

## REVIEW

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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 substituents are both important structural and functional motifs used in a range of applications. This review summarises the confluence of these two important moieties 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.

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## 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,<sup>1</sup> 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,<sup>2</sup> bioconjugation,<sup>2a,3</sup> carbohydrate,<sup>4</sup> peptide,<sup>5</sup> and DNA chemistry,<sup>6</sup> supramolecular chemistry,<sup>7</sup> polymer science<sup>8</sup> and sensing applications,<sup>9</sup> amongst others.<sup>10</sup>

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<sup>11</sup> and later formalised and popularised by Huisgen,<sup>12</sup> 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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Frances E. Bugden

Frances Bugden obtained her integrated MChem in Chemistry with Drug Discovery from the University of Strathclyde, Glasgow in 2020 which included a year in the pharmaceutical industry. She then moved to the University of Warwick to carry out her PhD studies under the supervision of Dr Mark Greenhalgh in the area of chalcogen bonding catalysis using Se- and Te-functionalised triazoles. Since completing her PhD in

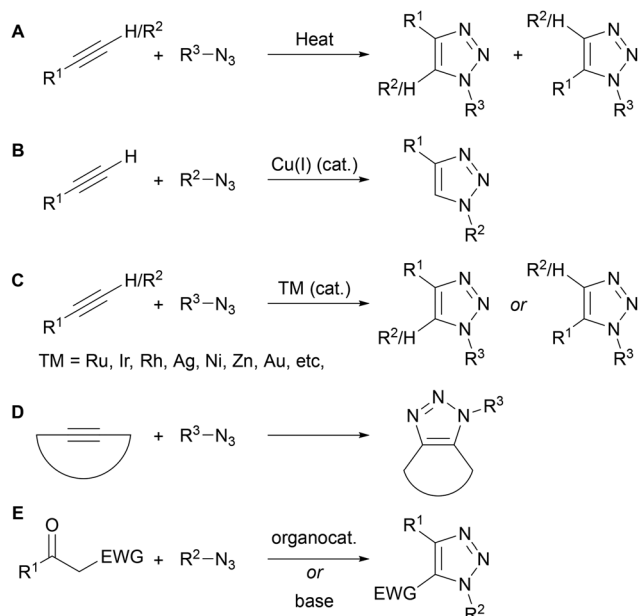
2024, she has transitioned from academia into the pharmaceutical industry.



Jason L. Westwood

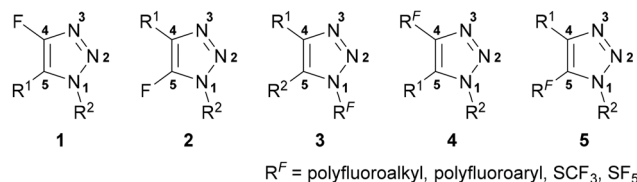
Jason L. Westwood was born in Birmingham and studied chemistry at the University of Warwick, obtaining a Bachelor of Science degree in 2022. He then completed a Master of Science by Research at the same institution, under the supervision of Dr Mark Greenhalgh. Currently, he is continuing his research 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).<sup>13</sup> Following this seminal work, a wide range of transition metal catalysts (Ru, Ir, Rh, Ag, Ni, Zn, Au) have been reported for AAC reactions.<sup>14</sup> 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,<sup>3b,c</sup> with this approach particularly suited to bio-conjugation 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).<sup>14e,15</sup> Finally, a range of azide-free approaches have been developed, which typically use hydrazine, hydrazone or diazo derivatives as the nitrogen-rich substrate.<sup>14e,15b,c,16</sup>

Organofluorine compounds have also attracted significant interest in a range of fields due to their unique physico-chemical, electrochemical and biological properties, which are often distinct from their non-fluorinated analogues.<sup>17</sup> 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.<sup>18</sup> The main area of application is within medicinal chemistry,<sup>19</sup> 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<sup>20</sup> and functional materials.<sup>17,21</sup>

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 polyfluoroalkyl/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



**Henry Stone**

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 stereo-selective 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**

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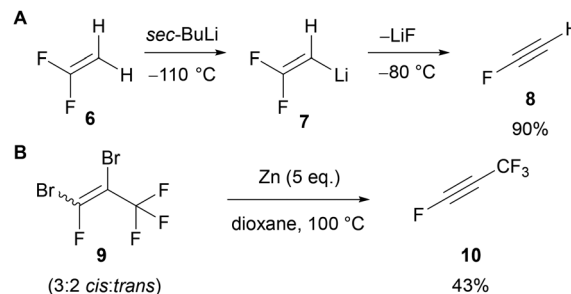
of triazoles, in addition to an overview of their applications. Focus has been devoted to applications where the properties of both the 1,2,3-triazole and organofluorine substituent are proposed to play essential roles in the compound's functionality. Several specialised reviews have been released on aspects of the synthesis or applications of fluorinated triazoles,<sup>22–24</sup> 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.<sup>25</sup> 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).<sup>26</sup> In 1982, Sauvêtre reported that lithiation of 1,1-difluoroethylene **6** and subsequent  $\beta$ -elimination of LiF gave fluoroacetylene **8** (Scheme 2A). However, both fluoroacetylene **6** and the lithiated intermediate **7** are unstable and explosive.<sup>26,27</sup> In the same year Taylor<sup>28</sup> 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.<sup>29</sup> In general, these 'surrogates' are fluoroalkenes bearing an elec-



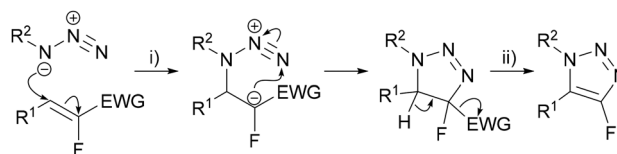
Scheme 2 Preparation of fluoroalkynes.

tron-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).

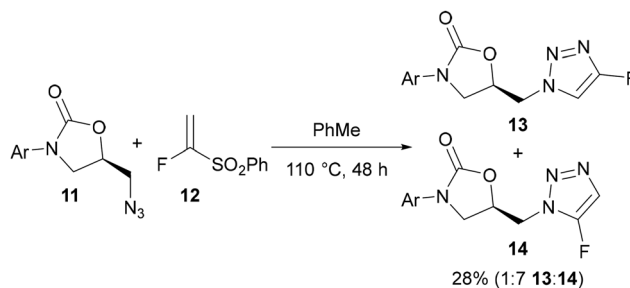
The first example of this 'surrogate' approach was reported by Reck in 2005,<sup>29a</sup> using  $\alpha$ -fluorovinylsulfone **12** (Scheme 4). A thermal AAC reaction with oxazolidinone-functionalised azide **11** at 110 °C gave a 1:7 mixture of the 1,4- and 1,5-regioisomers **13** and **14** in a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

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

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



Scheme 3 Fluoroalkyne 'surrogate' approach.



Scheme 4 Cycloaddition-elimination using  $\alpha$ -fluorovinylsulfone fluoroalkyne surrogate **12**.<sup>29a</sup>

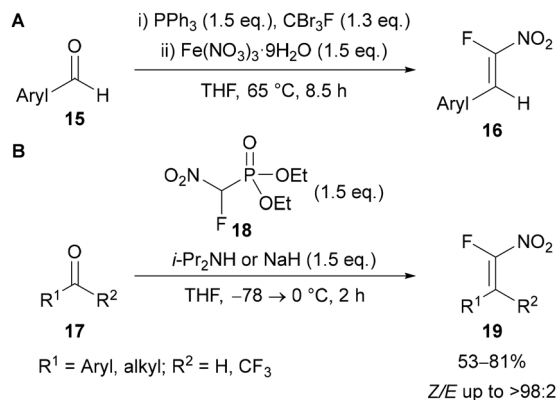


Mark Greenhalgh

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 method-

ologies. 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.



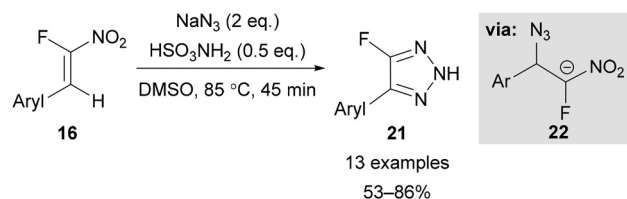


**Scheme 5** Preparation of  $\alpha$ -fluoronitroalkenes (A) via an  $\alpha$ -fluorobromoalkene intermediate; (B) through a Horner–Wadsworth–Emmons approach.

conversion of the  $\alpha$ -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  $\beta$ -alkyl- and  $\beta$ -aryl  $\alpha$ -fluoronitroalkenes.<sup>31</sup> However, to the best of our knowledge these  $\beta$ -alkyl  $\alpha$ -fluoronitroalkenes have not yet been applied for triazole synthesis.

