synthesised through nucleophilic substitution are those bearing other activating groups, such as benzylic and α-carbonyl substrates (Scheme 48).[90,96] In these examples it is possible they may operate through a radical rather than S_N2 mechanism. Dolbier Jr reported the kinetics for the substitution of α,α-difluorobenzyl bromide with azide, with the relative rates for $PhCH_2Br$ and $PhCF_2Br$ measured as 1 and 0.000005, respectively (Scheme 44B).[90] As such, high reaction temperatures and times are required for this reaction (Scheme 48A).[96a] The original synthesis of ethyl 2-azido-2,2-difluoroacetate **155** (R = Et) was first reported at 50 °C in DMSO,[96b] however it has since been noted that these conditions can lead to an alternative substitution pathway to give ethyl azide and sodium bromodifluoroacetate.[96c,f] Alternative conditions in DMF or MeCN have also been reported,[96g,h] without the side-reaction being noted (Scheme 48B). Although yields have been reported, the α-azido ester is often simply used as a crude product in the next step of the synthesis. The use of sodium azide in DMSO at 50 °C has however been successfully used for the synthesis of the *tert*-butyl ester and amide analogues, where the same dealkylation side-reaction is not possible (Scheme 48B and C).[96c,e,f] α-Azido-α,α-difluoro amides **157** have also been synthesised by amidation of the corresponding ethyl or methyl ester.[96e,97] Finally, two examples of α-azido-α,α-difluoroketones **159** have been reported, in both cases starting from the corresponding α-chloroacetophenone derivative **158** (Scheme 48D).[98]

The apparent nucleophilic substitution of vicinal dibromo- and diiodofluoroalkanes (**160** and **162**) by sodium azide was reported by Knunyants in 1986 (Scheme 49A).[99] Based on previous work,[100] an ionic chain mechanism was proposed, in which the reaction is initiated by the attack of azide on bromine to form BrN_3, elimination of bromide and formation of alkene intermediate **164** (Scheme 49B). Addition of azide to alkene **164** forms anionic intermediate **165**, which can abstract another bromine from the substrate to propagate the chain mechanism.[101] Evidence for this mechanism was provided by similar yields being achieved through the reaction of one of the proposed alkene intermediates **166** with sodium azide and bromine, giving addition product **167** in 70% yield (Scheme 49C). This provides a general approach to the synthesis of fluorinated alkyl azides **169** from polyfluoroalkenes **168** by the addition of sodium azide in the presence of an electrophile (Scheme 50). This method has been applied using a range of electrophiles, including sodium dihydrogen phosphate (acid),[102] ICl,[103] aryl thiocyanates,[104] carbon dioxide[105] and perfluoroalkanoates[106] for the synthesis of diversely functionalised polyfluoroalkyl azides (Scheme 50).

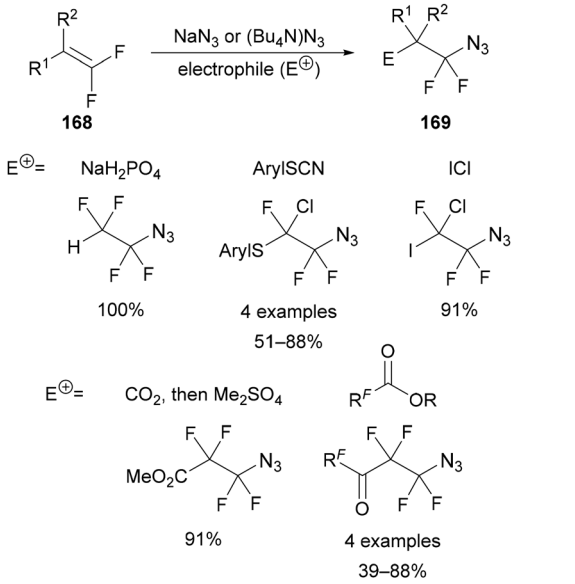
In addition to fluorinated alkenes, difluorocarbene is a suitable electrophile for reaction with sodium azide (Scheme 51). Originally described in a 1973 patent,[107] and again in 1985 by Bock,[108] base mediated decomposition of chlorodifluoro-



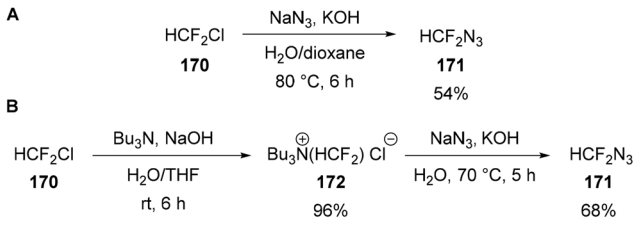
Scheme 48 Preparation of α,α-difluorinated benzylic and α-carbonyl azides.



Scheme 49 Synthesis of β-bromo- and β-iodo-fluoroalkylazides through an ionic chain mechanism.



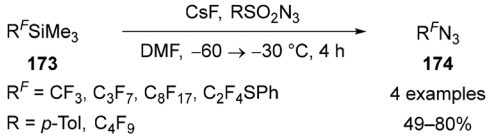
Scheme 50 General approach for the synthesis of β-functionalised fluoroalkylazides.



Scheme 51 Methods for the synthesis of difluoromethyl azide **171**.

methane **170** in the presence of sodium azide provides difluoromethyl azide **171** in 54% yield (Scheme 51A). More recently, Beier has shown that difluoromethyl azide **171** can also be accessed in a similar way *via* quaternary salt $Bu_3N^+(HCF_2)Cl^-$ **172** (Scheme 51B).[109]

Beier has reported a series of relatively simple methods for the synthesis of fluoroalkyl azides **174** through the nucleophilic fluoroalkylation of electrophilic azide sources. Treatment of the commercially available Ruppert–Prakash reagent **173** (R^F = CF_3) with caesium fluoride in DMF in the presence of tosyl azide provides trifluoromethyl azide **174** (R^F = CF_3) in high yield (Scheme 52).[110] The crude reaction product mixture has been applied in subsequent reactions, or the azide can be co-



Scheme 52 Synthesis of azidoperfluoroalkanes **174** through nucleophilic fluoroalkylation of sulfonyl azides.

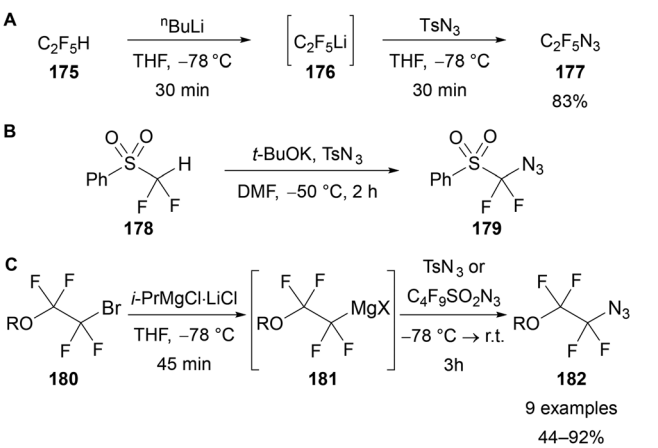
distilled with THF to produce a THF solution of the fluoroalkylazide product **174**. Trifluoromethyl azide is significantly more thermally stable than methyl azide, with explosive decomposition only reported over 330 °C.[111] Longer chain perfluoroalkyl azides could be prepared in a similar way, however in some cases the more electrophilic nonaflyl azide ($F_9C_4SO_2N_3$) was required as the azide source (Scheme 52).[110,112]

As an alternative to using trimethylsilyl-substituted polyfluoroalkanes **173**, polyfluoroalkyl azides can also be synthesised by formation of a polyfluoroalkyl carbanion equivalent through deprotonation (Scheme 53A and B),[110,113] or magnesium–halogen exchange (Scheme 53C),[112] followed by reaction with tosyl or nonaflyl azide.

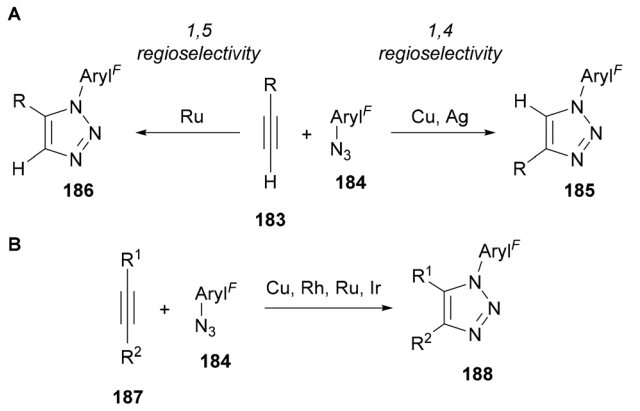
4.3. Synthesis of *N*-polyfluoroaryl-1,2,3-triazoles

N-Polyfluoroaryl triazoles are most often synthesised through a thermal or transition metal catalysed azide–alkyne cycloadditions (Scheme 54). Whilst thermal methods usually give mixtures of regioisomers, high regioselectivity can be achieved for one regioisomer by using a transition metal catalyst.[12–14] When using a terminal alkyne **183**, the vast majority of examples in the literature involving polyfluoroaryl azides **184** focus on the copper-catalysed synthesis of the 1,4-regioisomer **185**;[13] however there are also reports on using silver[114] and ruthenium[115] catalysts giving 1,4- and 1,5-regioselectivity (**185** and **186**), respectively (Scheme 54A). The use of internal alkynes **187** provides access to trisubstituted triazoles **188**, with examples of polyfluoroaryl azides **184** being used in copper (specifically for iodo- and telluro-alkynes),[116] rhodium,[117] ruthenium[82a,118] and iridium[119] catalysed AAC reactions (Scheme 54B).

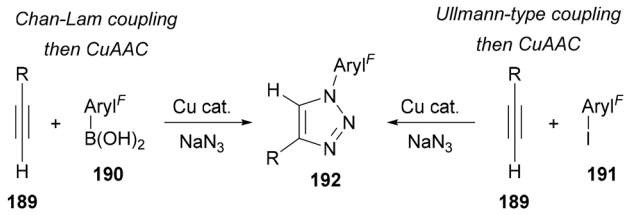
As previously outlined, aryl azides can be synthesised from aryl boronic acids and aryl iodides through copper-catalysed Chan Lam and Ullmann-type couplings, respectively (Scheme 43).[85,87] The telescoped copper-catalysed synthesis of triazoles through *in situ* generation of aryl azides from aryl boronic acids **190** or iodides **191** and subsequent CuAAC has



Scheme 53 Synthesis of azidoperfluoroalkanes **177**, **179** and **182** through nucleophilic fluoroalkylation of sulfonyl azides.



Scheme 54 Transition metal-catalysed azide–alkyne cycloaddition approaches for the synthesis of *N*-polyfluoroaryl triazoles.



Scheme 55 Telescoped copper-catalysed synthesis of *N*-polyfluoroaryl triazoles **192** from aryl boronic acids **190** and iodides **191**.

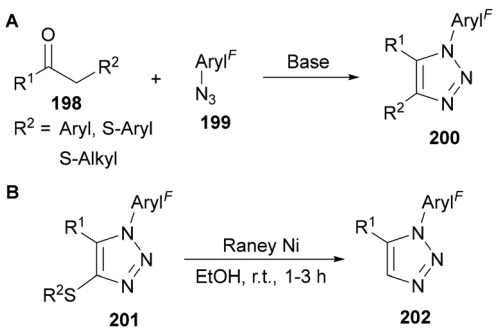
therefore been developed,[85a,120] with a range of examples including polyfluorinated aryl groups (Scheme 55).[121,122] This approach is convenient to avoid the synthesis and isolation of the aryl azide and is particularly suited to library synthesis where a large range of aryl boronic acids and iodides are commercially available.

Polyfluoroaryl azides **194** have also been applied in base- and secondary amine-catalysed synthesis of triazoles from 1,3-diketones, β-keto esters, amides and nitriles **193** (Scheme 56A).[73a,74,123] These reactions proceed *via* an enolate or enamine (in the case of secondary amines) intermediate that reacts with the electrophilic azide, followed by ring closing and elimination of water.[15] The electron-withdrawing nature of the polyfluoroaromatic group can therefore have a beneficial effect by increasing the electrophilicity of the azide. The ester-functionalised products **196** are particularly useful as hydrolysis followed by decarboxylation provides access to the less usual 1,5-disubstituted **197** triazole regioisomer (Scheme 56B).

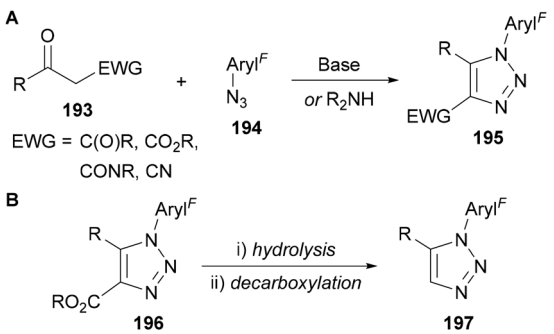
Other α-substituted ketones, where the α-substituent provides an acidifying effect can also be applied in these reactions, such as α-aryl and α-thioalkyl/aryl ketones **198** (Scheme 57A).[123h,124] The 4-thio-substituted triazoles **201** can also be converted into 1,5-disubstituted triazoles **202** through desulfurisation using RANEY® nickel (Scheme 57B).[124a]

Another approach to access 1,5-disubstituted triazoles **206** is through the addition of *in situ*-generated magnesium acetylides to azides (Scheme 58).[125–127] The azide acts as an electrophile in this reaction and therefore the use of azides bearing electron-withdrawing groups (such as polyfluorinated azides **204**) accelerate the reaction and provides high yields of triazole product. This is evidenced by the reaction with azides bearing electron-withdrawing groups being complete within an hour at room temperature, whereas azides bearing neutral or electron donating groups required 24–48 h to reach completion. This method also allows for the magnesiated triazole intermediate **205** to be trapped by a range of electrophiles to provide access to 1,4,5-trisubstituted triazoles **207**.

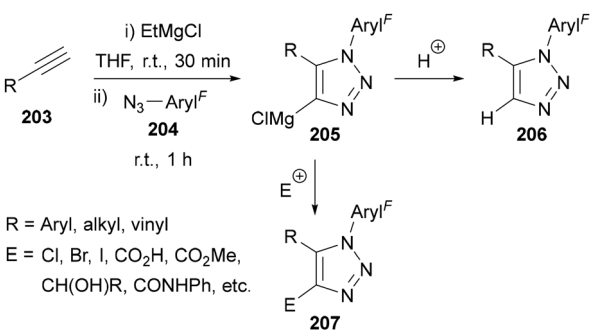
The magnesiated triazole intermediate **205** is apparently stable at high temperatures for long reaction times, however



Scheme 57 Base-catalysed synthesis of triazoles **200** from α-substituted ketones **198**.