Roy utilised  $\beta$ -aryl  $\alpha$ -fluoronitroalkenes **16** for the regioselective preparation of 1,5-disubstituted-4-fluoro-1,2,3-triazoles **20** in good yields (Scheme 6).<sup>29b</sup> 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.<sup>29b</sup>  $\alpha$ -Fluoronitroalkenes bearing  $\beta$ -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  $\beta$ -aryl  $\alpha$ -fluoronitroalkene **16** in the presence of sulfamic acid led to the formation of 4-fluoro-1,2,3-*NH*-triazoles **21** (Scheme 7).<sup>29c</sup> Low nitroalkene concentration was necessary for a successful

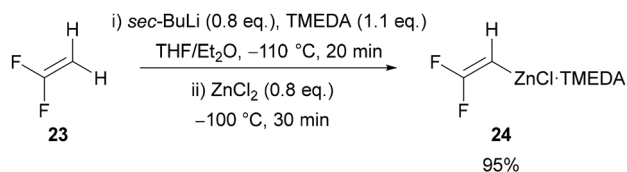


**Scheme 7** Synthesis of 4-fluoro-*NH*-1,2,3-triazoles **21**.<sup>29c</sup>

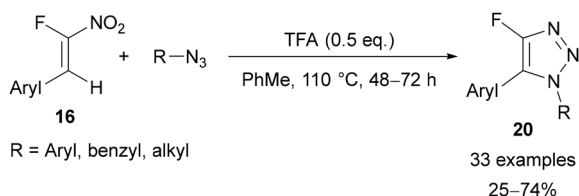
reaction, with this requirement suggested to minimise the polymerisation of proposed intermediate **22** (Scheme 7). In addition to activating the  $\alpha$ -fluoronitroalkene to nucleophilic addition, sulfamic acid was also suggested to promote protonation of intermediate **22** to favour triazole formation over polymerisation. The *NH*-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),<sup>27</sup> Ichikawa reported difluorovinylzinc *N,N,N',N'*-tetramethylethylenediamine (TMEDA) complex **24** as a thermally stable fluoroacetylene equivalent (Scheme 8).<sup>32</sup> 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<sub>2</sub>O. Ichikawa initially used this reagent in palladium-<sup>32</sup> and copper-catalysed<sup>32,33</sup> 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.<sup>34</sup>

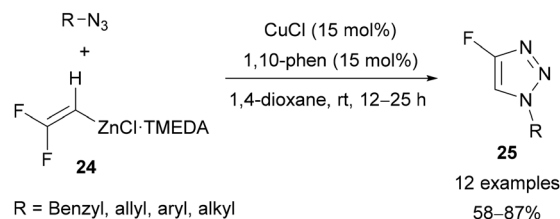
In the presence of CuCl and 1,10-phenanthroline, Ichikawa demonstrated that difluorovinylzinc TMEDA complex **24** could be applied in the copper-catalysed synthesis of a variety of 4-fluoro-triazoles **25** in good yields (Scheme 9).<sup>34</sup> A range of substituted benzylic azides were tolerated;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



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



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



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

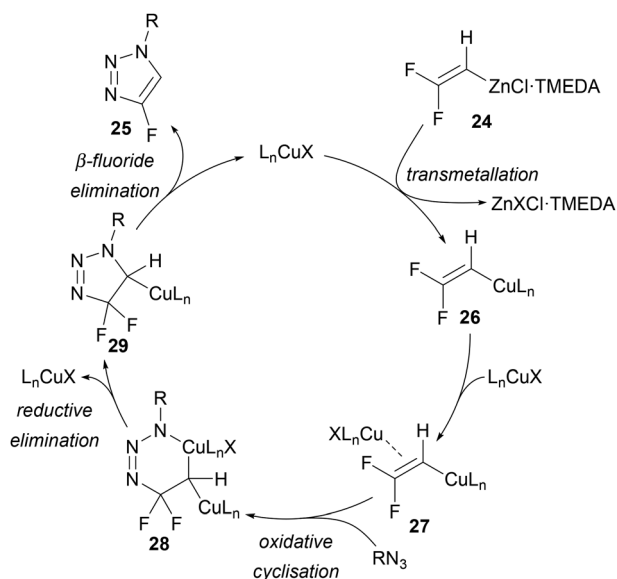




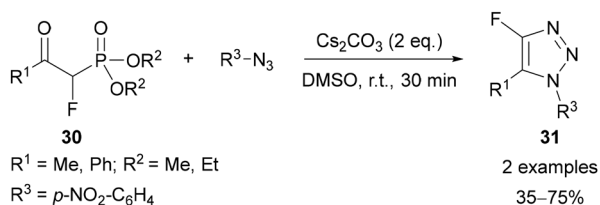
cation of aryl and allylic azides required the use of 2.5 eq. of **24** to achieve good yields.

A mechanism for this reaction was proposed to begin with transmetalation 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  $\beta$ -fluoride elimination to give the triazole product **25**. The proposal of one  $\sigma$ -bonded Cu and one  $\pi$ -complexed Cu is in line with the mechanism described by Fokin for copper-catalysed alkyne-azide cycloadditions.<sup>35</sup> An alternative pathway through initial  $\beta$ -fluoride elimination to give *in situ* fluoroacetylene was considered but discounted through preliminary mechanistic experiments.<sup>34</sup>

Building on previous work on the reaction of  $\beta$ -ketophosphonates and azides to give 1,5-disubstituted triazoles,<sup>36</sup> Chou demonstrated that a range of 1,4,5-trisubstituted triazoles could be produced in the base-mediated reaction of  $\alpha$ -substituted- $\beta$ -ketophosphonates and azides.<sup>37</sup> 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  $\alpha$ -fluoro- $\beta$ -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**.



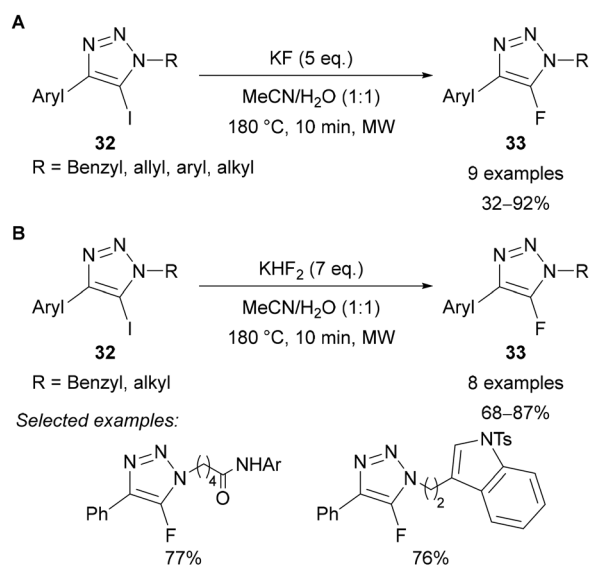
**Scheme 11** Base-mediated synthesis of 4-fluoro-1,2,3-triazoles **31** from  $\alpha$ -fluoro- $\beta$ -ketophosphonates **30** and azides.

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

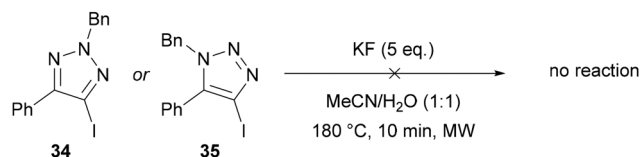
The synthesis of 5-fluoro-1,2,3-triazoles **33** has been exclusively achieved from 5-iodo-1,2,3-triazoles **32** through a so-called "halogen exchange" (Halex) reaction.<sup>38</sup> This approach was first reported by Fokin in 2012 using KF at 180 °C under microwave irradiation (Scheme 12A).<sup>38</sup> 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<sub>2</sub> reagent in place of KF (Scheme 12B).<sup>38</sup>

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).<sup>38</sup>

Since 5-iodotriazole **32** can undergo a Dimroth-like fragmentation through ring-chain isomerisation,<sup>39</sup> 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.<sup>40</sup> Although this

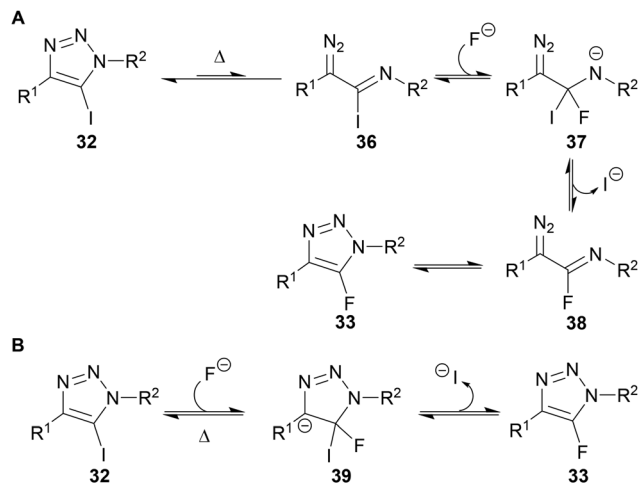


**Scheme 12** Halex reaction reported by Fokin<sup>38</sup> using (A) KF; (B) KHF<sub>2</sub>.



**Scheme 13** Alternative iodotriazole regioisomers unreactive under Halex reaction conditions.





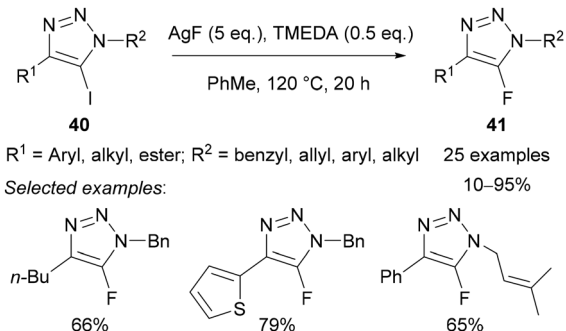
**Scheme 14** (A) Fokin's proposed mechanism for Halex reaction; (B) alternative  $S_NAr$  mechanism.<sup>38</sup>

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

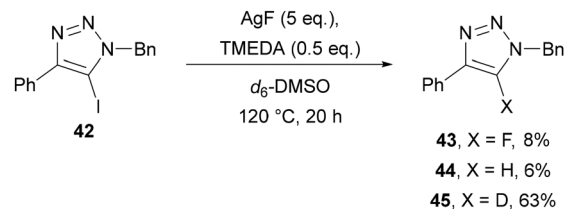
In 2015, Chu further developed the Halex reaction by demonstrating that AgF could be used as the fluoride source in the presence of TMEDA as a solubilising agent in toluene at reflux (Scheme 15).<sup>41</sup> This method was applicable to a wider substrate scope, in particular triazoles bearing C(4)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

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.