Scheme 56 Base- and amine-catalysed synthesis of triazoles **195** from α-activated ketone derivatives **193**.



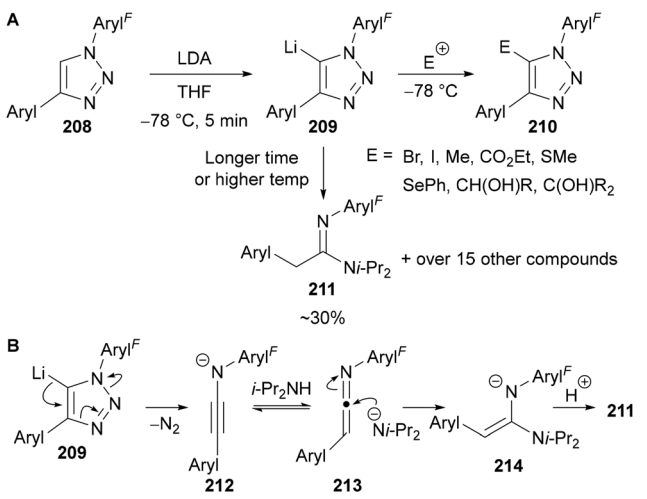
Scheme 58 Synthesis of 1,5-di- and 1,4,5-trisubstituted triazoles **206** and **207** from magnesium acetylides.

metalated triazoles of the other triazole regioisomer are known to be unstable when bearing electron-withdrawing *N*-substituents. 1,4-Disubstituted triazoles bearing *N*-polyfluoroaryl groups **208** were shown to undergo rapid deprotonation with lithium diisopropylamide (LDA) at −78 °C, with the lithiated intermediate **209** subsequently trapped at −78 °C with a variety of electrophiles (Scheme 59A).[128] However if the lithiated intermediate **209** was left for extended times or allowed to warm above −78 °C, rapid decomposition led to over 15 compounds, including amidine **211**. Based on related literature on *N*-phenyl- and *N*-sulfonyl triazoles,[129] it was believed that the electron-withdrawing *N*-substituent accelerates nitrogen extrusion through stabilisation of the intermediate acetylenamide **212** (Scheme 59B). Protonation, followed by nucleophilic attack by LDA provides the amidine product **211** upon protonation during reaction work-up.

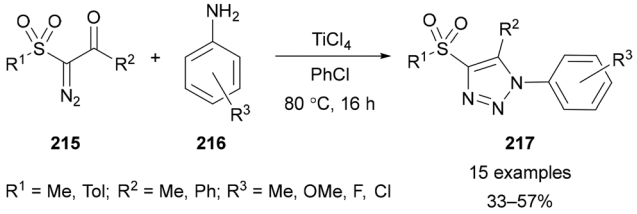
Avoiding the use of azides,[16] the cyclocondensation of α-diazoketones and amines provides access to triazoles.[130] This approach is sometimes referred to as the Wolff triazole synthesis.[131] Typically, an α-electron-withdrawing group and a Lewis or Brønsted acid is required to promote condensation of the amine and ketone. In 2019, Krasavin reported an example of this approach using sulfonyl-substituted α-diazoketones **215** and anilines **216**, in which examples using fluorinated aniline derivatives were demonstrated (Scheme 60).[132] Presumably fluorinated aniline derivatives could also be applied in other Wolff triazole syntheses,[130] however to the best of our knowledge this has not been reported.

4.4. Synthesis of *N*-polyfluoroalkyl-1,2,3-triazoles

Thermal azide–alkyne cycloaddition (AAC) reactions between polyfluoroalkyl azides and terminal and internal alkynes have been reported at 90–140 °C to give *N*-polyfluoroalkyl triazoles.[133] In the case of terminal alkynes, low regioselectivity was generally reported. The most common method to synthesise *N*-polyfluoroalkyl triazoles is through CuAAC reactions,



Scheme 59 Formation, trapping and decomposition of lithiated triazoles **209** bearing *N*-polyfluoroaryl groups.



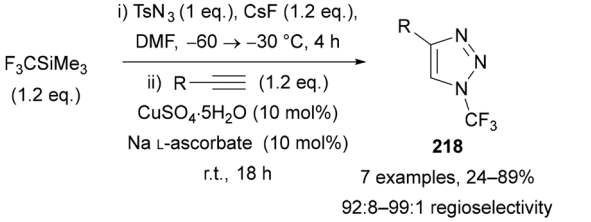
Scheme 60 Triazole synthesis *via* Wolff cyclocondensation.

with nearly all examples in the literature synthesised this way. There is also a single example of a RuAAC reaction between thioalkynes and polyfluoroalkyl azides,[134] demonstrating that this metal/fluorinated azide combination is tolerated.

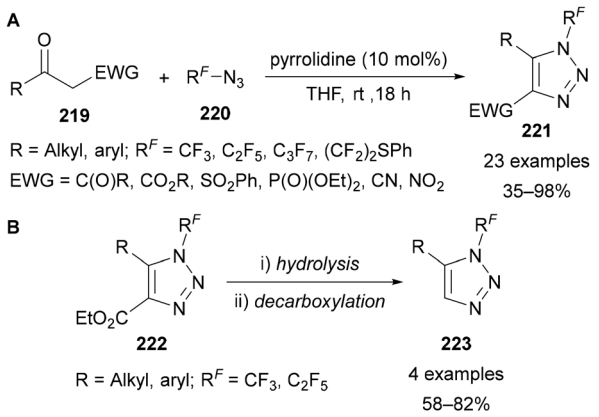
Beier has demonstrated that perfluoroethyl azide reacts twice as fast as ethyl azide with a terminal alkyne in a CuAAC reaction.[110] As previously mentioned, short-chain perfluoroalkyl azides can be co-distilled with THF to allow isolation as a THF solution, however Beier also demonstrated that the crude perfluoroalkyl azide can be directly applied in a CuAAC reaction (Scheme 61).[110] This method significantly simplifies their application for the synthesis of *N*-polyfluoroalkyl triazoles **218** and removes any operational concerns about azide distillation; however in some cases the regioselectivity of triazole formation was slightly lower than when using the purified azide.

In addition to applications in CuAAC reactions,[91,101,102,109,110,112,113,135] Beier has demonstrated the use of polyfluoroalkyl azides **220** in an enamine-catalysed synthesis of triazoles **221** from 1,3-diketones and β-keto esters, sulfones, phosphonates, nitriles and α-nitroketones **219** (Scheme 62A).[136] The hydrolysis and decarboxylation of a select number of 4-ester-substituted products **222** was demonstrated to provide access to 1,5-disubstituted triazoles **223** (Scheme 62B). This approach is therefore complementary to the 1,4-disubstituted products obtained through CuAAC reactions.

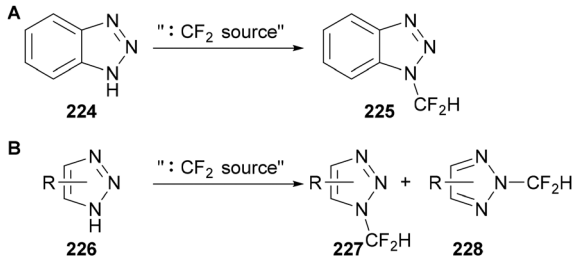
The direct fluoroalkylation of triazoles and benzotriazoles has been reported through a range of approaches.[23b] The difluoromethylation of triazole and benzotriazole derivatives has been reported using a range of difluorocarbene precursors.[137] Although the alkylation of benzotriazole **224** is regioselective (Scheme 63A), the alkylation of triazole derivatives **226** generally provides a mixture of the 1- and 2-difluoromethylated products **227** and **228** (Scheme 63B).



Scheme 61 One-pot synthesis of *N*-trifluoromethyl triazoles **218**.

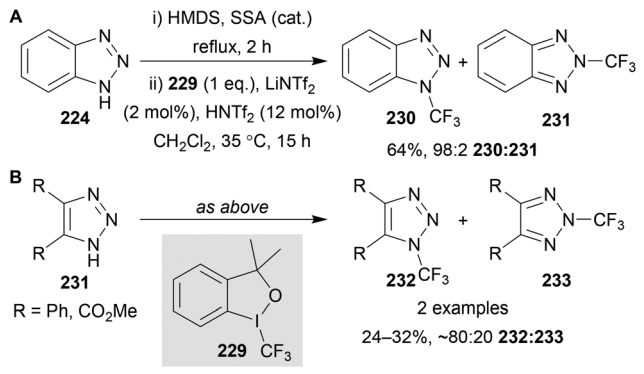


Scheme 62 Preparation of 1,4,5-trisubstituted *N*-polyfluoroalkyl triazoles **221** and subsequent decarboxylation to access 1,5-trisubstituted *N*-polyfluoroalkyl triazoles **223**.



Scheme 63 Difluoromethylation of triazoles using difluorocarbene precursors.

N-Trifluoromethylation of a range of azoles has been reported by Togni using Togni reagent I **229**.[138] Examples of benzotriazole and triazole *N*-trifluoromethylation was included in the reaction scope (Scheme 64). The *in situ* *N*-silylation of the azole substrate was achieved using hexamethyldisilazane (HMDS) and catalytic silica-supported sulfuric acid (SSA) at reflux. Following removal of excess HMDS, the addition of Togni reagent I **229** and sub-stoichiometric $HNTf_2$ and $LiNTf_2$ gave high N(1) regioselectivity for the trifluoromethylation of benzotriazole **224** (Scheme 64A), however when using triazoles **231** a mixture of both the N(1)- and N(2)-trifluoromethylated triazoles **232** and **232** was obtained (Scheme 64B).



Scheme 64 *N*-Trifluoromethylation of triazoles using Togni reagent I **229**.

Wang has also reported the use of hypervalent iodine-mediated trifluoromethylation for the synthesis of *N*–CF_3 azoles.[139] Inspired by earlier work from Togni,[140] Wang showed that trifluoromethylation of nitriles **234** could be efficiently achieved using $PhICF_3Cl$ **235**,[141] with the nitrilium intermediates trapped and isolated as DMAP salts **236**.[139] Wang has subsequently applied this strategy in a range of applications,[142] including formal [3 + 2] cycloadditions with diazo compounds **237** to give a range of *N*–CF_3 triazole products **238** (Scheme 65).[139]

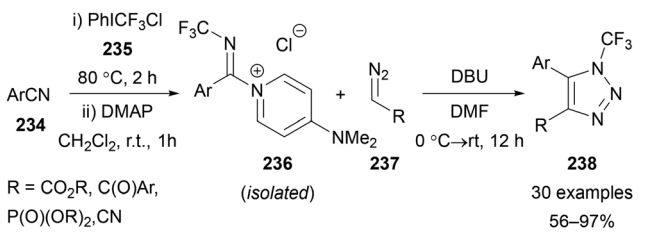
5. Applications of C(4) and C(5) fluorinated 1,2,3-triazoles

5.1. Pharmaceutical applications

Two recent patents have been published concerning the use of 5-fluoro-1,2,3-triazoles within drugs for cancer treatment. In 2017, Gilead Sciences prepared compounds such as **239** (Fig. 2)[143] to test against the cancer Osaka thyroid (COT) protein, which is involved in the formation of tumour necrosis factor α: a cytokine also involved in inflammatory diseases such as diabetes, sepsis and multiple sclerosis. Interestingly, the triazole C(5) substituent was shown to be important, as changing from a proton to either an iodine or fluorine atom improved the IC_{50} value by a factor of $\sim 10^4$. The C(5)-fluorinated triazole was synthesised from the iodine analogue using Fokin's Halex methodology.[38]

In 2019, Idorsia Pharmaceuticals prepared drug candidates **240** to inhibit two key dioxygenases (Fig. 3),[144] which are involved in catalysing the kynurenine pathway causing tryptophan degradation. This pathway is prevalent in various cancers to create an immunosuppressed environment which is key to their growth. In this example, Chu's Halex reaction conditions[41] were used to prepare the fluorinated derivative, and whilst the addition of a C(5)-fluorine did not reduce the IC_{50} value compared to the iodinated or protonated analogues, the value is in the low nanomolar range and thus still represents a good candidate for the inhibition of these enzymes.

A patent from Dogma therapeutics was released in 2020 using fluorinated-1,2,3-triazoles in compounds targeting pro-



Scheme 65 Synthesis of *N*-CF_3 triazoles **238** from DMAP-stabilised nitrilium salts **236** and diazo compounds **237**.

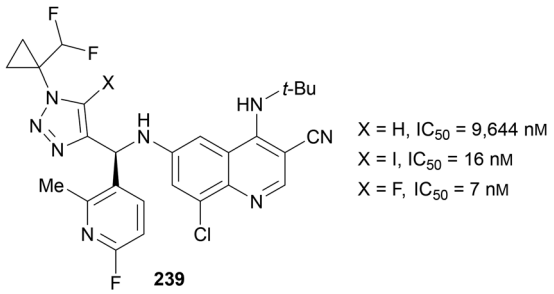


Fig. 2 5-Fluoro-triazole-containing COT treatments.

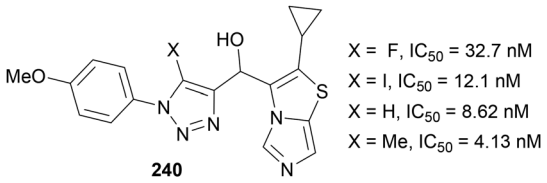


Fig. 3 5-Fluoro-triazole-containing dioxygenase inhibitors.

protein convertase subtilisin/kexin 9 (PCSK9), which is important in cholesterol metabolism.[145] Inhibiting PCSK9 is important in treating conditions such as cardiovascular disease and sepsis/septic shock. Triazole containing candidate **241** (Fig. 4) was one of the promising compound scaffolds, giving good K_D values for the C(5) protonated and fluorinated analogues. Again, Fokin's Halex reaction[38] was used for late-stage fluorination of the iodinated analogue.

In 2018, Abell reported the use of 5-fluoro-1,2,3-triazoles for the inhibition of biotin protein ligases (BPL) present in *Staphylococcus aureus* bacteria.[146] It was found that the presence of a fluorine atom in inhibitor compound **242** decreased the minimum inhibitory concentration (MIC) drastically to within clinical levels (>100 μM to 16 μM, Fig. 5). Further cell studies determined the likely reason for this was increased uptake of the compound into the cell meaning a higher concentration was present allowing for greater inhibition of BPL across the whole cell. Importantly, this did not affect the cytotoxicity against healthy HepG2 liver cells indicating this compound would be an ideal drug candidate. Abell also demonstrated that *N*-benzyl-5-fluoro-1,2,3-triazoles **243** were also effective against *S. aureus* whilst not being cytotoxic to human cells.