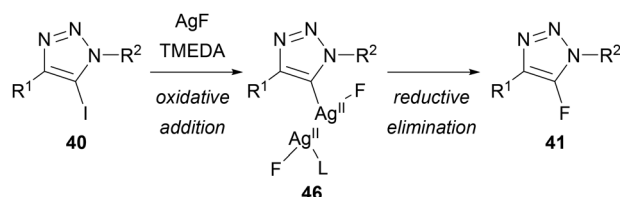
not simply providing a nucleophilic source of fluoride. Based on a related mechanism proposed by Ritter for the fluorination of stannanes,<sup>42</sup> Chu suggested that oxidative addition of silver into the carbon-iodine bond of **40** gives a bimetallic silver(II) fluoride intermediate **46**, which 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

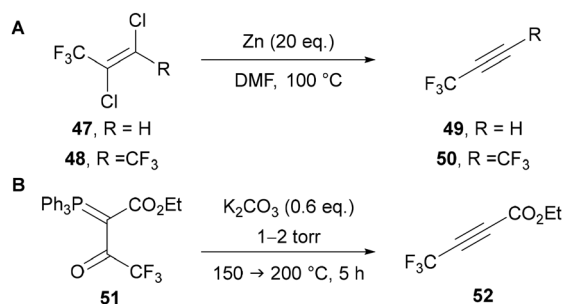
The preparation of C(4) and C(5) polyfluoroalkyl-1,2,3-triazoles would be most easily attempted through the use of polyfluoroalkyl-substituted alkynes, however simple analogues are gaseous and potentially unstable species. In the 1960s, Norris<sup>43</sup> and then Moore<sup>44</sup> used the zinc mediated reduction of dichloroalkenes **47** and **48** for the preparation of 3,3,3-trifluoropropyne **49** and hexafluorobut-2-yne **50**, respectively (Scheme 18A). Hamper<sup>45</sup> also showed it was possible to prepare  $\alpha$ -acetylenic esters through the vacuum pyrolysis of  $\alpha$ -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  $\alpha$ -acetylenic esters.<sup>46</sup>

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).<sup>47</sup> Under basic reaction conditions, fluoroform can be used as a source of the  $^-CF_3$  carbanion, or as the more

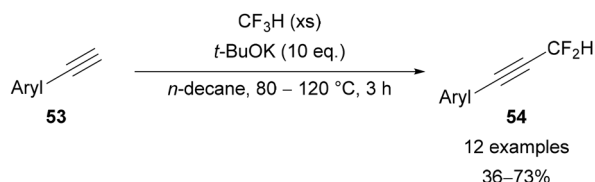


**Scheme 17** Mechanistic proposal for Chu's Halex reaction.<sup>41</sup>





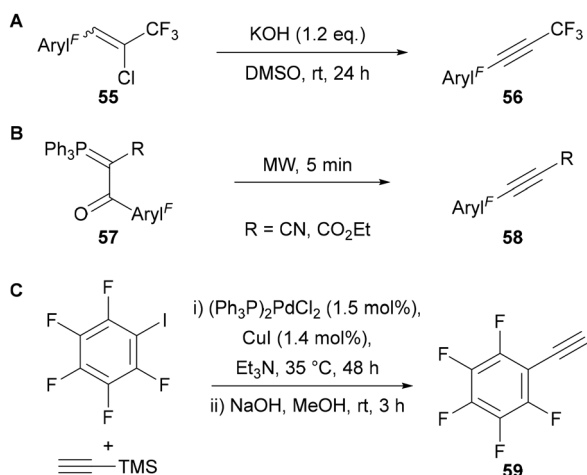
**Scheme 18** Preparation of perfluoroalkyl-alkynes.



**Scheme 19** Synthesis of CF<sub>2</sub>H-substituted phenylacetylene derivatives.

stable difluorocarbene and a fluoride anion.<sup>48</sup> 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<sup>49</sup> showed that polyfluoroaryl-alkynes bearing a CF<sub>3</sub>-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  $\beta$ -oxo-alkylidenetriphenylphosphoranes **57** could be transformed to the corresponding polyfluoroaryl-alkynes **58** follow-



**Scheme 20** Preparation of polyfluoroaryl-alkynes. Aryl<sup>F</sup> = polyfluoroaryl.

ing just 5 minutes of microwave irradiation (Scheme 20B).<sup>50</sup> Finally, polyfluoroaryl-substituted alkynes, such as **59**, can be prepared from the corresponding polyfluoroaryliodide through a Sonogashira cross-coupling reaction (Scheme 20C).<sup>51</sup>

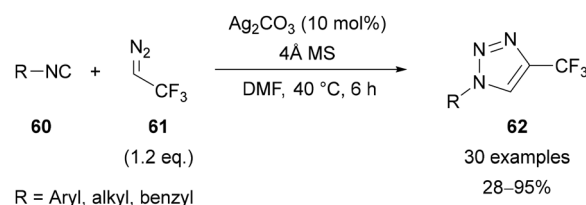
Due to the relative ease with which polyfluoroaryl-substituted alkynes can be accessed, the corresponding triazoles are generally synthesised using well-established metal-catalysed azide-alkyne cycloaddition reactions. As such, these synthetic methods have not been explicitly discussed in this review 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,<sup>23a,b,44,46b,49,52</sup> 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<sub>3</sub>-1,2,3-triazoles **62** from isocyanides **60** and 2,2,2-trifluorodiazoethane **61** (Scheme 21).<sup>52,53</sup> It should be noted that low molecular weight diazo compounds are potentially explosive,<sup>54</sup> and previous explosions have been reported with 2,2,2-trifluorodiazoethane.<sup>55</sup> 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.

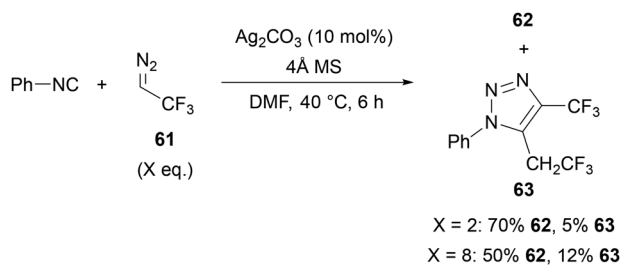
Interestingly, it was reported that if two or more equivalents of the diazo reagent were used, 1,4,5-trisubstituted triazole **63** was isolated in up to 12% yield (Scheme 22). Treatment of the triazole product **62** with 2,2,2-trifluorodiazoethane **61** under the reaction conditions did not lead to 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* <sup>13</sup>C NMR and IR monitoring, it was suggested that the isocyanide co-ordinates to the silver catalyst to give a silver (i) isocyanide complex,<sup>56</sup> 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

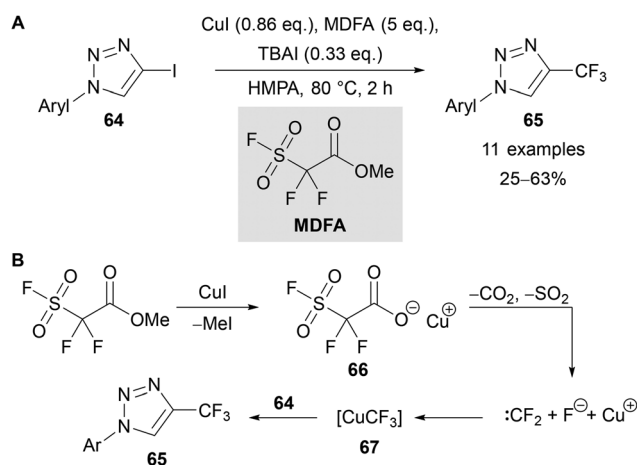


**Scheme 21** Synthesis of 4-trifluoromethyl-triazoles from isocyanides and 2,2,2-trifluorodiazoethane.





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

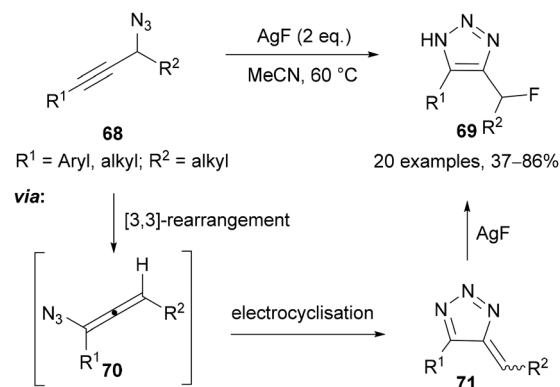


**Scheme 23** Synthesis and proposed mechanism for the copper-mediated formation of 4-trifluoromethyltriazoles **65**.

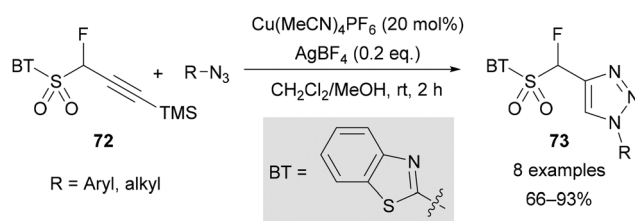
trifluoromethylation of 4-iodotriazoles **64** (Scheme 23A).<sup>57</sup> The use of CuI, methyl-2,2-difluoro-2-(fluorosulfonyl) acetate (MDFA, also known as Chen's reagent),<sup>58</sup> and tetrabutylammonium iodide (TBAI) gave the desired trifluoromethyl triazole products **65** in moderate yields. 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<sub>2</sub> and SO<sub>2</sub> to give difluorocarbene<sup>59</sup> and a fluoride ion, which can combine to form Cu-CF<sub>3</sub> intermediate **67**. Finally, this intermediate mediates the cross-coupling with iodotriazole **64** to give the trifluoromethylated triazole product **65**.<sup>58,60</sup>

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

Zajc reported the synthesis of fluorinated 1,4-disubstituted-1,2,3-triazoles **73** from novel fluorinated benzothiazole sulfones **72** (Scheme 25).<sup>64</sup> This transformation involves silyl-deprotection followed by a copper-catalysed AAC reaction with



**Scheme 24** Banert cascade approach to  $\alpha$ -fluoro-NH-1,2,3-triazoles **69**.



**Scheme 25** Copper-catalysed synthesis of  $\alpha$ -fluoro-benzothiazole sulfone-substituted triazoles.

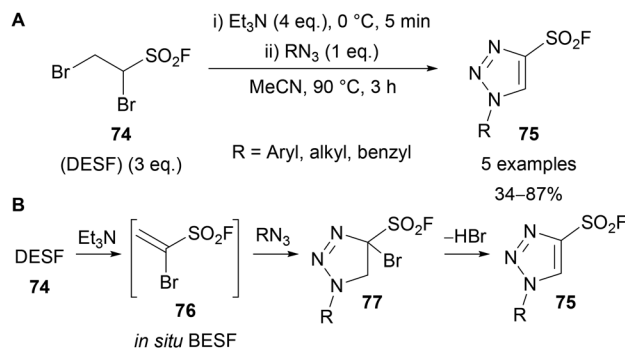
aryl or alkyl azides. The benzothiazole sulfone-substituted triazoles **73** were subsequently applied in Julia–Kocienski olefination reactions (see section 6.2).<sup>64</sup>

In 2018, both Moses<sup>65a</sup> and Fokin<sup>65b</sup> used 1-bromoethene-sulfonyl 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.<sup>66</sup> Moses showed this reagent could be formed *in situ* by reacting 1,2-dibromoethane-1-sulfonyl fluoride **74** (DESF) with Et<sub>3</sub>N 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).<sup>65a</sup> 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  $\beta$ -sulfams.