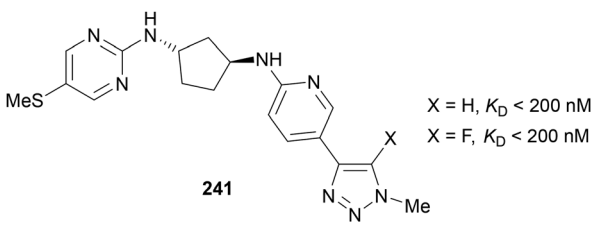


Fig. 4 5-Fluoro-triazole-containing PCSK9 inhibitors.

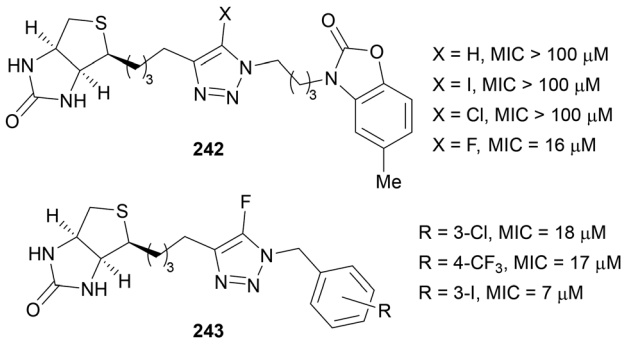


Fig. 5 5-Fluoro-triazole-containing BPL inhibitors.

Fluorinated triazole motifs have also been incorporated into anaesthetics by Chengdu MFS Pharma Co. as alternatives to the more well-known imidazole-based Etomidate and cyclopropyl–methoxycarbonate metomidate (CPMM) (Fig. 6).[147] In the examples shown below, the ED_{50} and therapeutic index (TI) values are improved with both C(4)–H and C(4)–F triazole derivates **244**. A higher TI value indicates better efficacy of the drug.

As well as their use in pharmaceuticals, fluorinated triazoles have also been applied in other medicinal applications. Crousse reported that incorporating 5-fluoro-1,2,3-triazoles into peptides **245** altered their electronic properties (Fig. 7).[148] It was shown through X-ray crystallography and a series of calculations that the fluorine atom within model compound **246** could act as a hydrogen bond acceptor with N–H and C–H contacts from nearby amino acid residues. Furthermore, the dipole moment induced by the fluorine caused a negative potential surface on one side of the peptide, resulting in a folded conformation in solution. The properties gained from the presence of fluorine include improved stability, hydrophobicity, and acidity which may be important for biological applications. A patent released in 2023 also showed the use of 5-fluoro-triazoles in polymeric materials for biological implant

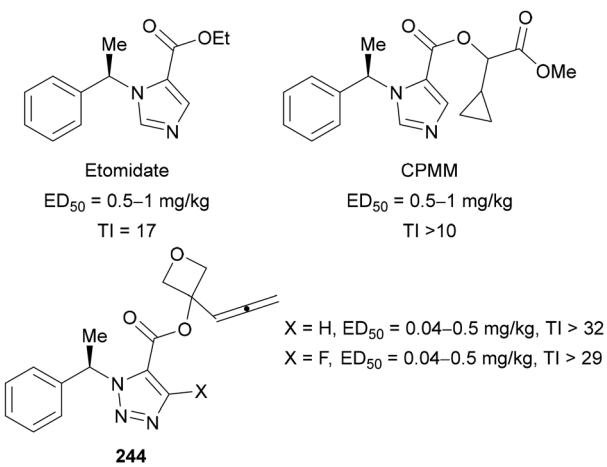


Fig. 6 4-Fluoro-triazole-containing anaesthetics.

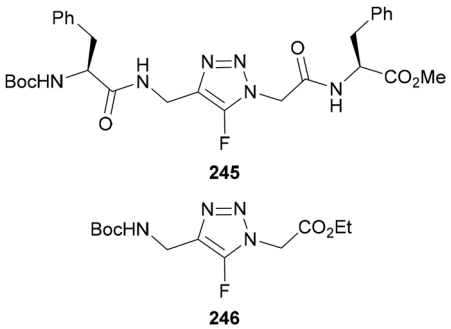


Fig. 7 5-Fluoro-triazoles in peptides.

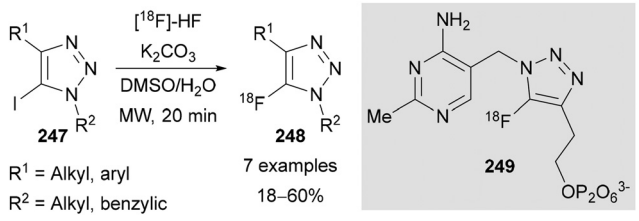
devices, for use in the slow release of a pharmaceutical agents.[149]

Zhang demonstrated in 2021 a modification of Fokin's Halex conditions[38] in the preparation of ^{18}F labelled-1,2,3-triazoles **248** for use in positron emission tomography (PET) imaging.[150] The method was developed without the need to dry [^{18}F]-HF, which, in combination with K_2CO_3 was presumed to form the required [^{18}F]-KF *in situ* (Scheme 66). A probe targeting thiamine-dependant enzymes **249** was prepared using this method in 10–16% radiochemical yield (RCY).

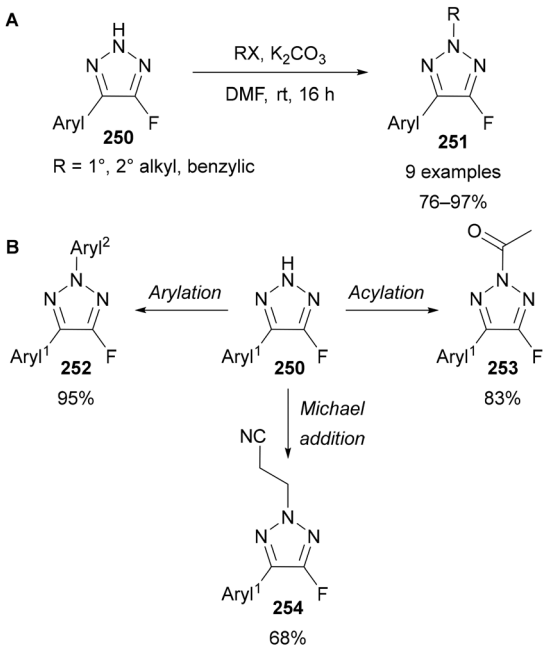
5.2. Use as synthetic intermediates

Regioselective alkylation of N*H*-triazoles in the N(2) position is typically difficult to achieve, requiring the use of directing[151] or bulky[152] groups to form the N(2) alkylated product as the major regioisomer. Nenajdenko demonstrated that a C(4)–fluorine substituent allows for complete N(2) regioselectivity when using primary and secondary alkyl halides (Scheme 67A).[30] X-ray crystallography and DFT showed the 2*H* tautomer of **251** is energetically favoured the over the 1*H* and 3*H* tautomers.[30] In the case of methyl iodide, ~80% selectivity for the 2-methylated product was obtained, with small amounts of the 1- and 3-methylated products also observed. N(2)-Selective functionalisation, including arylation, acylation, tosylation, hydroxymethylation and Michael addition reactions were used to demonstrate the versatility of this method (Scheme 67B).

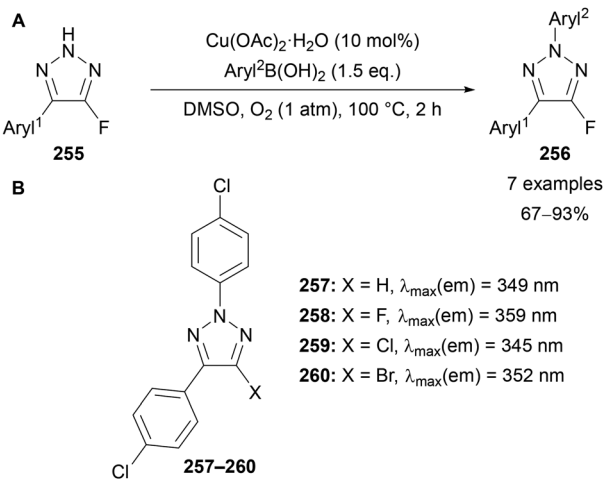
Nenajdenko noted that the 2,5-diaryl-4-fluoro-triazoles possessed fluorescence properties, with their synthesis and application further expanded by Nenajdenko and Tabolin in 2018 (Scheme 68A).[153] All triazoles **256** were found to absorb light in the near-middle UV range with maxima at 300–325 nm.



Scheme 66 Radiolabelled synthesis of 5-^{18}F-triazoles and use in thiamine-dependant enzyme inhibitor **249**.



Scheme 67 Selected examples of N(2) substitutions of 4-fluoro-triazoles **250**. (A) Alkylations; (B) arylation: ArylB(OH)$_2$, Cu(OAc)$_2$ (10 mol%), O_2, DMSO, 100 °C, 2 h; or (S_NAr) aryl–F, K_2CO_3, DMSO, 70 °C, 1 h; acylation: Ac_2O, Et_3N, CH_2Cl_2, rt, 3 h; Michael addition: CH_2=CHCN, Et_3N, DMF, rt, 20 h.[30]



Scheme 68 Synthesis and fluorescence properties of 2,5-diaryl-4-fluoro-triazoles.

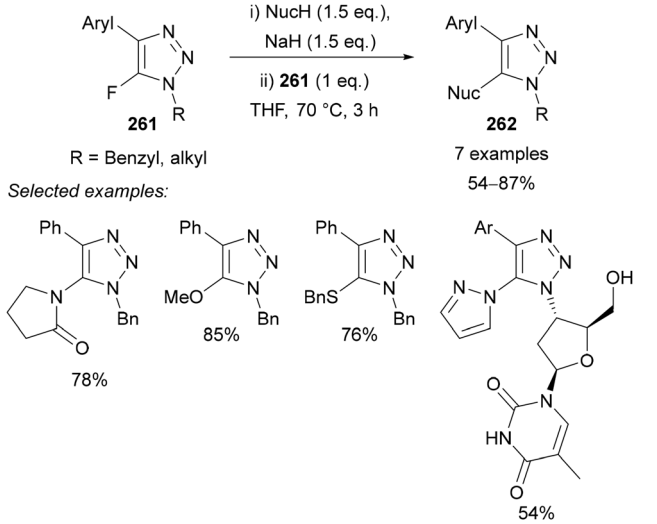
Emission was recorded in near-UV to violet/blue range, demonstrating the compounds to be blue light emitting fluorophores. Incorporation of a *p*-methoxybenzene substituent in N(2) position (Aryl^2) led to a red shift in the emission spectrum, whilst electron-withdrawing *p*-cyanobenzene caused a red shift in the absorption and emission spectra. Furthermore, a *p*-bromobenzene derivative diminished nearly all activity due to the heavy atom effect. When comparing the C(4) fluorinated triazole **258** with proto- (**257**) other halo-triazoles (**259**, **260**), the fluori-

nated derivative **258** was shown to most significantly increase the emission maximum (359 nm, Scheme 68B). These fluorinated-triazoles may therefore have applications in medicine or materials.

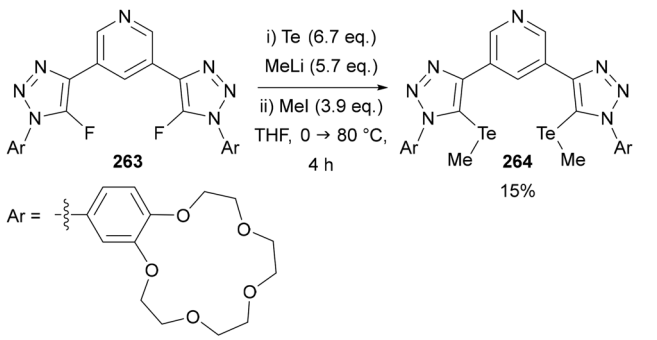
Following the development of the Halex reaction, Fokin demonstrated the use of 5-fluoro-triazoles **261** as substrates for S_NAr reactions (Scheme 69).[38] This worked well for *N*-, *O*-, and *S*-based nucleophiles in the presence of sodium hydride. The methodology was also applicable to relatively complex examples including stereocentres with no epimerisation observed during either the Halex reaction or the subsequent S_NAr reaction.

Beer utilised this approach for the synthesis of C(5)-tellurated bis-triazole **264** from the corresponding C(5)-fluoro bis-triazole **263** using *in situ* formed MeTeLi as a nucleophile (Scheme 70).[154] The tellurated bis-triazole compound **264** was used as a heteroditopic receptor for binding sodium halide salts. NMR, X-ray crystallography, and DFT calculations indicated the crown ether substituents bound the sodium ion, whilst the tellurated triazoles acted as Lewis acidic chalcogen bond donors to bind the halide anion.

Finally, Ichikawa used 4-fluoro-triazoles **265** and **266** in rhodium catalysed C–H activation-[4 + 2] annulations[155] with diarylalkynes **267** to give tricyclic systems **268** and **269** (Scheme 71).[34] The triazoles were proposed to act as directing groups for the C–H activation.



Scheme 69 S_NAr of 5-fluoro-triazoles **261** using *N*-, *O*-, and *S*-based nucleophiles.



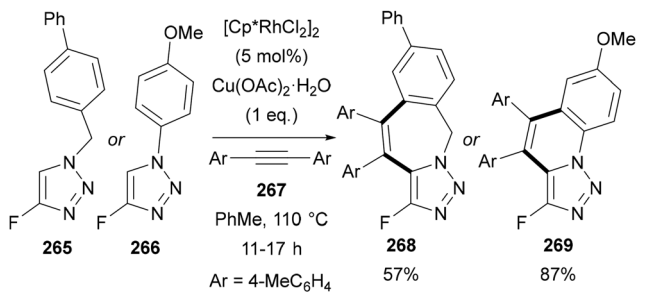
Scheme 70 S_NAr of 5-fluoro-triazoles **263** for the synthesis of chalcogen bond donor 5-telluro-triazoles **264**.

6. Applications of N(1), C(4) and C(5) polyfluoroalkyl- and polyfluoroaryl-1,2,3-triazoles

6.1. Pharmaceutical applications

In 2011, Chen studied the efficacy of triazole-containing inhibitors **270** of the dipeptidyl peptidase IV enzyme, which is implicated in type 2 diabetes. The introduction of CF_3 and CF_2H substituents at the C(4) position of the triazole was shown to significantly increase the potency of the inhibitor in comparison to C(4)–H and C(4)–Me analogues (Fig. 8).[156] It was assumed this effect was due to the electronegativity of the fluorinated groups as other aromatics bearing electron-withdrawing groups also improved the IC_{50} values to <50 nM. Out of 25 derivatives tested, the C(4)–CF_3-susbtituted triazole showed the best pharmacokinetic profile and *in vivo* efficacy and hence was selected for further studies.