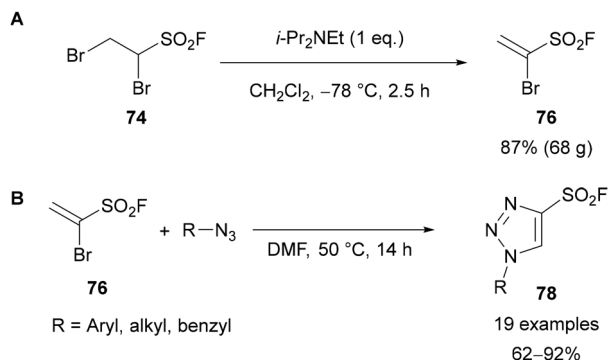
Fokin showed it was possible to synthesise and isolate BESF **76** on a 68 g scale by elimination of HBr from 1,2-dibromoethane-1-sulfonyl fluoride at –78 °C (Scheme 27A).<sup>65a,67</sup> In the absence of a catalyst, the reaction of BESF **76** with both aryl and alkyl azides gave a wide range of 4-sulfonyl 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.

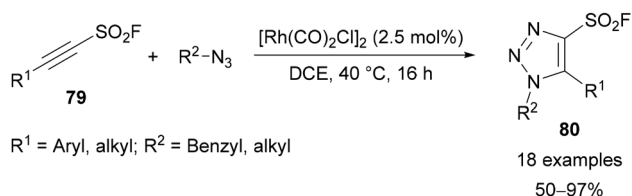


**Scheme 27** (A) Large-scale synthesis and isolation of BESF **76**; (B) preparation of 4-sulfonyl fluoride-substituted triazoles **78** using BESF **76**.

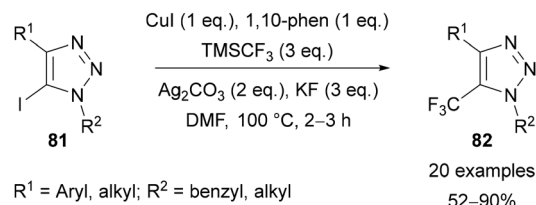
In 2020, Moses extended and improved on this approach with the development of alkynyl sulfonyl fluoride reagents **79** that were applied for the synthesis of 12 different classes of heterocycle.<sup>68</sup> Within this broad scope, the synthesis of 4-sulfonyl fluoride-substituted triazoles **80** was 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<sup>57</sup> above was reported by Cao in 2013.<sup>69</sup> The



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

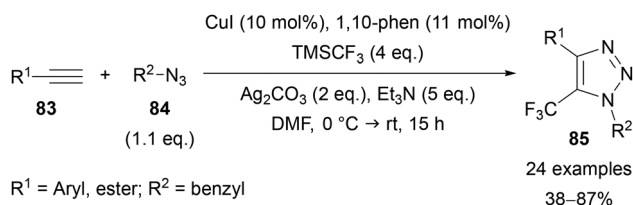


**Scheme 29** Copper-mediated synthesis of 5-trifluoromethyl-substituted 1,2,3-triazoles **82**.

copper-mediated transformation of 1,4-diaryl-5-iodo-1,2,3-triazole derivatives **81** to the trifluoromethylated analogue **82** was achieved using  $\text{TMSCF}_3$  (Ruppert–Prakash reagent)<sup>70</sup> 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).<sup>71a</sup> The cycloaddition of a range of alkynes with azides was achieved using a combination of  $\text{CuI}$ , 1,10-phenanthroline,  $\text{TMSCF}_3$ ,  $\text{Ag}_2\text{CO}_3$ , and  $\text{Et}_3\text{N}$ . 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  $\text{TMSCF}_3$  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<sup>72</sup> with control reactions showing that formation of a  $\text{CF}_3$ -substituted internal alkyne **89** or the protonated triazole **91** prior to  $\text{CF}_3$  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  $\text{CF}_3$ -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  $\text{TMSCF}_3$  in combination with  $\text{Ag}_2\text{CO}_3$ -mediated oxidation, gives proposed copper(III) intermediate **92**. This copper(III) species can undergo reductive elimination to form the product and regenerate catalyst **86**.<sup>71a</sup> 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.<sup>71b</sup> Of note, a specific glycine bis-tri-



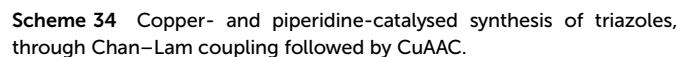
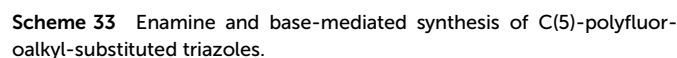
**Scheme 30** Interrupted copper-catalysed azide-alkyne cycloaddition for the synthesis of 5-trifluoromethyl-substituted 1,2,3-triazoles **85**.





Building on their previous work,<sup>71a</sup> Tsui published an interrupted copper-mediated AAC reaction for the preparation of 5-C<sub>2</sub>F<sub>5</sub>-substituted triazoles **95** (Scheme 32A).<sup>71c</sup> This method requires the preparation of [CuC<sub>2</sub>F<sub>5</sub>] from gaseous HCF<sub>2</sub>CF<sub>3</sub>, CuCl, *t*-BuOK and Et<sub>3</sub>N·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<sub>2</sub>F<sub>5</sub> group. Interestingly, applying Et<sub>3</sub>SiC<sub>2</sub>F<sub>5</sub> under the conditions reported in their previous methodology for the synthesis of 5-trifluoromethyl-substituted 1,2,3-triazoles (see Scheme 30)<sup>71a</sup> led to

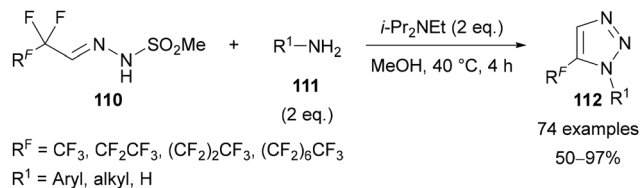
In 2013, Cao reported a combined copper- and piperidine-catalysed reaction of (hetero)aryl boronic acids **104**, ketones **103** and sodium azide for the preparation of 1,4,5-trisubstituted-1,2,3-triazoles **105** (Scheme 34).<sup>73c</sup> In this method, the aryl boronic acids **102** are converted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



enamine catalysis.<sup>15,74</sup> The ketones used all required an anion-stabilising substituent in the  $\beta$ -position, such as another ketone, an ester or a nitrile. Of relevance to this review, trifluoromethyl and difluoromethyl ketones were applied to give  $\text{CF}_3$  and  $\text{CF}_2\text{H}$  substituents in the C(5) position, in addition to fluorinated aryl N(1) substituents.<sup>73c</sup>

Tverdekhelebov 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).<sup>75</sup> Calculation of frontier orbital energies by Kascheres in 1993,<sup>76</sup> 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.<sup>76</sup> 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).<sup>77</sup> 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.

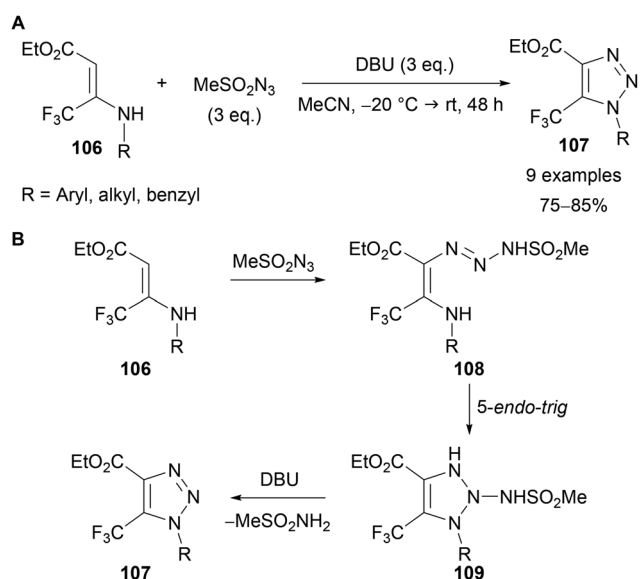


**Scheme 36** Defluorinative [4 + 1] annulation of perfluoroalkyl *N*-mesylhydrazones **110** with primary amines **111**.

Wu has also reported an alternative approach to C(5)-polyfluoroalkylated triazoles **115** using diazo compounds **113** and polyfluoroalkyl-imidoyl chlorides **114** (Scheme 37).<sup>78</sup> 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  $\text{CF}_3$  groups in both the C(4) and C(5) positions.

Interrupted copper-mediated AAC reactions have also been used for the synthesis of (5)- $\text{SCF}_3$ -substituted triazoles **118** (Scheme 38).<sup>79</sup> A combination of Cu(I) iodide, elemental sulfur,  $\text{AgCO}_3$  and  $\text{TMSCF}_3$  was proposed to generate a  $\text{CuSCF}_3$  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.

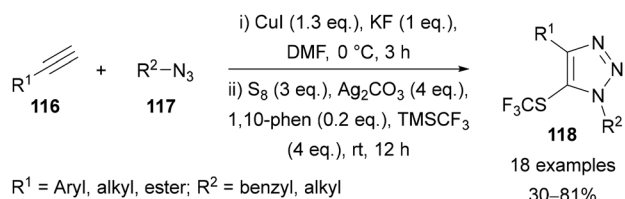
Xu reported an interrupted CuAAC that allowed for the isolation of stable 5-stannyl-1,2,3-triazoles **119**, which could be reacted with a range of electrophiles and applied in cross-



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



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



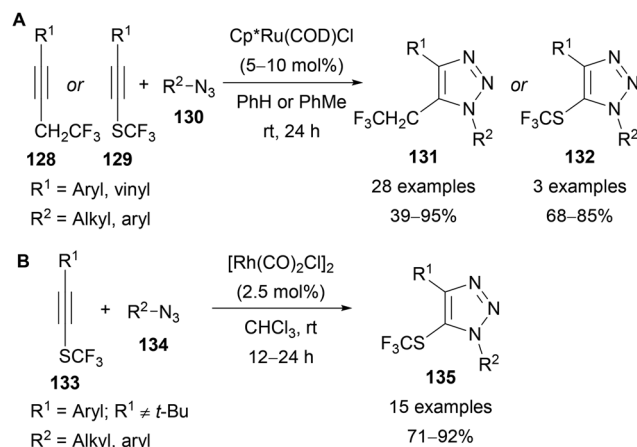
**Scheme 38** Copper-mediated synthesis of 5- $\text{SCF}_3$ -1,2,3-triazoles **118**.



coupling reactions.<sup>80</sup> The reaction of these 5-stannyl-1,2,3-triazoles **119** with Togni reagent **120** or *N*-trifluoromethylthiosaccharin **122** provided access to a range of 5-CF<sub>3</sub> and 5-SCF<sub>3</sub> triazoles **121** and **122**, respectively (Scheme 39).<sup>80</sup>

Billard reported an alternative approach to the synthesis of 5-SCF<sub>3</sub>-triazoles **125** through the direct reaction of NaN<sub>3</sub> with a SCF<sub>3</sub>-substituted alkyne **124** (Scheme 40).<sup>81</sup> A one-pot two-step cycloaddition-alkylation process was also demonstrated to give ring-fused triazole **127**.

More general access to 5-SCF<sub>3</sub>-triazoles from SCF<sub>3</sub>-substituted alkynes has been reported by Guo and Song using ruthenium and rhodium catalysis, respectively (Scheme 41).<sup>82</sup> 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<sub>2</sub>CF<sub>3</sub> or SCF<sub>3</sub> substituent in the C(5) position (Scheme 41A).<sup>82a</sup> 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<sub>3</sub>-triazoles **132** were also synthesised under analogous conditions with good



**Scheme 41** Preparation of 5-CH<sub>2</sub>CF<sub>3</sub> and 5-SCF<sub>3</sub>-1,2,3-triazoles.

yields obtained. The regioselectivity of the 5-CF<sub>3</sub>CH<sub>2</sub>-triazoles **131** was confirmed for several products by X-ray crystallography.

Song reported a complementary rhodium-catalysed AAC reaction of SCF<sub>3</sub>-substituted alkynes **133**, where once again a range of alkyl and aryl azides were utilised, but only aryl-substituted alkynes were demonstrated (Scheme 41B).<sup>82b</sup> The only alkyl-substituted alkyne attempted ( $\text{R}^1 = t\text{-Bu}$ ) gave no reaction, however Song also reported an extended scope of thio- and seleno-alkynes bearing alkyl and aryl substituents (*i.e.* not CF<sub>3</sub>) where examples of alkynes bearing linear alkyl chains were also successfully demonstrated.

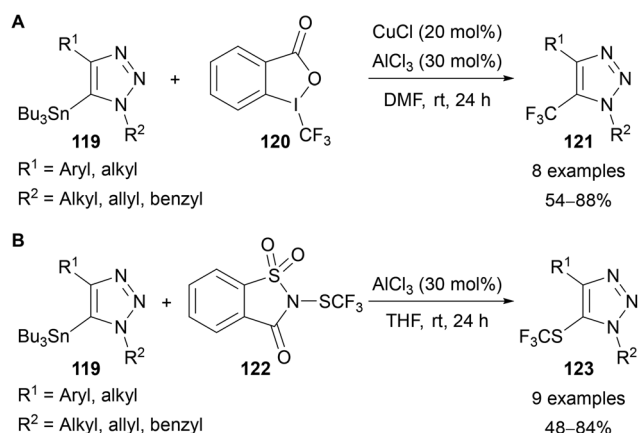
## 4. Synthesis of *N*-polyfluoroalkyl- and -aryl-1,2,3-triazoles

### 4.1. Introduction

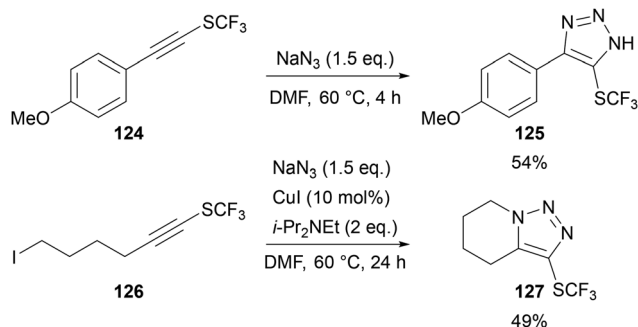
Whilst *N*-fluorinated 1,2,3-triazoles are known, their low stability means few syntheses or applications have been reported.<sup>23a</sup> The synthesis of *N*-polyfluoroalkyl- and aryl triazoles is much more common and is usually achieved through transition metal-catalysed AAC reactions (Scheme 42),<sup>13,14</sup> 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

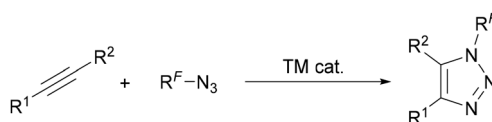
Polyfluoroaryl azides **136** are readily accessed in several ways,<sup>83</sup> including from polyfluoroaryl amines **137** (*via* the diazonium salt **138**),<sup>84</sup> boronic acids **139** (through Cu(II)-catalysed Chan



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



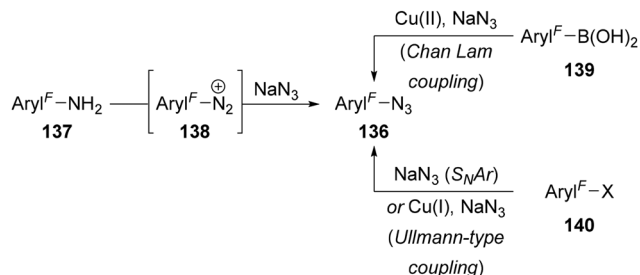
**Scheme 40** Synthesis of 5-SCF<sub>3</sub>-triazoles utilising NaN<sub>3</sub>.



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





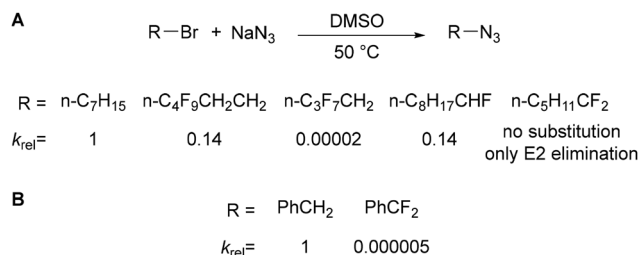


**Scheme 43** General procedure for synthesis of polyfluoroaryl (Aryl<sup>F</sup>) azides **136**.

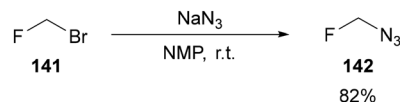
Lam coupling)<sup>85</sup> and halides **140** (through either S<sub>N</sub>Ar<sup>86</sup> or Cu (I)-catalysed Ullmann-type coupling)<sup>87</sup> (Scheme 43).

The synthesis of polyfluoroalkyl azides is significantly more challenging.<sup>88</sup> Alkyl azides are most conveniently synthesised by S<sub>N</sub>2 substitution of a (pseudo)halide leaving group by azide,<sup>83,89</sup> 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).<sup>90</sup> Comparing a simple alkyl bromide to γ- and β-fluorinated alkyl bromides revealed a significant deceleration in S<sub>N</sub>2 rate upon introduction of fluorine close to the reaction centre [relative rates: *n*-C<sub>7</sub>H<sub>15</sub>Br (1); *n*-R<sup>F</sup>CH<sub>2</sub>CH<sub>2</sub>Br (0.14); *n*-R<sup>F</sup>CH<sub>2</sub>Br (0.00002)]. Whilst introduction of single α-fluorine substituent on an alkyl chain is tolerated [relative rates: *n*-C<sub>7</sub>H<sub>15</sub>Br (1); *n*-C<sub>8</sub>H<sub>17</sub>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<sub>N</sub>2 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).<sup>91</sup> The azide was obtained in quantitative yields and could be isolated by co-distillation with THF in 82%.



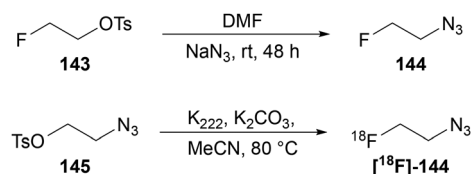
**Scheme 44** Kinetic studies on the nucleophilic substitution of fluorinated alkyl bromides by azide.



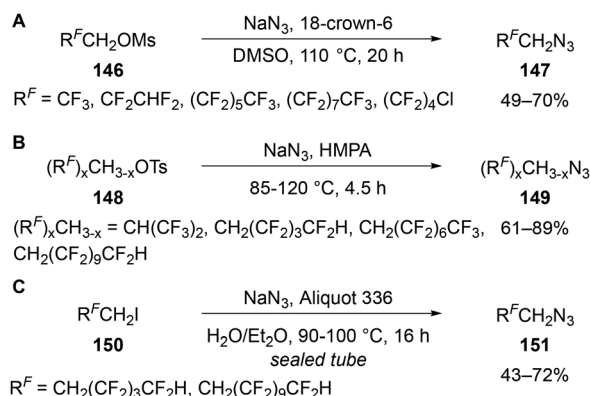
**Scheme 45** Synthesis of monofluoromethyl azide **142**.