Also targeting type 2 diabetes, Al-Harrasi reported compounds containing 4-fluorophenyl-triazoles **271** as α-glucosidase inhibitors (Fig. 9).[157] The triazoles were installed in the penultimate step of the synthesis *via* standard CuAAC conditions from 1-ethynyl-4-fluorobenzene and the appropri-



Scheme 71 Rhodium-catalysed C–H activation-[4 + 2] annulation using 4-fluoro-triazoles **265** and **266** and diarylalkynes **267**.

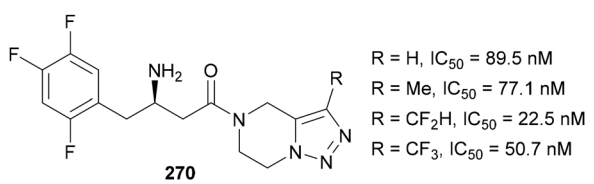


Fig. 8 4-Polyfluoroalkyl-triazole-containing dipeptidyl peptidase IV inhibitors.

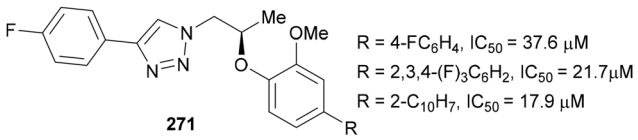


Fig. 9 4-Fluorophenyl-triazole containing α-glucosidase inhibitors.

ate azide. The IC_{50} values show these compounds are all potent inhibitors of this enzyme, outperforming the marketed oligosaccharide-based drug Acarbose (IC_{50} = 942 μM). Through structure–activity relationship docking studies, it was suggested that the triazole could form a hydrogen bond to an asparagine residue in the active site.

In 2022, Maze therapeutics released a patent targeting the glycogen synthase 1 enzyme with compounds containing fluorinated 1,2,3-triazoles **272** (Fig. 10).[158] This enzyme is responsible for the conversion of glucose to glycogen; hence inhibition of this enzyme can be used to treat diseases related to glycogen accumulation. The installation of a CF_3 group on the triazole dramatically reduced the IC_{50} value, with similar trends also observed with other derivatives of this scaffold.

Tang and Zheng reported the use of fluorinated-1,2,3-triazoles in a scaffold for use as kinase inhibitors to treat cancer in 2016.[159] SAR studies determined that the electronegativity of the fluorinated groups was key in increasing the potency of the inhibitor structure **273** (Fig. 11). Substituting CH_3 for CF_3 had the largest impact, with a decrease in electron-density within the triazole ring proposed to have a significant effect on inhibitory ability. Based on docking studies, it was also proposed that CF_3 group can act as a hydrogen bond acceptor to provide additional hydrogen bonding contacts in the binding site. The addition of an electron-withdrawing group in the R^2 position further increasing potency to bring the IC_{50} value down to 1.68 nM, below that of Foretinib (IC_{50} = 1.92 nM), a kinase inhibitor that progressed to Phase II clinical trials.[160]

Wu reported the use of 4-trifluoroacetyl-1,2,3-triazoles as potential anticancer agents in 2018.[161] A solvent- and catalyst-free synthesis of these triazoles was reported by the thermal [3 + 2]-cycloaddition of trifluoroacetyl-substituted alkynes **274** and azides **275** (Scheme 72). The 4-trifluoroacetyl regioisomer **276** was favoured over the 5-fluoroacetyl regioisomer **277** in all cases (≥83 : 17 C4 : C5). These compounds were tested against six cancer cell lines, with some showing comparable or improved activity relative to Erianin, a natural product with anticancer properties. Triazole **278** had the greatest potency against HepG2 cells, with an IC_{50} value of 0.03 μM.

Teixeira reported the ability of fluorinated-triazole compounds to act as anti-fungal agents in 2022,[162] for the treatment of papaya crops, which are prone to fungal growth. Derivatives of compound **279** (Fig. 12) were prepared and tested against the *Colletotrichum* pathogen which is responsible for this fungus. The EC_{90} values were shown to be between 1 and 5 mg mL^{-1}, with the effect of the fluorinated aryl derivatives having a clear effect in reducing this value. Unfortunately, these were not as effective as eugenol, the fungicide used currently (<0.05 mg mL^{-1}), however, this eugenol is prone to degradation *via* heat, light and oxygen, hence

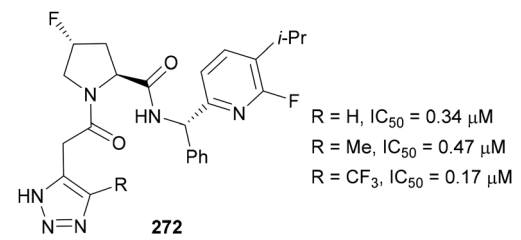


Fig. 10 CF_3-substituted triazole-based glycogen synthase 1 inhibitors.

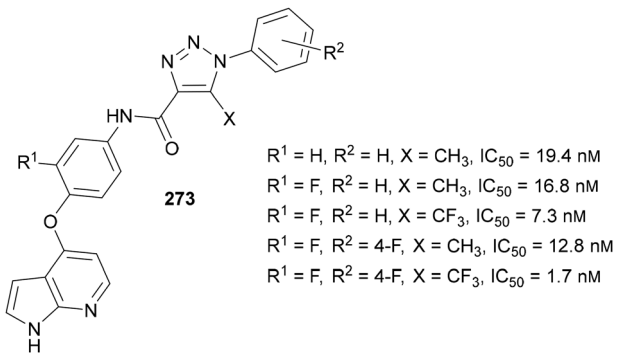
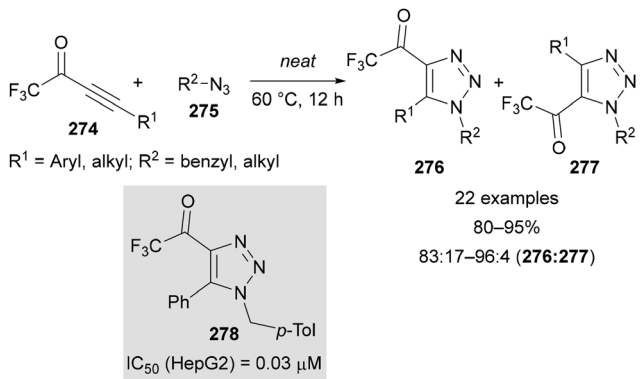


Fig. 11 CF_3-substituted triazole-based kinase inhibitors.



Scheme 72 4-Trifluoroacetyl-triazole anticancer agents.

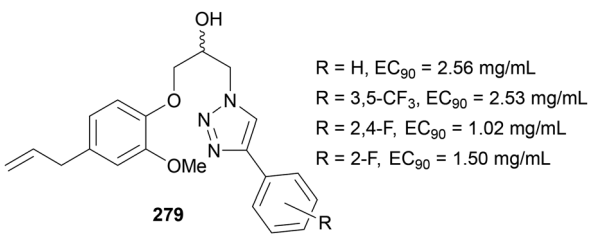


Fig. 12 C(4)-(Poly)fluoroaryl-triazole fungicide candidates.

further modifications on these triazole compounds could provide a solution.

Fluorinated benzylic groups are the most commonly used *N*-polyfluoroalkyl substituents in medicinal chemistry applications. The phenyl ring is often modified with differing numbers of fluorine or trifluoromethyl groups. A notable example of this is the anticonvulsant Rufinamide **280**, where the introduction of one or two fluorines on the *N*-benzyl substituent was shown to improve activity (Fig. 13).[163]

Another anticonvulsant bearing the 1,2,3-triazole moiety was reported by Kelley.[164] The authors examined fused pyridine-1,2,3-triazoles, where pyridine is fused at the C(4) and C(5) positions of the triazole ring (Fig. 14). The *o*-fluorobenzyl analogue **281** showed strong anticonvulsant effects but also caused nausea. By modifying the structure to **282**, the authors maintained a similar oral administration MES ED_{50}, while eliminating the nausea side-effect.

N-Polyfluoroalkyl-1,2,3-triazoles **283** have also been investigated for use as anti-inflammatory drug candidates. Xu studied triazole-based inhibitors of the NLRP3 inflammasome:[165] an important target for treating inflammatory diseases.[166] Generally however, the addition of substituents on the benzyl group reduced the potency of the drug candidates, demonstrating that adding fluorine substituents to triazoles is not always beneficial to activity (Fig. 15).

Fluorinated triazoles are often incorporated into the structures of known drugs to produce drug hybrids. For example, 28 triazole hybrids **284** derived from the antiretroviral drug Cabotegravir were recently explored by Mao, Li and Wang (Fig. 16).[167] Some of the synthesised 1,2,3-triazole hybrids were effective against the human cancer cell lines tested, with

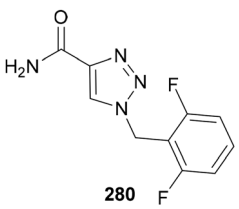


Fig. 13 Structure of Rufinamide **280**.

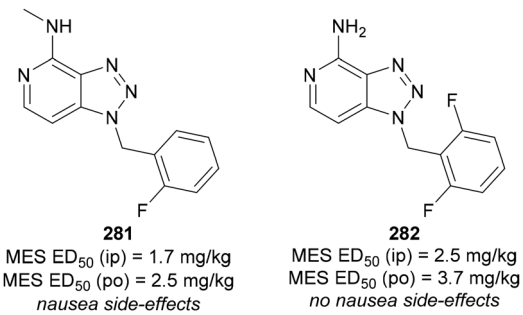


Fig. 14 Anticonvulsants **281** and **282**. ip = intraperitoneal injection; po = oral administration.

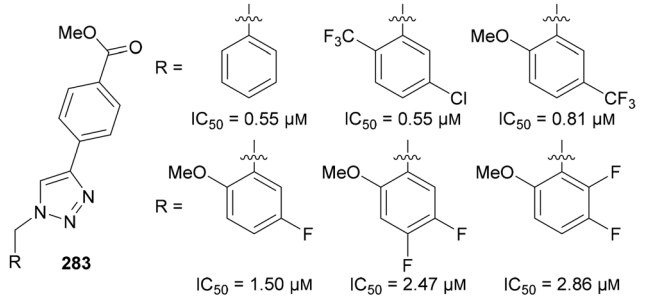


Fig. 15 Fluorinated benzyl derivatives of a NLRP3 inhibitor and their IC_{50} values.

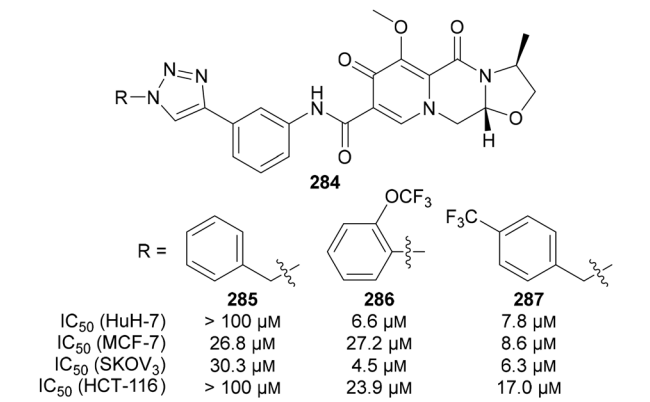


Fig. 16 IC_{50} values for activity of 1,2,3-triazole-cabotegravir hybrids **284** against several cancer cell lines. HuH-7 = human hepatocellular carcinoma; MCF-7 = human breast cancer; SKOV3 = human ovarian cancer; HCT-116 = human colon cancer.

fluorinated compounds **286** and **287** reported to be the most active. **287** was active against all tested cell lines, while **286** was strongly active against two cell lines. By comparison, the non-fluorinated analogue **285**, in addition to the other 25 derivatives tested, displayed significantly lower activity.

Fluorinated 1,2,3-triazole hybrids have also been investigated as anticancer drug candidates by Liu, who reported a series of novel 1,2,3-triazole-containing dithiocarbamates **289**. These were evaluated against human esophageal, cervical, prostate, lung and breast cancer cell lines.[168] Fluorinated triazole-containing dithiocarbamates **289** compared favourably to dithiocarbamate **288** hybrids reported previously by Liu (Fig. 17).[169]

In 1988, Kadaba reported an early example of *N*-polyfluorophenyl 1,2,3-triazoles in medicinal chemistry.[170] The authors described promising anti-convulsant properties of aryl- and pyridyl-functionalised triazolines and 1,2,3-triazoles. Of the triazoles tested, chlorinated and fluorinated derivatives showed promising activity in combination with relatively high toxic doses compared to the non-halogenated analogues.

The antibacterial activity of 1,2,3-triazoles-functionalised tetrahydroisoquinolinium-salts **290** has been reported by Ung.[85d] Screening a range of *N*-aryl triazoles revealed that the

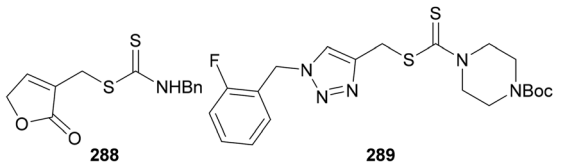


Fig. 17 IC_{50} values for activity of fluorinated 1,2,3-triazole dithiocarbamate **289**, and previously reported dithiocarbamate hydrid **288**, against several cancer cell lines.

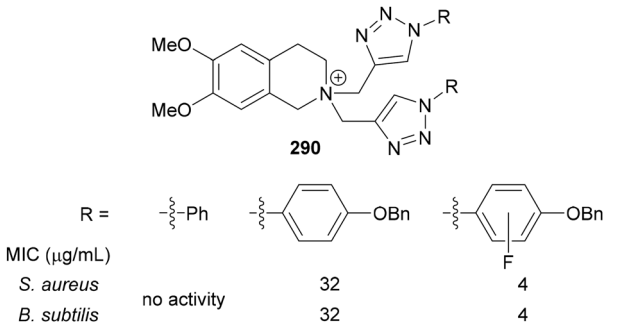


Fig. 18 Select examples of 1,2,3-triazoles-functionalised tetrahydroisoquinolinium-salts **290** investigated for antibacterial activity.