The preparation of 2-fluoroethyl azide **144** is also relatively simple through displacement of the respective tosylate **143** with sodium azide (Scheme 46).<sup>92</sup> 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 <sup>18</sup>F-labelled azide [<sup>18</sup>F]-**144** using <sup>18</sup>F isotopically enriched KF (Scheme 46).<sup>92,93</sup>

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).<sup>94</sup> Koroniak-Szejn subsequently investigated the use of both alkyl mesylates and tosylates **148**, with the latter providing higher yields (Scheme 47B).<sup>95</sup> 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-fluoroalkyl azides.



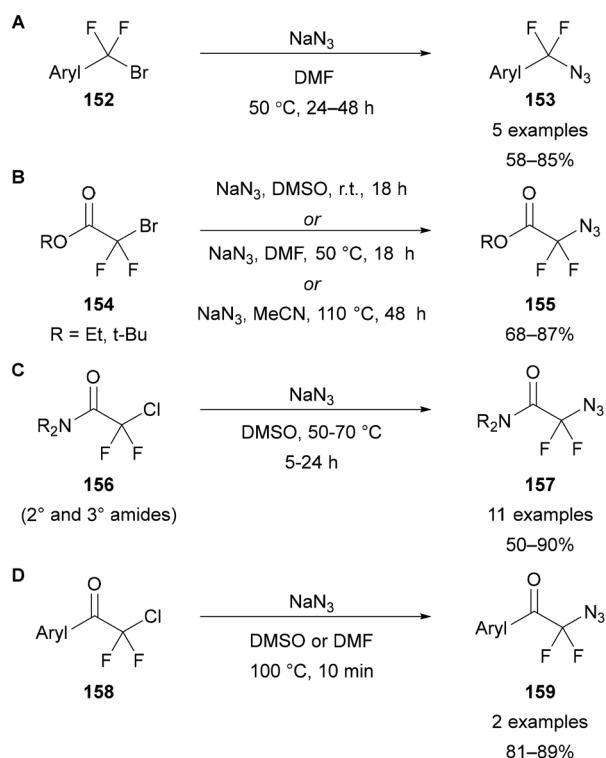
catalyst) in a water/Et<sub>2</sub>O mixture in a sealed tube at 90–100 °C (Scheme 47C).<sup>95</sup> The yields obtained were generally lower, suggesting the methods from mesylate or tosylate substrates are the best option for the synthesis of these polyfluorinated azides.

The only examples of  $\alpha,\alpha$ -difluorinated azides that can be synthesised through nucleophilic substitution are those bearing other activating groups, such as benzylic and  $\alpha$ -carbonyl substrates (Scheme 48).<sup>90,96</sup> In these examples it is possible they may operate through a radical rather than S<sub>N</sub>2 mechanism. Dolbier Jr reported the kinetics for the substitution of  $\alpha,\alpha$ -difluorobenzyl bromide with azide, with the relative rates for PhCH<sub>2</sub>Br and PhCF<sub>2</sub>Br measured as 1 and 0.000005, respectively (Scheme 44B).<sup>90</sup> As such, high reaction temperatures and times are required for this reaction (Scheme 48A).<sup>96a</sup> The original synthesis of ethyl 2-azido-2,2-difluoroacetate **155** (R = Et) was first reported at 50 °C in DMSO,<sup>96b</sup> however it has since been noted that these conditions can lead to an alternative substitution pathway to give ethyl azide and sodium bromodifluoroacetate.<sup>96c,f</sup> Alternative conditions in DMF or MeCN have also been reported,<sup>96g,h</sup> without the side-reaction being noted (Scheme 48B). Although yields have been reported, the  $\alpha$ -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).<sup>96c,e,f</sup>  $\alpha$ -Azido- $\alpha,\alpha$ -difluoro

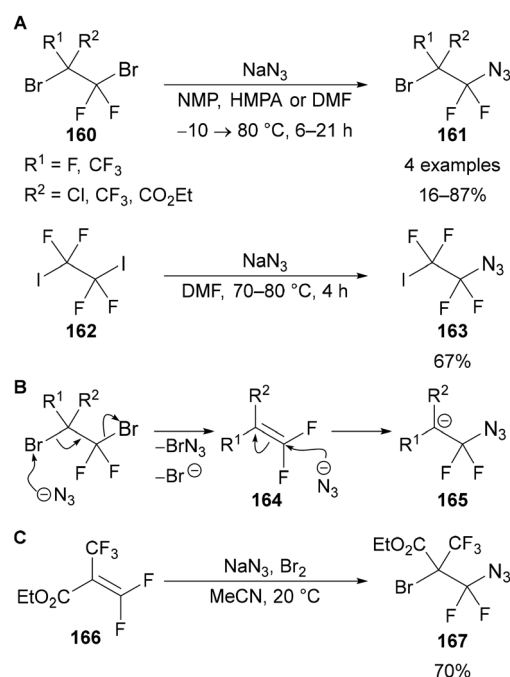
amides **157** have also been synthesised by amidation of the corresponding ethyl or methyl ester.<sup>96e,97</sup> Finally, two examples of  $\alpha$ -azido- $\alpha,\alpha$ -difluoroketones **159** have been reported, in both cases starting from the corresponding  $\alpha$ -chloroacetophenone derivative **158** (Scheme 48D).<sup>98</sup>

The apparent nucleophilic substitution of vicinal dibromo- and diiodofluoroalkanes (**160** and **162**) by sodium azide was reported by Knunyants in 1986 (Scheme 49A).<sup>99</sup> Based on previous work,<sup>100</sup> an ionic chain mechanism was proposed, in which the reaction is initiated by the attack of azide on bromine to form BrN<sub>3</sub>, 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.<sup>101</sup> 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),<sup>102</sup> ICl,<sup>103</sup> aryl thiocyanates,<sup>104</sup> carbon dioxide<sup>105</sup> and perfluoroalkanoates<sup>106</sup> 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,<sup>107</sup> and again in 1985 by Bock,<sup>108</sup> base mediated decomposition of chlorodifluoro-

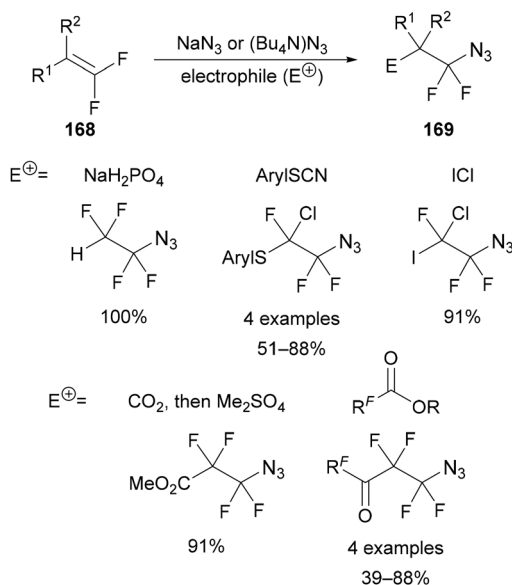


**Scheme 48** Preparation of  $\alpha,\alpha$ -difluorinated benzylic and  $\alpha$ -carbonyl azides.

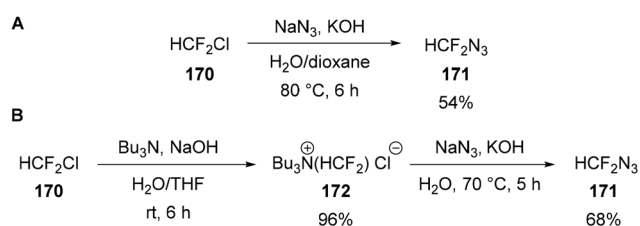


**Scheme 49** Synthesis of  $\beta$ -bromo- and  $\beta$ -iodo-fluoroalkylazides through an ionic chain mechanism.





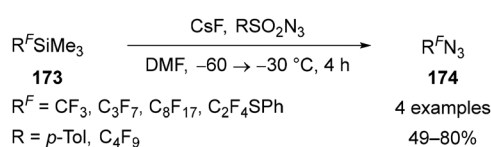
**Scheme 50** General approach for the synthesis of  $\beta$ -functionalised fluoroalkylazides.



**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  $\text{Bu}_3\text{N}^+(\text{HCF}_2)\text{Cl}^-$  **172** (Scheme 51B).<sup>109</sup>

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** ( $\text{R}^F = \text{CF}_3$ ) with caesium fluoride in DMF in the presence of tosyl azide provides trifluoromethyl azide **174** ( $\text{R}^F = \text{CF}_3$ ) in high yield (Scheme 52).<sup>110</sup> 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.

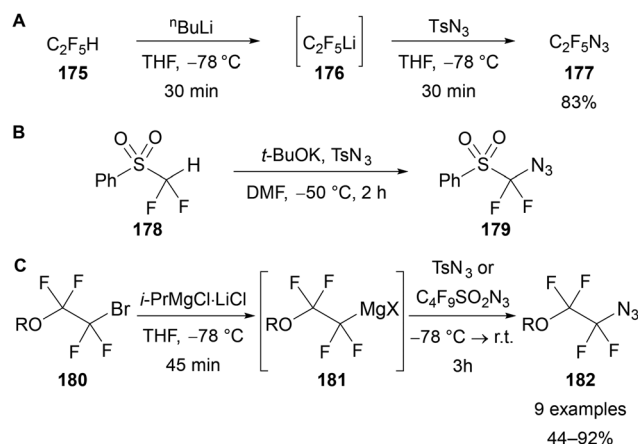
distilled with THF to produce a THF solution of the fluoroalkylazide product **174**. Trifluoromethyl azide is significantly more thermally stable than methyl azide, with explosive decomposition only reported over 330 °C.<sup>111</sup> Longer chain perfluoroalkyl azides could be prepared in a similar way, however in some cases the more electrophilic nonafluoryl azide ( $\text{F}_9\text{C}_4\text{SO}_2\text{N}_3$ ) was required as the azide source (Scheme 52).<sup>110,112</sup>

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),<sup>110,113</sup> or magnesium–halogen exchange (Scheme 53C),<sup>112</sup> followed by reaction with tosyl or nonafluoryl azide.