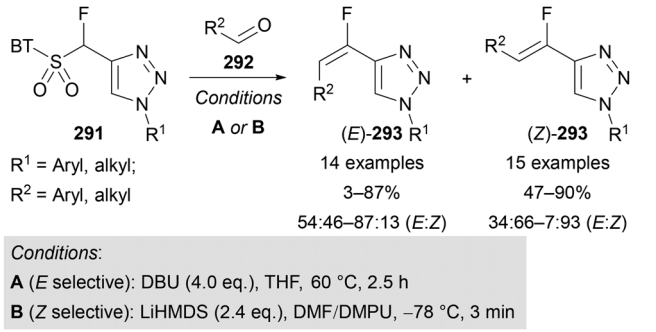
incorporation of hydrophobic groups resulted in increased activity against both *S. aureus* and *B. subtilis* (Fig. 18). *p-tert*-Butyl substitution of the aryl ring resulted in a large increase in activity, and whilst substitution with CF_3 groups resulted in a smaller increase in activity, the combination of a *p*-OBn-substituent and either an *o*- or *m*-fluorine resulted in the same effect as *tert*-butyl substitution. This was suggested to reflect the combination of hydrophobicity of the OBn group, as well as synergistic electron donation from OBn and withdrawal by fluorine.

6.2. Use as synthetic intermediates

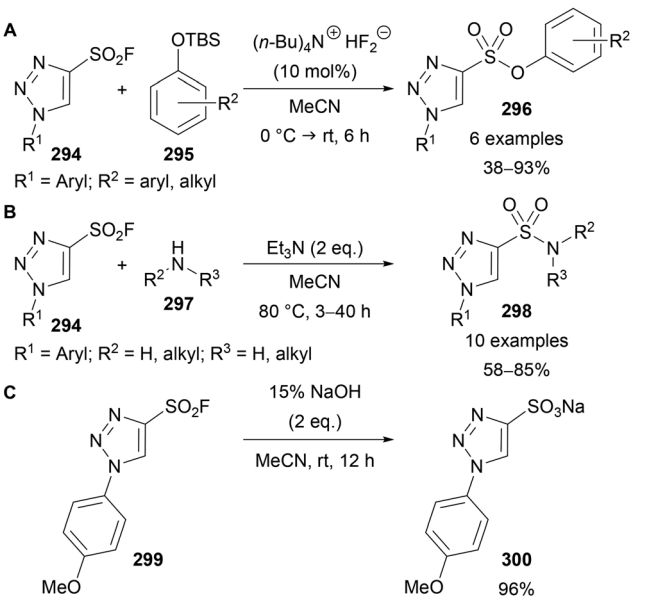
The α-fluorosulfone-substituted triazoles **291** synthesised by Zajc (section 2.3, Scheme 25),[64] were used as Julia–Kocienski olefination reagents for the stereoselective formation of fluoroalkenes **293**.[64] By varying the reaction conditions, formation of either the *E*- or *Z*-fluoro-alkene could be favoured (Scheme 73).[64b] Both aliphatic and aryl aldehydes **292** bearing electron-withdrawing or -donating substituents were successfully applied, with higher yields and stereoselectivities typically achieved for the synthesis of the *Z*-alkene products (*Z*)-**293**. Five examples involving symmetric and unsymmetric ketones were also demonstrated for the synthesis of tetra-substituted alkenes.[64b]

The applicability of 4-sulfonyl fluoride substituted triazoles **294** in SuFEx click reactions was demonstrated by Fokin and Moses (Scheme 74).[65] Reaction with phenolates **295** or amines **297** provided access to sulfonates **296** (Scheme 74A) and sulfonamides **298** (Scheme 74B) in moderate to high yields, including biologically relevant examples, including amino acids, steroids and N-heterocycles. Furthermore, base hydrolysis of **299** provided sodium sulfonate **300** in high yield (Scheme 74C). The direct sulfonation of triazoles is not possible using standard sulfonation conditions, thus this route provides a useful alternative approach to access these potentially useful compounds.

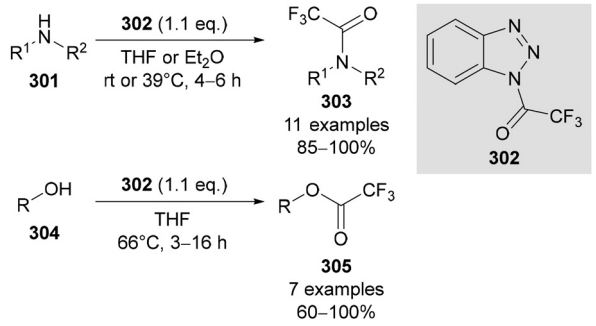
N-Polyfluoroalkyl-1,2,3-triazoles have also been used as synthetic intermediates and reagents for a range of transformations. For example, in 1997, Katritzky reported the use of (trifluoroacetyl)benzo-1,2,3-triazole **302** to trifluoroacetylate amines **301** and alcohols **304** in good to excellent yields (Scheme 75).[171] Previously reported reagents for trifluoroacetylation were unstable or produced difficult to remove byproducts, however this reagent was both simple to prepare (from benzotriazole and triflic anhydride), bench-stable and con-



Scheme 73 Use of α-fluorosulfone-substituted triazoles **291** as Julia–Kocienski olefination reagents. BT = benzo[*d*]thiazole.



Scheme 74 Example SuFEx applications of 4-sulfonyl fluoride substituted triazoles.

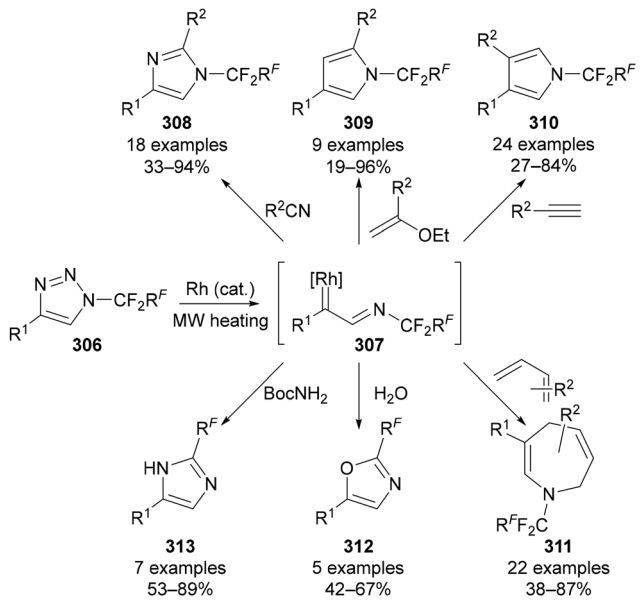


Scheme 75 Trifluoroacetylation of amines and alcohols.

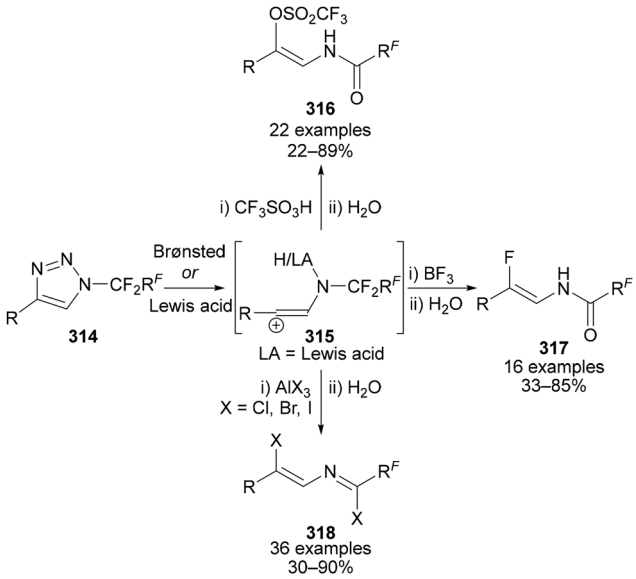
venient to use. Katritzky extended this methodology for the polyfluoroacetylation of primary and secondary amines by using polyfluoroacetylated benzo-1,2,3-triazoles.[172]

More recently, Beier has reported a range of synthetic applications of *N*-polyfluoroalkyl triazoles **306**,[23c] which all take advantage of the electron-withdrawing nature of the *N*-polyfluoroalkyl group. Taking inspiration from the formation of rhodium–carbenoids from *N*-sulfonyl-triazoles with concomitant extrusion of N_2,[173] Beier has demonstrated analogous reactivity can be achieved from *N*-polyfluoroalkyl-substituted triazoles **306** (Scheme 76). Heating the triazole substrates **306** with a Rh(II) catalyst provides access to the key Rh–carbenoid intermediate **307**, which has been exploited for the synthesis of imidazoles, pyrroles, azepines, oxazoles and indoles (Scheme 76).[101,174]

The reaction of *N*-polyfluoroalkylated triazoles **314** with both Brønsted and Lewis acids has also been investigated (Scheme 77). In these reactions, loss of N_2 was proposed to generate a vinyl cation intermediate **315**, which, depending on



Scheme 76 Synthetic use of the Rh-carbenoid intermediates generated from *N*-polyfluoroalkyl triazoles.



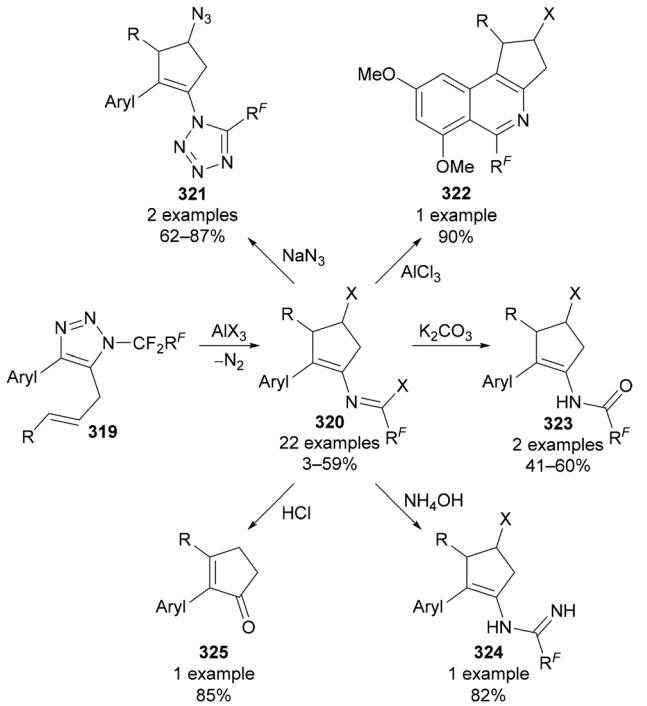
Scheme 77 Treatment of *N*-polyfluoroalkyl-triazoles **314** with Brønsted or Lewis acids followed by hydrolysis leads to β-(*Z*)-enamido triflates **316**, fluorides **217** or β-(*Z*) imidoyl halides **318**.

the identity of the Brønsted or Lewis acid could, following hydrolysis, result in the formation of (*Z*)-vinyl triflate enamides **316**,[101,175] β-(*Z*)-enamido fluorides **317**,[176] and β-(*Z*) imidoyl chlorides, bromides and iodides **318** (Scheme 77).[135b] Beier also demonstrated the use of these products in subsequent transformations, such as cross-coupling and displacement reactions.

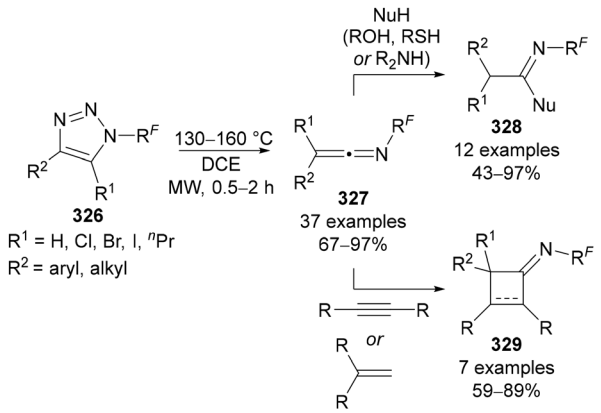
Extending this reactivity, Beier demonstrated that the vinyl cation intermediate could be trapped through an intramolecular alkene insertion when *N*-polyfluoroalkylated triazoles bearing a C(5) allylic substituent **319** were used (Scheme 78).[135a] The cyclopentenyl imidoyl halides **320** formed could be further transformed into a range of products, including tetrazoles **321**, isoquinolines **322**, *N*-alkenyl amides **323**, amidines **324** and cyclopentenones **325** (Scheme 78).

Beier has also reported the formation of ketenimine intermediates **327** from the thermal aza-Wolff rearrangement of *N*-polyfluoroalkyl-triazoles **326** (Scheme 79).[177] Treatment of the ketenimine intermediate **327** with oxygen-, sulfur- and nitrogen-based nucleophiles provides access to *N*-polyfluoroalkylated imidates, thioimidates and amidines **328**, whilst treatment with alkenes or alkynes results in iminocyclobutanes and -butenes **329**, respectively.

N-Fluoroalkyl-triazoles have been applied for the formation of foldamers (Scheme 80). The conformation of peptides is essential to their biological function, and whilst peptides can be highly active pharmaceuticals their poor *in vivo* stability can be an obstacle to their application. The introduction of triazoles into peptides increases their stability, and the fluorinated triazole–peptide hybrid **330** was reported by Crousse in 2017 (Scheme 80).[96e] DFT studies of the peptide indicated the presence of hydrogen bonding between the amide and fluorine

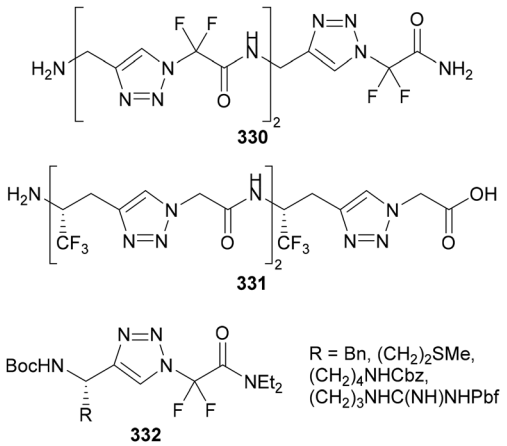


Scheme 78 Formation and synthetic versatility of cyclopentenyl imidoyl halides **320**.



Scheme 79 Formation and synthetic applications of ketenimine intermediate **327** from the aza-Wolff rearrangement of *N*-polyfluoroalkyl-triazoles **326**.

as well as non-classical hydrogen bonding from the methylene group to fluorine. The authors concluded that these interactions involving the CF_2 group could help the structure adopt a single, rigid conformation. Ongeri reported the synthesis of triazole–peptide hybrid **331** with stereogenic CF_3 substituents on the backbone (Scheme 80).[96h] These two triazole–peptide hybrids were found to adopt unique conformations, with the more rigid **330** forming long β-strands, whilst **331** formed short multistrand β-sheets.[96h] Olsen has also reported a selection of triazole–peptide dipeptide mimics that utilise an *N*–CF_2 functionalised triazole **332**. The authors synthesised Fmoc-

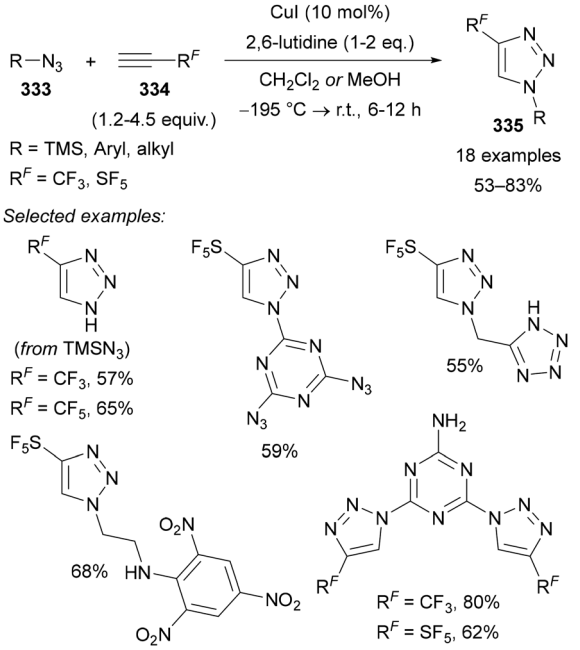


Scheme 80 Fluorinated triazole–peptide hybrid foldamers. Pbf = 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl.

and Boc-protected dipeptide mimics, which were used for the synthesis of Leu-enkephalin analogues (Scheme 80).[96f]

6.3. Materials applications

Shreeve has reported the use of 4-CF_3 and SF_5-triazoles **335** as energetic materials,[178] where the fluorinated group is proposed to impart increased thermal stability, chemical resistance, electronegativity, and hydrophobicity (Scheme 81). The preparation of these triazoles is procedurally challenging due to the use of gaseous, relatively unstable acetylene substrates **334**, which must be condensed into the reaction mixture at −195 °C. A range of triazole products **335** were obtained



Scheme 81 Synthesis and application of 4-CF_3 and SF_5-triazoles **335** as energetic materials.

however in good yields and as single regioisomers. These compounds were tested for their density, detonation pressure (P), and detonation velocity (D) which were found to be comparable to TNT. Furthermore, the SF_5-contained triazoles were found to have higher densities and more favourable detonation properties relative to the CF_3 analogues. Due to these detonation properties, extreme caution should be taken if preparing these triazoles.

6.4. Anion binding and catalysis

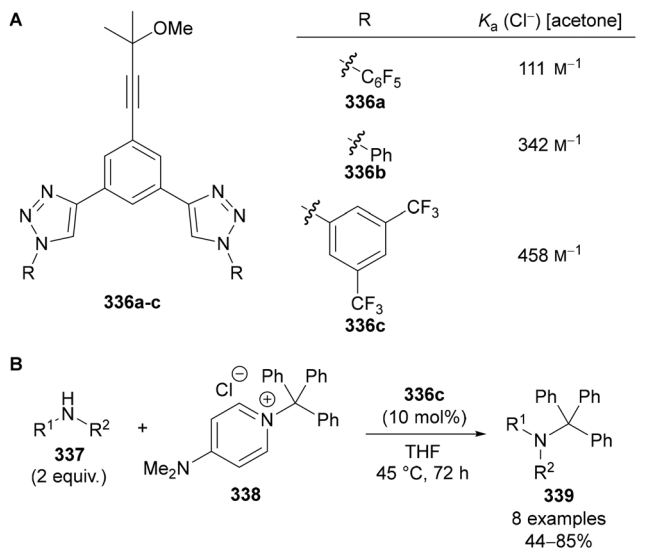
N-Polyfluoroaryl 1,2,3-triazoles have seen considerable application within anion binding and catalysis due to the numerous non-covalent interactions these motifs can engage in. For example, the triazole and *N*-aryl substituents can engage in π-π stacking; the triazole proton can act as a hydrogen bond donor (where this ability may be enhanced by the electron withdrawing nature of the *N*-polyfluorophenyl group); and the fluorines on the *N*-polyfluorophenyl group can act as hydrogen bond acceptors.

Several groups have reported the use of polyfluorinated *N*-aryl triazoles within anion binding, as either anion binding catalysts or as anion transporters. The earliest of these studies was performed by Mancheño where the chloride ion binding ability of a range of bis-triazoles **336a–c** was evaluated (Scheme 82A).[179]

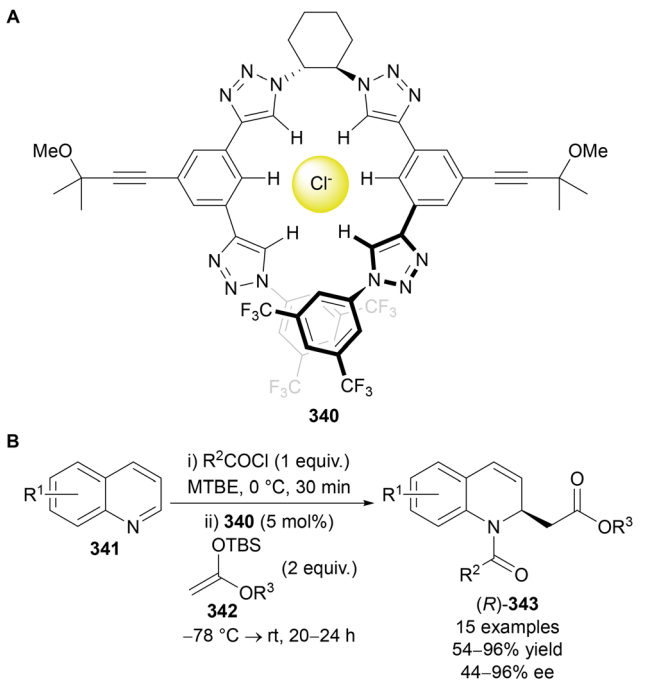
The chloride binding association constant for bis-triazole **336c**, bearing *N*-3,5-CF_3-phenyl groups, was significantly improved relative to the use of a simple *N*-phenyl substituent **336b** (K_a = 458 M^{-1} *vs.* K_a = 342 M^{-1}). In contrast, the use of an *N*-pentafluorophenyl substituent **336a** led to a decrease in chloride binding (K_a = 111 M^{-1}). It was suggested that the stronger chloride binding observed for the bis-CF_3-phenyl triazole **336c** was due to the *ortho*-protons present on the bis-CF_3-phenyl ring, which provide an additional non-classical hydrogen bond to the chloride anion. DFT studies suggested that the bis-CF_3-phenyl ring of **336c** sits co-planar with the triazole, thus facilitating the formation of this additional non-classical hydrogen bond. In contrast, the pentafluorophenyl group of **336a** sits at an angle due to its inability to engage in any additional non-covalent interactions with the chloride anion. The bis-triazoles synthesised in this work (two additional structures in addition to those in Scheme 82) were applied as catalysts for the tritylation of amines **337** (Scheme 82B). The trend in kinetic performance of the bis-triazole catalysts matched the trend of chloride binding ability, hence demonstrating a useful proof-of-concept study.

Mancheño applied the knowledge from this fundamental study to design chiral analogues, by incorporating a *trans*-1,2-cyclohexane linkage in place of a phenyl bis CF_3 group in order to obtain a chiral tetra-triazole anion binder **340** (Scheme 83A).[180] Due to the relatively rigid structure of **340**, it is proposed to form a chiral helix and thus was employed as an enantioselective catalyst for anion abstraction reactions through asymmetric counterion-directed catalysis.[181] Initially reported for the asymmetric dearomatisation of quinolines **341** (Scheme 83B),[180] the catalyst has since been applied for further studies into the dearomatisation of quinolines, isoquinolines, pyridines, diazarenes and pyryliums.[182] In addition, investigations into the spatial folding of the catalyst[183] and in-depth NMR studies on the effects of changing the anion have been reported.[184]

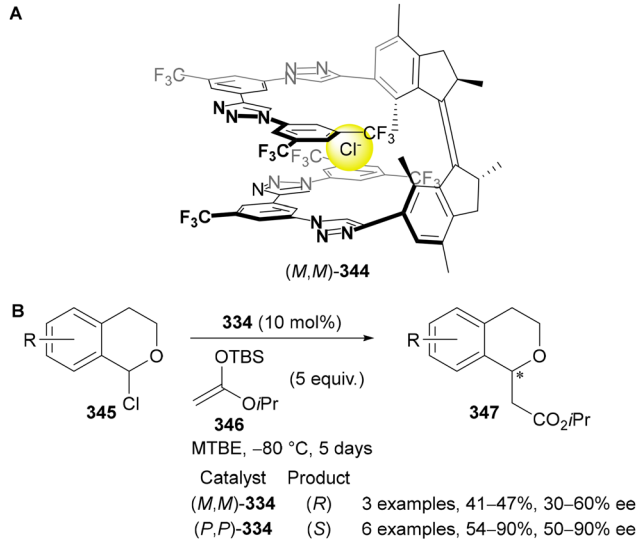
Based on Mancheño's work, Feringa developed an asymmetric anion-binding catalyst **344** which incorporated a molecular motor functionality (Scheme 84A).[185] The authors



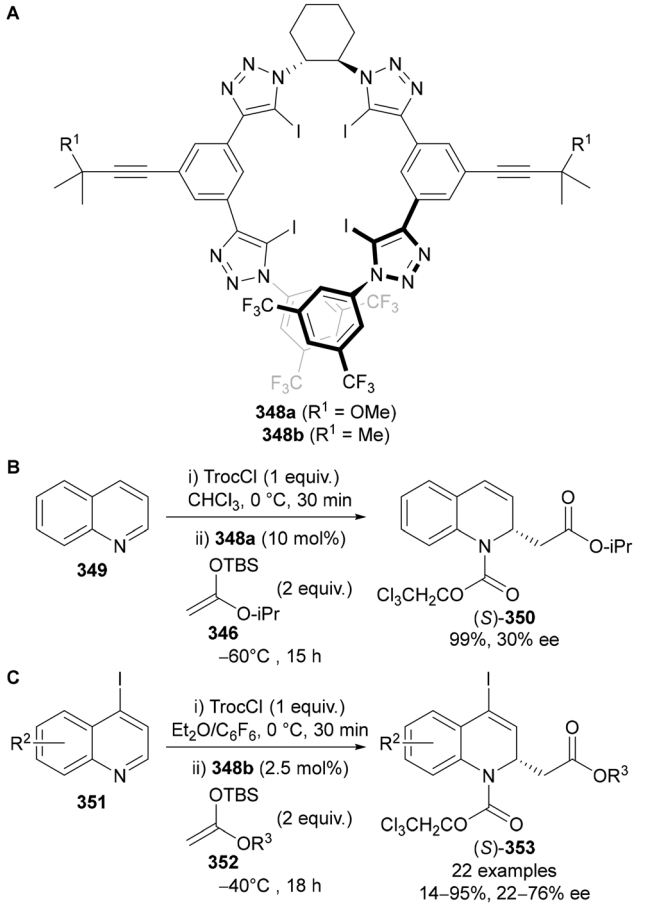
Scheme 82 Mancheño's first generation 1,2,3-triazole chloride anion binding catalyst **336c**.



Scheme 83 Mancheño's point, and helically chiral tetratriazole anion binding catalyst **340**.



Scheme 84 Molecular motor-based anion binding catalysis.



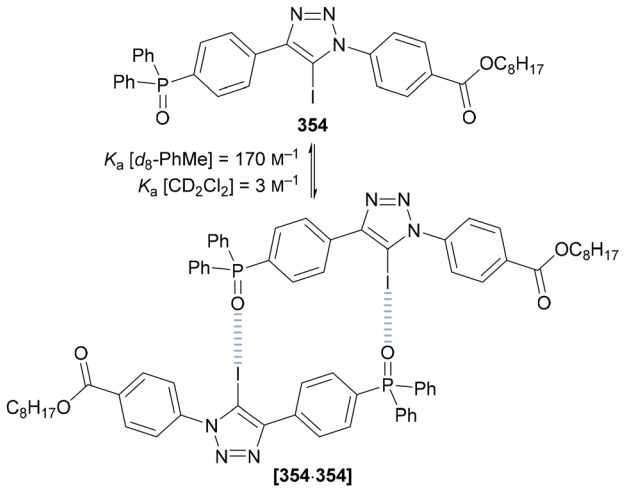
Scheme 85 Helically chiral halogen bond catalyst **348**.

described a unidirectional motor which, upon irradiation with light, transitions from a racemic *trans*-form of the catalyst into a helical pseudochiral *cis*-form, from which the configuration can be switched by heating. The catalyst was applied for chloride abstraction to promote the addition of a silyl ketene acetal **346** to 1-chloroisochromene **345** (Scheme 84B). The (*M*,*M*)- and (*P*,*P*)-pseudoenantiomers of the catalyst provided the (*R*)- and (*S*)-product **347**, respectively, thus stereodivergent access to both enantiomers was achieved with the same catalyst.

Beyond the use of polyfluoroaryl-substituted triazoles in hydrogen bonding applications, more recent interest has focused on their use in halogen and chalcogen bonding applications. Mancheño showed that modification of their helically-chiral tetra-triazole **340** by substitution of the C(5)–proton of the triazole with iodine created chiral halogen bond donors **348** (Scheme 85A).[116c,k] Chiral halogen bond donor **348a** was found to bind halide and acetate anions more strongly than the hydrogen bond donor analogue **340** (for example, **348a:** K_a (Cl^-) = 1125 M^{-1}; **340:** K_a (Cl^-) = 99 M^{-1}). Conversely, lower association constants were observed for the binding between halogen bond donor **348a** and bisulphate, hydrogen phosphate and nitrate, relative to the hydrogen bonding donor analogue **340**. Whilst no rationale was provided for this change in selectivity, similar observations have previously been reported for multi-dentate triazole-based halogen bond donors.[186] Interestingly, the halogen and hydrogen bond donor analogues **340** and **348a** displayed opposite selectivities for binding mandelic acid salts, with halogen bond donor **348a** binding more strongly with (*R*)-mandelic acid ($K_a(R)/K_a(S)$ = 1.41) and hydrogen bond donor **340** binding more strongly with (*S*)-mandelic acid ($K_a(R)/K_a(S)$ = 0.78). This divergence in enantiomeric preference was also observed when halogen bond donor **348a** was applied as a catalyst. Using the asymmetric dearomatisation of quinoline as a benchmark reaction, the use of halogen bond donor **348a** as a catalyst provided the (*S*)-enantiomer of product with moderate enantioselectivity (65 : 35 er (*R* : *S*)) (Scheme 85B). Under analogous conditions, hydrogen bond donor **340** provided the (*R*)-enantiomer of product with higher enantioinduction (78 : 22 er (*S* : *R*)). This intriguing switch in enantioselectivity between the seemingly analogous halogen and hydrogen bond donors **340** and **348a** was investigated through DFT studies and was suggested to originate from distortion of the helicity of **348a** due to the additional steric hindrance imposed by the large iodine groups. Mancheño subsequently demonstrated that through slight modulation of the catalyst and substrate structures, enantioselectivities of up to 76% ee were achieved for the dearomatisation of quinolines **351** (Scheme 85C), and up to 90% ee for the dearomatisation of isoquinolines.[116k]

In 2017, Philp reported the design of bifunctional phosphine oxide–iodotriazole compounds **354**, which were shown to undergo halogen bond-induced dimerisation in solution (Scheme 86).[116a] An *N*-polyfluorinated substituent was used to enhance the strength of halogen bonding, with a long-chain *para*-ester substituent required to increase solubility.