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

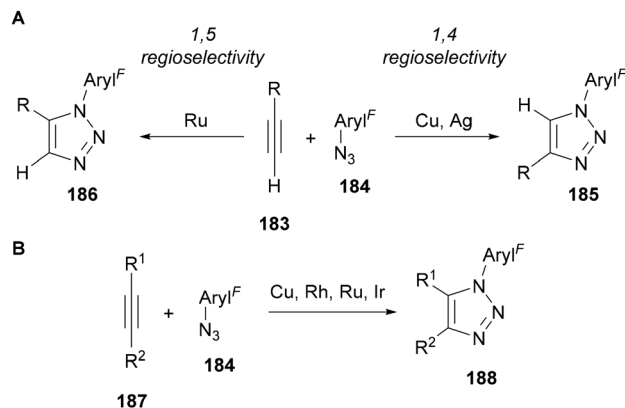
*N*-Polyfluoroaryl triazoles are most often synthesised through a thermal or transition metal catalysed azide–alkyne cycloadditions (Scheme 54). Whilst thermal methods usually give mixtures of regioisomers, high regioselectivity can be achieved for one regioisomer by using a transition metal catalyst.<sup>12–14</sup> 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**;<sup>13</sup> however there are also reports on using silver<sup>114</sup> and ruthenium<sup>115</sup> 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),<sup>116</sup> rhodium,<sup>117</sup> ruthenium<sup>82a,118</sup> and iridium<sup>119</sup> 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).<sup>85,87</sup> 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

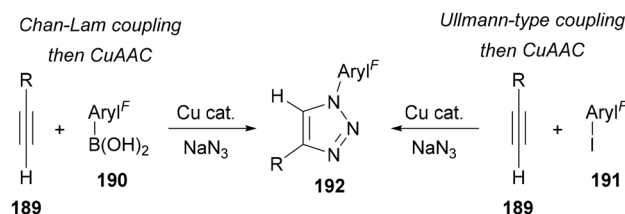


**Scheme 53** Synthesis of azidoperfluoroalkanes **177**, **179** and **182** through nucleophilic fluoroalkylation of sulfonyl azides.





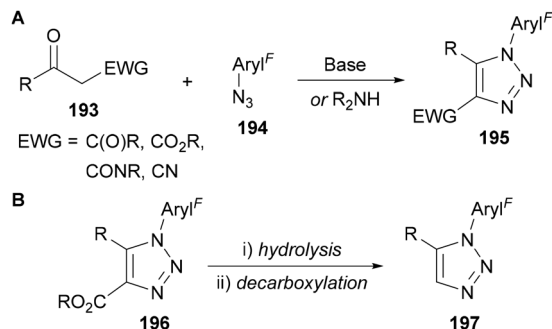
**Scheme 54** Transition metal-catalysed azide-alkyne cycloaddition approaches for the synthesis of *N*-polyfluoroaryl triazoles.



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

therefore been developed,<sup>85a,120</sup> with a range of examples including polyfluorinated aryl groups (Scheme 55).<sup>121,122</sup> 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,  $\beta$ -keto esters, amides and nitriles **193** (Scheme 56A).<sup>73a,74,123</sup> 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.<sup>15</sup> The electron-withdrawing nature of the



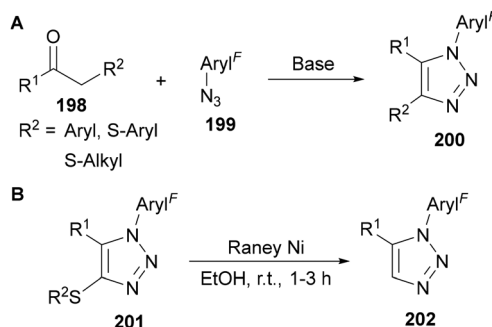
**Scheme 56** Base- and amine-catalysed synthesis of triazoles **195** from  $\alpha$ -activated ketone derivatives **193**.

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).

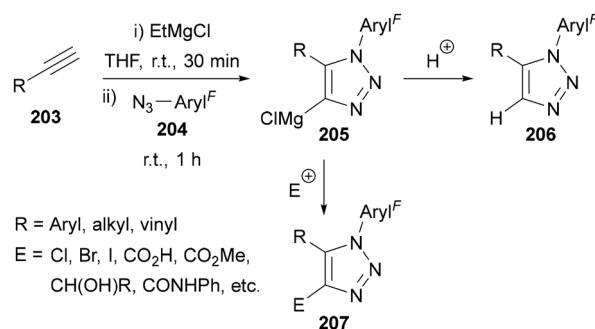
Other  $\alpha$ -substituted ketones, where the  $\alpha$ -substituent provides an acidifying effect can also be applied in these reactions, such as  $\alpha$ -aryl and  $\alpha$ -thioalkyl/aryl ketones **198** (Scheme 57A).<sup>123h,124</sup> The 4-thio-substituted triazoles **201** can also be converted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

Another approach to access 1,5-disubstituted triazoles **206** is through the addition of *in situ*-generated magnesium acetylides to azides (Scheme 58).<sup>125–127</sup> 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  $\alpha$ -substituted ketones **198**.



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



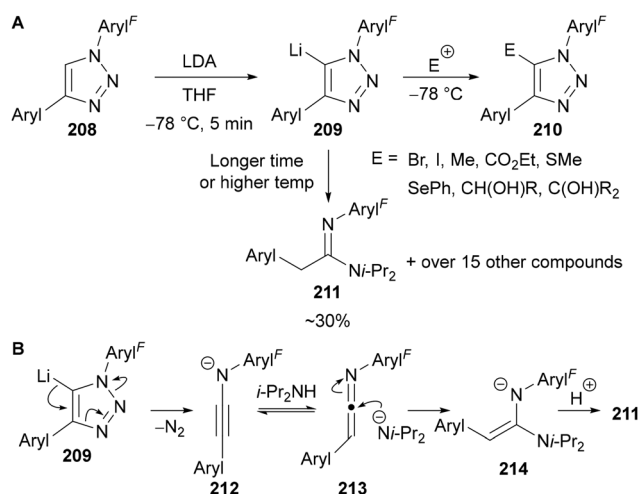


metalated triazoles of the other triazole regioisomer are known to be unstable when bearing electron-withdrawing *N*-substituents. 1,4-Disubstituted triazoles bearing *N*-polyfluoroaryl groups **208** were shown to undergo rapid deprotonation with lithium diisopropylamide (LDA) at  $-78\text{ }^{\circ}\text{C}$ , with the lithiated intermediate **209** subsequently trapped at  $-78\text{ }^{\circ}\text{C}$  with a variety of electrophiles (Scheme 59A).<sup>128</sup> However if the lithiated intermediate **209** was left for extended times or allowed to warm above  $-78\text{ }^{\circ}\text{C}$ , rapid decomposition led to over 15 compounds, including amidine **211**. Based on related literature on *N*-phenyl- and *N*-sulfonyl triazoles,<sup>129</sup> 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.

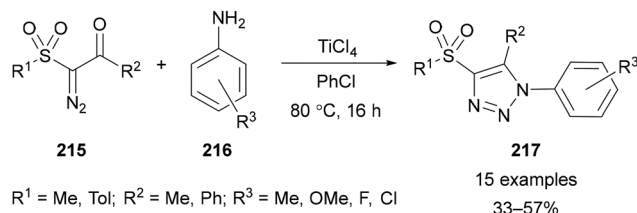
Avoiding the use of azides,<sup>16</sup> the cyclocondensation of  $\alpha$ -diazoketones and amines provides access to triazoles.<sup>130</sup> This approach is sometimes referred to as the Wolff triazole synthesis.<sup>131</sup> Typically, an  $\alpha$ -electron-withdrawing group and a Lewis or Brønsted acid is required to promote condensation of the amine and ketone. In 2019, Krasavin reported an example of this approach using sulfonyl-substituted  $\alpha$ -diazoketones **215** and anilines **216**, in which examples using fluorinated aniline derivatives were demonstrated (Scheme 60).<sup>132</sup> Presumably fluorinated aniline derivatives could also be applied in other Wolff triazole syntheses,<sup>130</sup> 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  $90\text{--}140\text{ }^{\circ}\text{C}$  to give *N*-polyfluoroalkyl triazoles.<sup>133</sup> 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.



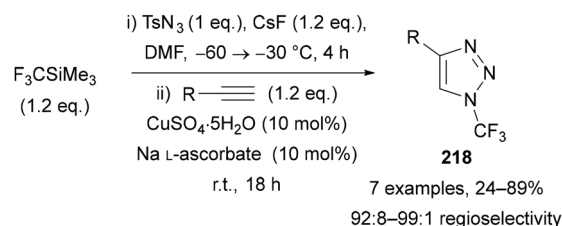
**Scheme 60** Triazole synthesis via Wolff cyclocondensation.

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,<sup>134</sup> 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.<sup>110</sup> 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).<sup>110</sup> 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.

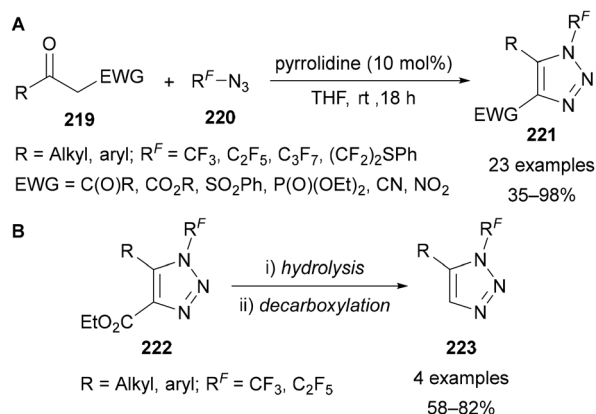
In addition to applications in CuAAC reactions,<sup>91,101,102,109,110,112,113,135</sup> Beier has demonstrated the use of polyfluoroalkyl azides **220** in an enamine-catalysed synthesis of triazoles **221** from 1,3-diketones and  $\beta$ -keto esters, sulfones, phosphonates, nitriles and  $\alpha$ -nitroketones **219** (Scheme 62A).<sup>136</sup> 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.<sup>23b</sup> The difluoromethylation of triazole and benzotriazole derivatives has been reported using a range of difluorocarbene precursors.<sup>137</sup> 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).