Beer has reported a series of studies on the use of *N*-polyfluorophenyl-1,2,3-triazoles for applications in anion binding and transport. As part of a study into the utility of halogen bonding to template [2]rotaxane synthesis, Beer inves-



Scheme 86 Halogen bond-induced dimerisation of **354**.

tigated the anion binding ability of a range of pyridinium bis-iodotriazole halogen bond donors **355a–d** (Fig. 19).[187] Modulating the triazole *N*-substituent revealed that the polyfluorophenyl derivate **355d** provided significantly enhanced anion binding for chloride in particular. Based on this finding, a related cyclodextrin-capped 'thread' was synthesised to investigate chloride anion-templated [2]rotaxane synthesis. The importance of chloride anion binding for [2]rotaxane templating was demonstrated with the optimal halogen bond donor providing a 91% yield of a [2]rotaxane, whilst a non-fluorinated analogue gave the [2]rotaxane in only 45%.

Extending this work, Beer reported an in-depth study into the use of *neutral* halogen and chalcogen bond donors based on a 3,5-bis-triazole pyridine scaffold for anion binding (Fig. 20).[116b] Systematic variation of the electron-withdrawing nature of the aryl substituents on both the nitrogen of the triazole and the Te substituent of the chalcogen bond donors allowed modulation in the Lewis acidity of the halogen and chalcogen bond donors, which was assessed through halide anion binding. Increasing the degree of fluorination of *N*-aryl substituents resulted in a systematic increase in the anion binding ability of the chalcogen bond donor **356** (Fig. 20A). Introduction of an *N*-pentafluorophenyl substituent provided an association constant ~30 times greater than the analogous chalcogen bond donor bearing a simple *N*-phenyl substituent (18 500 M^{-1} *vs.* 590 M^{-1}). Similarly, modulation of the Lewis acidity of the chalcogen bond donor through the introduction of polyfluorinated aryl groups on Te led to a similar magnitude increase in anion binding for chalcogen bond donor **357** (Fig. 20B). Davis and Beer built on this work to show that the incorporation of a ferrocene substituent on Te provided redox-switchable chalcogen-bond donors, where oxidation to the ferrocenium derivative resulted in three orders of magnitude stronger anion binding.[116g]

Beer and Langton applied related neutral bis-triazoles, incorporating the optimal *N*-pentafluorophenyl substituent for anion binding and transport (Fig. 21).[116f] *N*-Polyfluorophenyl-1,2,3-triazoles **358a–c** were synthesised with halogen, chalcogen and hydrogen bond donor groups at the C(5) position, and were assessed for their chloride binding affinity and lipid bilayer transport selectivity. The halogen bond donor **358a** had the strongest binding affinity toward chloride (>10^5 M^{-1}), followed by chalcogen bond donor **358b** (18 540 M^{-1}), and finally the hydrogen bond donor **358c** (1010 M^{-1}). The anion transport capability of anionophores **358a–c** was assessed using large unilamellar vesicles. The chloride *vs.* hydroxide transport selectivity was assessed using an adapted pH-gradient dissipation assay using *N*-methyl-D-glucamine chloride (NMDG–Cl) as the chloride source and incorporation of proton channel gramicidin D to investigate the relative rates of Cl^- and $H^+/^-OH$ transport.[188] Whilst hydrogen bond donor **358c** displayed minimal selectivity for chloride (S = 1.6), halogen bond donor **358a** showed good selectivity (S = 5) and however chalcogen

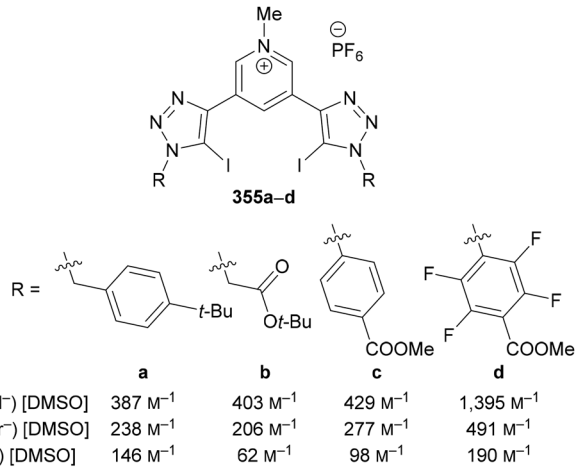


Fig. 19 Anion association constants for pyridinium bis-iodotriazole halogen bond donors **355a–d**.

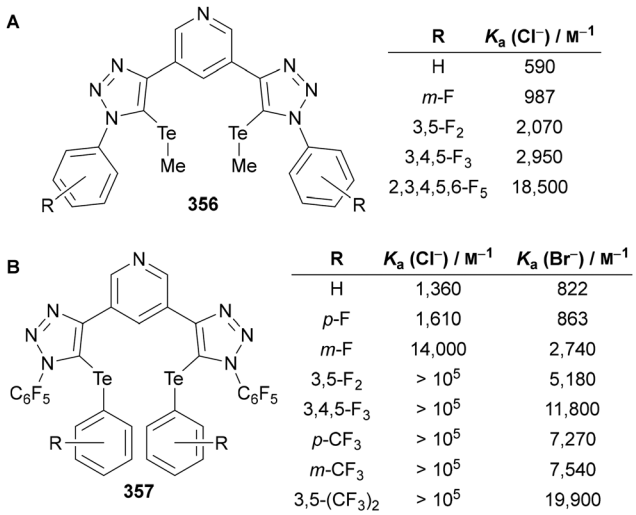
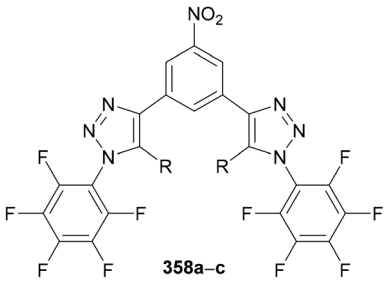


Fig. 20 Binding affinity (K_a) for halide anions with chalcogen bond donors **356** and **357**.



Compound	R	K_a (Cl^-) [acetone]	Selectivity (S)
358a	I	> 10^5 M^{-1}	5 ± 1.1
358b	TeMe	18,540 M^{-1}	70 ± 20
358c	H	1010 M^{-1}	1.6 ± 0.01

Fig. 21 Chloride anion binding and transport in lipid bilayer vesicles. Selectivity (S) is defined as $EC_{50}^{NMDG}/EC_{50}^{Gramicidin}$. S values >1 indicate chloride transport is faster than $H^+/^-OH$ transport.

bond donor **358b** showed excellent selectivity (S = 70). Based on the strong anion binding obtained with the neutral *N*-pentafluorophenyl substituted bis-iodotriazole **358a**, Beer subsequently reported the use a related halogen bonding motif for chloride anion templated [2]rotaxane synthesis.[116h] The [2]rotaxane products exhibited enhanced binding affinities for hydrophilic Cl^- and Br^- and diminished affinity for hydrophobic I^-, relative to the non-interlocked axle counterparts. This binding selectivity opposes Hofmeister bias and was proposed to originate from the effect of the mechanical bond in the [2]rotaxane.

Langton built on this work to develop stimuli-responsive anion transporters based on *N*-pentafluorophenyl substituted bis-iodotriazole halogen bond donors attached to a photo-cleavable linker **359** (Fig. 22A).[116j] The incorporation of long alkyl chains was used to anchor the halogen bond donor within the lipid bilayer.[189] Irradiation with 365 nm light promoted photo-triggered cleavage of the *ortho*-nitrobenzyl motif to release the mobile ion carrier and switch on the anion-transport ability of the halogen bond donor. In an alternative approach, Langton reported a halogen bonding ion relay in which transport is facilitated by the exchange of ions between lipid-anchored receptors **360** on opposite sides of the membrane (Fig. 22B).[116m] Once again, an *N*-pentafluorophenyl substituted bis-iodotriazole halogen bond donor was chosen for this application. The inclusion of polyfluorinated phenyl groups was proposed to serve two purposes: (i) to enhance halogen bond donor ability; and (ii) to make the receptor more lipophilic. In line with earlier work, high chloride *vs.* hydroxide transport selectivity was observed using the halogen bond donor.

Building on the exceptional chloride binding discovered from *N*-pentafluorophenyl substituted chalcogen bond donors, Beer has demonstrated that incorporation of 15-crown-5 motifs has allowed realisation of a selective KCl receptor **361** (Fig. 23).[116i] The binding of the potassium cation to the crown ether was proposed to enhance the chalcogen bond donor ability of the tellurium substituents. The chalcogen bond donor **361** was highly selective toward KCl over lighter alkali

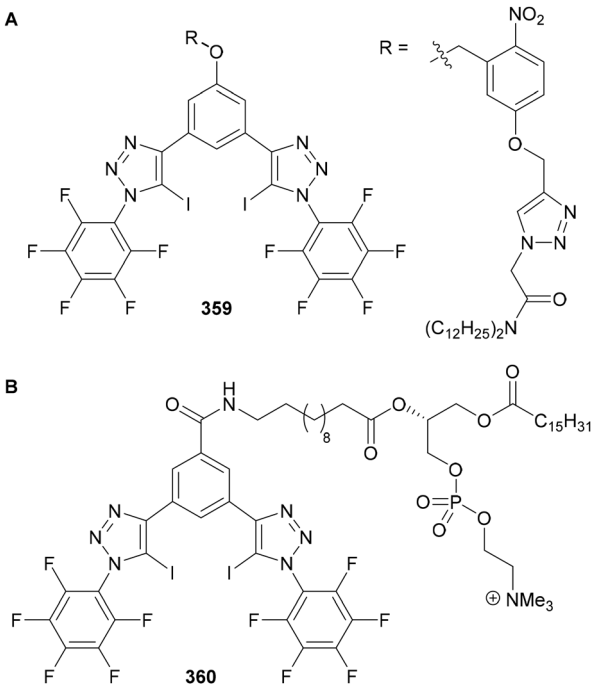


Fig. 22 Lipid bilayer anion transporters based on *N*-pentafluorophenyl substituted bis-iodotriazole halogen bond donors.

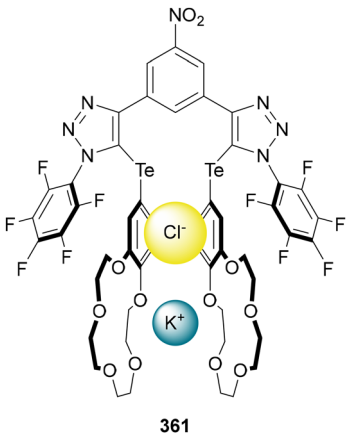


Fig. 23 Chalcogen bond donor KCl receptor **361**.

metal chlorides, however some binding was also observed for RbCl and CsCl. Preliminary studies also demonstrated the ability of **361** to promote extraction of KCl under solid–liquid and liquid–liquid extraction conditions, in addition to selective transmembrane transport of KCl over NaCl. Beer and Félix subsequently reported a related approach to potassium halide binding, using a fullerene-supported heteroditopic ion-pair receptor in which a crown ether and bis-iodotriazole halogen bond donor were spatially separated at opposite sides of the fullerene scaffold.[116l] In this example, an *N*-3,5-bis(trifluoromethyl)phenyl substituent was used on the triazole.

Beer and Langton also demonstrated the use of tetraphenylethene-based iodotriazole halogen bond donors for anion sensing and as photoswitchable halogen bond donor anion receptors (Fig. 24).[116e] Tetrakis-iodotriazole **362** was shown to undergo anion-induced aggregation, driven by halogen bond-mediated anion binding. The nanoscale aggregates displayed luminescent properties, providing a sensory mechanism for different anions. Of the anions tested chloride provided by far the largest response, followed by sulfate, nitrite, bromide, iodide, nitrate and acetate. An *N*-phenyl analogue of **362** displayed essentially no aggregation or luminescence, highlighting the importance of the polyfluorinated *N*-aryl substituent for promoting halogen bonding. Bis-iodotriazole **363** was synthesised as both the (*E*)- and (*Z*)-isomer, with the (*Z*)-isomer displaying a significantly higher chloride association constant [(*E*) = 4970 M^{-1}; (*Z*) = 23 200 M^{-1}]. When irradiated with 405 nm light, (*E*)-**363** isomerises to give a photostationary state of 48 : 52 (*E*) : (*Z*). Repeating the photoisomerism in the presence of 10 equivalents of chloride however resulted in a photostationary state of 32 : 68 (*E*) : (*Z*), indicating that the position of equilibrium is biased by the greater chloride binding ability of (*Z*)-**363**.

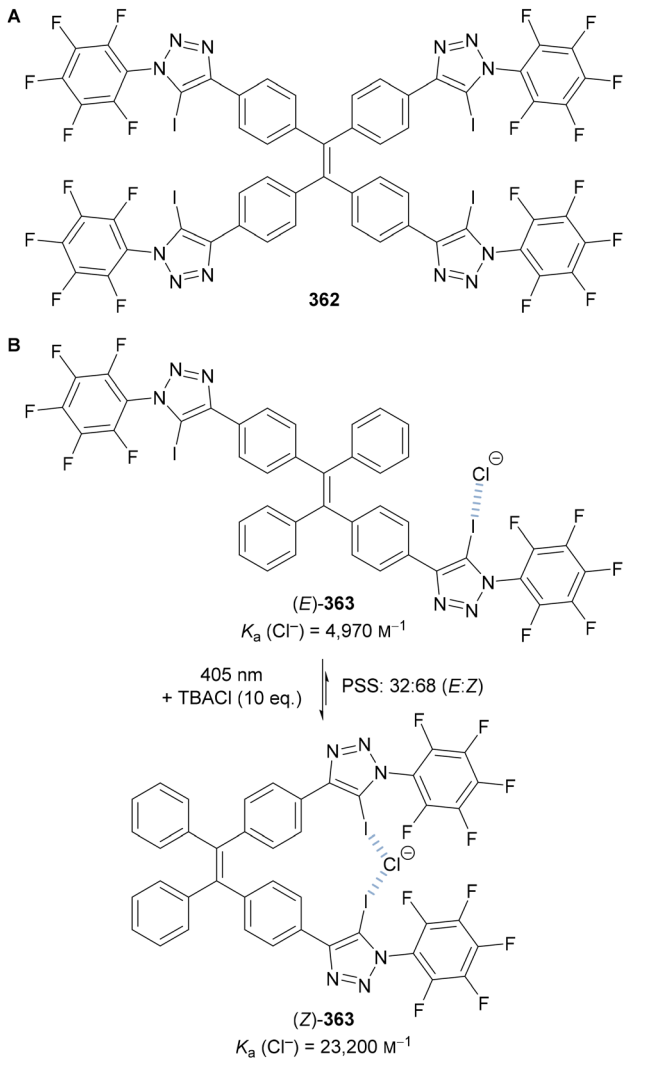
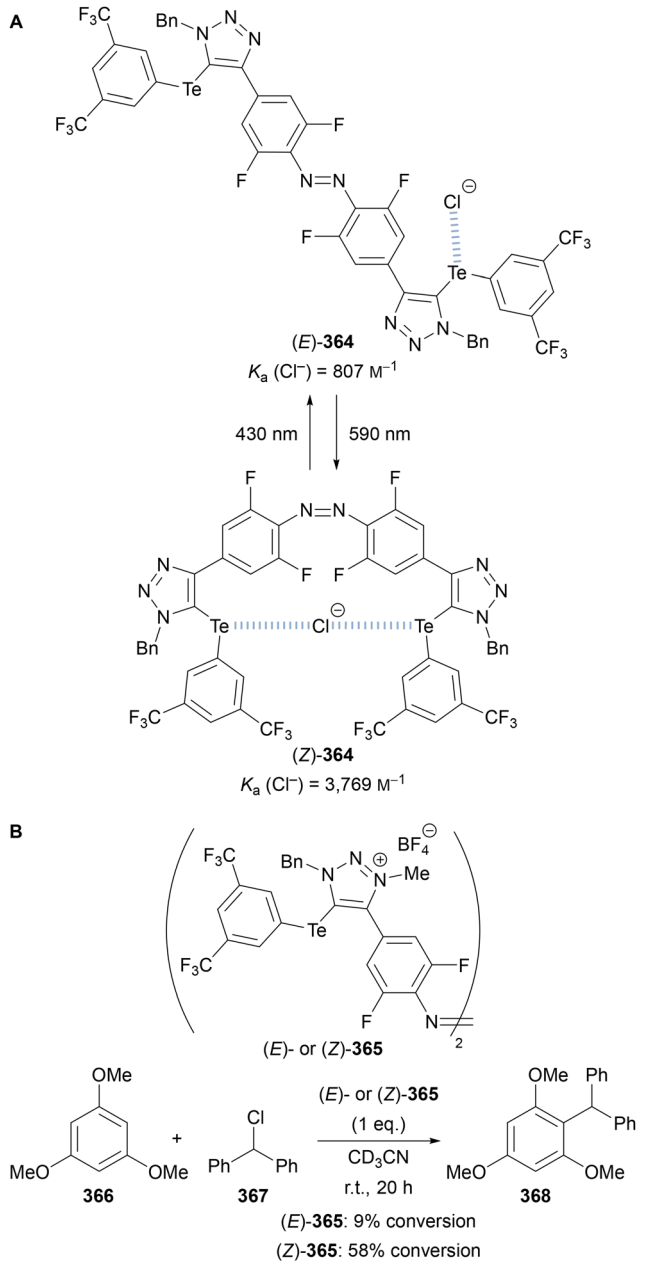


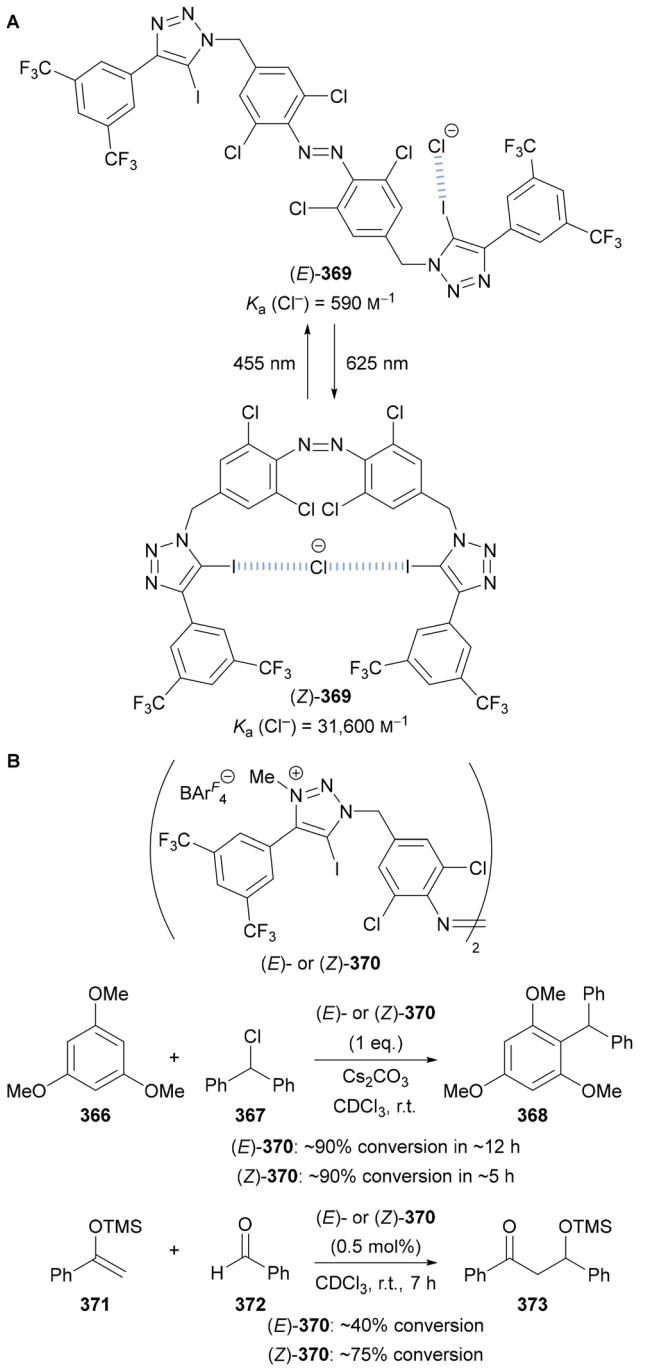
Fig. 24 Tetraphenylethene-based tetrakis-iodotriazole halogen bond donor fluorescent chloride anion sensor **362** (A) and bis-iodotriazole halogen bond donor photoswitch **363** (B).

Han and Zhang exploited the controlled (*E*)/(*Z*)-photoisomerisation of azobenzene[190] to design photoswitchable chalcogen bond donors, containing polyfluoroaryltellurium-functionalised triazoles (Scheme 87).[191] Whilst the (*E*)-isomer (*E*)-**364** displayed a relatively small association constant for chloride binding (807 M^{-1}), isomerisation to (*Z*)-**364** resulted in a significant increase in chloride affinity (3769 M^{-1}; $K_a(Z)/K_a(E) \approx 5$) (Scheme 87A). This effect was proposed to originate from the (*Z*)-isomer's ability to bind chloride in a bidentate fashion as a result of the two chalcogen bond donors being in closer proximity to each other. The cationic analogue **365** (Scheme 87B), provided larger association constants, as would be expected for a charge-assisted chalcogen bond donor,[7h,i] with the (*Z*)-isomer (*Z*)-**365** once again providing significantly higher anion binding affinities than the (*E*)-isomer (*E*)-**365**. The neutral and cationic chalcogen bond donors were then applied as stoichiometric activators for chloride abstraction from benzhydryl chloride **367**. Only the cationic chalcogen bond donor (*E*)/(*Z*)-**365** displayed appreciable activity, with (*Z*)-**365** providing significantly better activity than (*E*)-**365** (58% *vs.* 9% conversion after 24 h), in line with the higher chloride anion affinity of (*Z*)-**365** (Scheme 87B).

Langton reported a similar approach for the design of photoswitchable halogen bond donors (Scheme 88).[192] In this case, an electron-withdrawing 3,5-bis(trifluoromethyl) aryl group was included at the C(4) position of the triazole to enhance the Lewis acidity, and hence anion binding ability, of the iodine-based halogen bond donor. In line with Han and Zhang's work, the (*Z*)-isomer (*Z*)-**369** provided a higher chloride anion binding association constant, however in this case the difference in binding for the (*E*)- and (*Z*)-isomer was even more pronounced [(*E*)-**369**: 590 M^{-1}; (*Z*)-**369**: 31 600 M^{-1}; $K_a(Z)/K_a(E) \approx 54$] (Scheme 88A), suggesting a more optimal relative arrangement of the two Lewis acidic halogen bond donor sites. Once again, the cationic analogue (*E*)/(*Z*)-**370** displayed higher chloride anion binding affinity, however in this case the differentiation between (*E*)- and (*Z*)-**370** was significantly diminished [$K_a(Z)/K_a(E) \approx 3$]. Both isomers of the cationic halogen bond donor were effective stoichiometric activators for chloride and bromide anion abstract, with the (*Z*)-isomer (*Z*)-**370** providing ~2-fold rate enhancement, relative to the (*E*)-isomer (Scheme 88B). The cationic halogen bond donor was also applied as a catalyst for a Mukaiyama aldol reaction (0.5 mol% catalyst loading) and the Michael addition of 1-methylindole to an enone (10 mol% catalyst loading). The (*Z*)-isomer (*Z*)-**370** provided approximately twice as much of the aldol product **373** as the (*E*)-isomer (*E*)-**370**, whilst both isomers provided similar activity for the Michael addition. This last result was proposed to indicate that both isomers operate as mono-dentate halogen bond donors in this case.

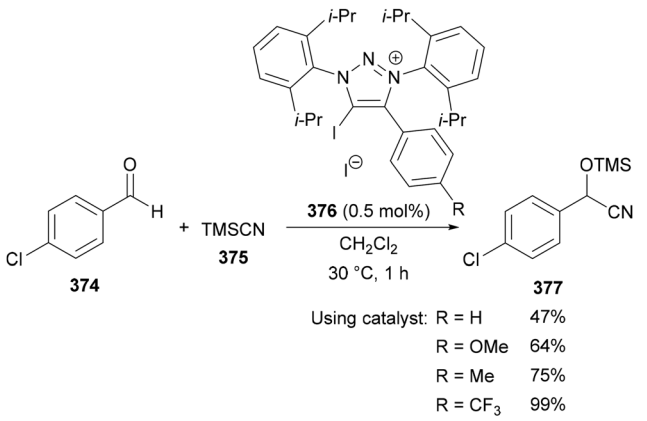


Scheme 87 (*E*)/(*Z*) Photo-switchable chalcogen bond donors (A) chloride anion binding affinities for neutral chalcogen bond donors (*E*)- and (*Z*)-**364**; (B) anion abstraction using cationic chalcogen bond donors (*E*)- and (*Z*)-**365**.



Scheme 88 (*E*)/(*Z*) Photo-switchable halogen bond donors (A) chloride anion binding affinities for neutral halogen bond donors (*E*)- and (*Z*)-**369**; (B) anion abstraction and catalysis using cationic halogen bond donors (*E*)- and (*Z*)-**370**.

Fukuzawa reported the use of 1,3,4-triaryl-5-iodotriazolium iodides **376** as halogen bond donor catalysts (Scheme 89).[193] The triazoliums were prepared *via* a previously reported method by Bertrand and Grubbs[194] from the corresponding triazene and terminal alkyne, followed by iodination of the triazolium ion through deprotonation with *t*-BuOK and electrophilic trapping with I_2. Varying the electronics of the C(4)–aryl substituent of the triazolium catalyst **376** revealed that an electron-withdrawing *p*-CF_3 group provided the highest yield for the cyanosilylation of *p*-chlorobenzaldehyde **374** over a standard 1 h reaction time (Scheme 89). It was proposed this effect could be attributed to the enhanced Lewis acidity of the halogen bond donor. The halogen bonding catalyst was also applied for the formation of cyclic carbonates from carbon dioxide and epoxides.[193]



Scheme 89 Effect of different C(4)–aryl substituents within triazole-based halogen bonding catalyst **376** for the cyanosilylation of aldehydes.

7. Conclusions

This review has highlighted the diversity of fluorinated 1,2,3-triazoles present in the literature, and has briefly described their synthesis and application.

Methods to access N(1), C(4) and C(5) polyfluoroalkyl- and aryl-substituted 1,2,3-triazoles have been summarised, in addition to methods to access 4- and 5-fluoro-1,2,3-triazoles. Although many of these triazoles can be synthesised through transition metal-catalysed azide–alkyne cycloaddition (AAC) reactions, a wide variety of other transition metal-catalysed, organocatalytic and stoichiometric approaches have been utilised. Generally, polyfluoroaryl-substituted 1,2,3-triazoles are the most straightforward to synthesise due to simple access to polyfluoroaryl-substituted azides, alkynes and other required substrates. Polyfluoroalkyl-substituted azides and alkynes are more challenging to access, however Beier has made significant recent progress in the synthesis of short-chain polyfluoroalkyl azides. In contrast, there are significantly fewer methods to synthesise 4- and 5-fluoro-1,2,3-triazoles. 5-Fluoro-1,2,3-triazoles are generally only synthesised through the so-called Halex reaction from the corresponding 5-iodo triazole;[38,41] whilst 4-fluoro-1,2,3-triazoles have recently been synthesised through a small selection of alternative routes. All current approaches have limitations and thus represents an area where more advances could be made.

Fluorinated 1,2,3-triazoles have also found extremely widespread applications in drug discovery, materials chemistry, anion binding and catalysis and as use as synthetic intermediates. In many of these applications the unique structural, chemical and biological properties of both the 1,2,3-triazole and organofluorine group have been exploited.

Overall, this review has showcased the versatility and potential of fluorinated 1,2,3-triazoles in many fields of research. We believe that this summary will assist both academic and industrial practitioners in finding appropriate methods and provide inspiration for future advances in both the synthesis and application of fluorinated 1,2,3-triazoles.

Data availability

As this is a review we have not generated any new data.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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