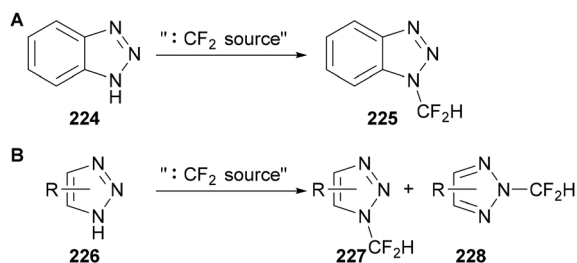


**Scheme 61** One-pot synthesis of *N*-trifluoromethyl triazoles **218**.



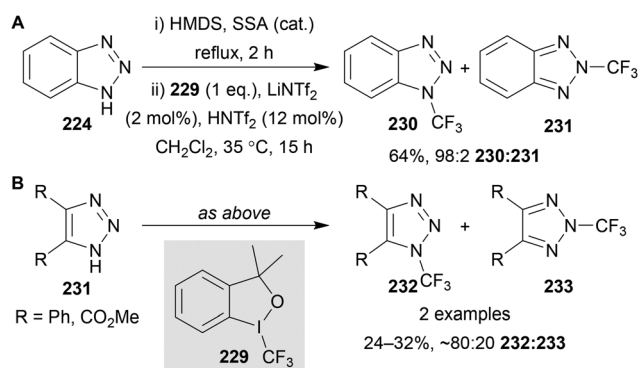


**Scheme 62** Preparation of 1,4,5-trisubstituted *N*-polyfluoroalkyl triazoles **221** and subsequent decarboxylation to access 1,5-trisubstituted *N*-polyfluoroalkyl triazoles **223**.



**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**.<sup>138</sup> 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<sub>2</sub> and LiNTf<sub>2</sub> gave high *N*(1) regioselectivity for the trifluoromethylation of



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

benzotriazole **224** (Scheme 64A), however when using triazoles **231** a mixture of both the *N*(1)- and *N*(2)-trifluoromethylated triazoles **232** and **233** was obtained (Scheme 64B).

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

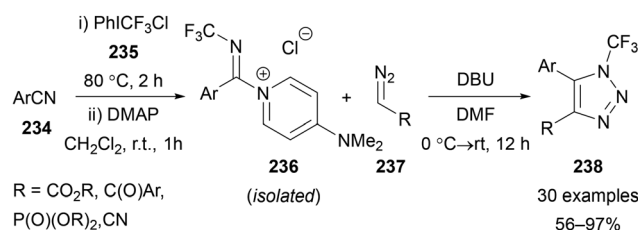
## 5. Applications of C(4) and C(5) fluorinated 1,2,3-triazoles

### 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)<sup>143</sup> to test against the cancer Osaka thyroid (COT) protein, which is involved in the formation of tumour necrosis factor  $\alpha$ : 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<sub>50</sub> value by a factor of  $\sim 10^4$ . The C(5)-fluorinated triazole was synthesised from the iodine analogue using Fokin's Halex methodology.<sup>38</sup>

In 2019, Idorsia Pharmaceuticals prepared drug candidates **240** to inhibit two key dioxygenases (Fig. 3),<sup>144</sup> 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<sup>41</sup> were used to prepare the fluorinated derivative, and whilst the addition of a C(5)-fluorine did not reduce the IC<sub>50</sub> 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<sub>3</sub> triazoles **238** from DMAP-stabilised nitrilium salts **236** and diazo compounds **237**.



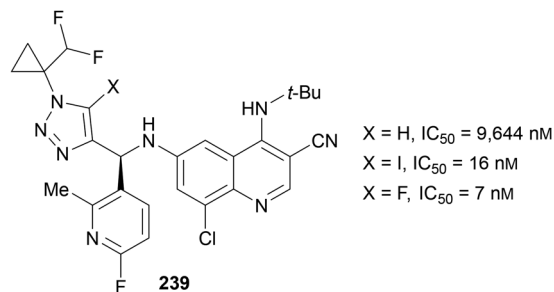


Fig. 2 5-Fluoro-triazole-containing COT treatments.

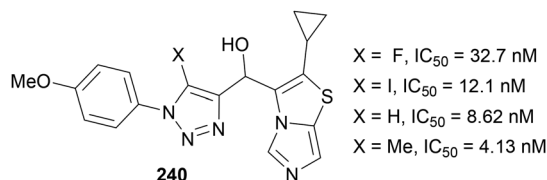


Fig. 3 5-Fluoro-triazole-containing dioxxygenase inhibitors.

protein convertase subtilisin/kexin 9 (PCSK9), which is important in cholesterol metabolism.<sup>145</sup> 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<sup>38</sup> 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.<sup>146</sup> 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 ( $>100 \mu\text{M}$  to  $16 \mu\text{M}$ , 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.

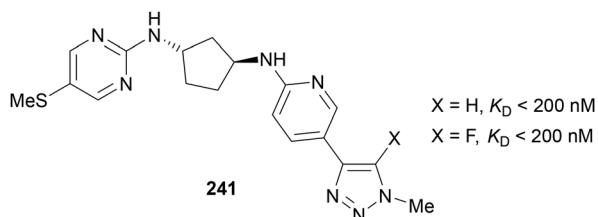


Fig. 4 5-Fluoro-triazole-containing PCSK9 inhibitors.

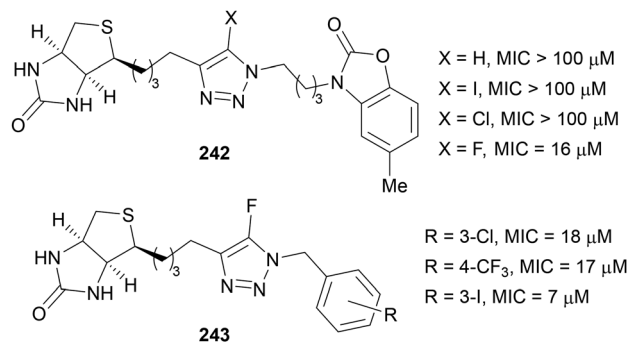


Fig. 5 5-Fluoro-triazole-containing BPL inhibitors.

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).<sup>147</sup> In the examples shown below, the  $\text{ED}_{50}$  and therapeutic index (TI) values are improved with both C(4)-H and C(4)-F triazole derivatives **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).<sup>148</sup> 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

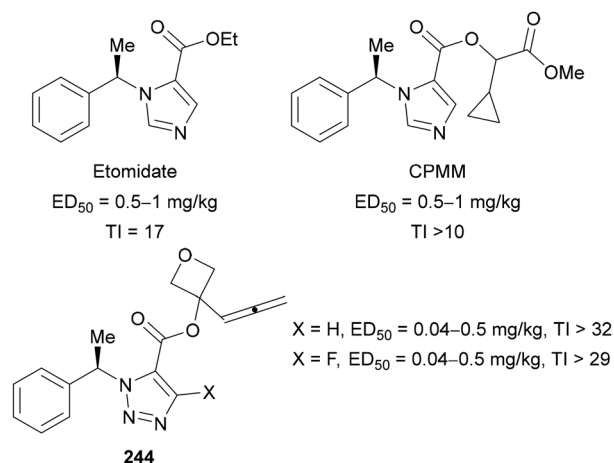
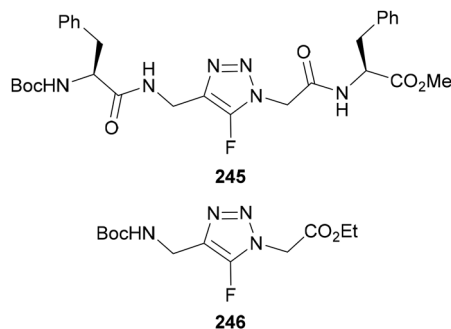


Fig. 6 4-Fluoro-triazole-containing anaesthetics.





**Fig. 7** 5-Fluoro-triazoles in peptides.

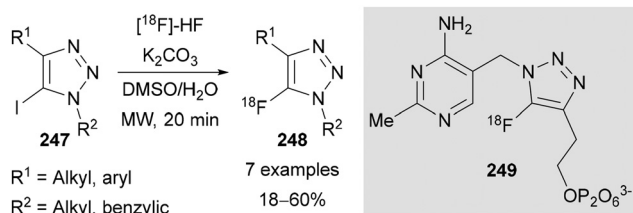
devices, for use in the slow release of a pharmaceutical agents.<sup>149</sup>

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

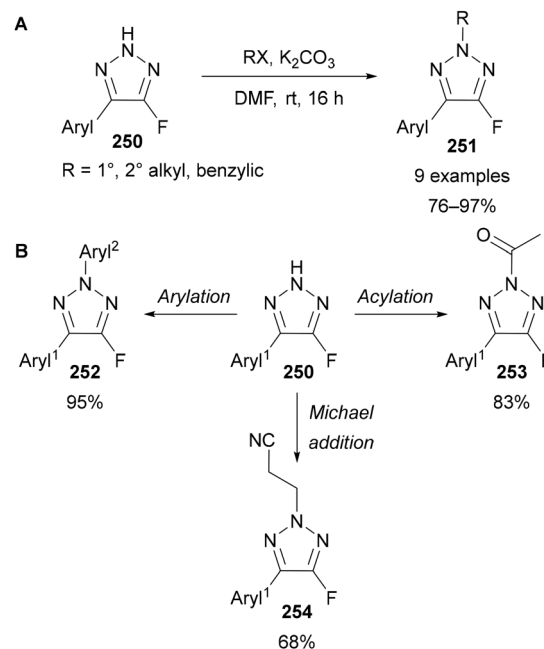
## 5.2. Use as synthetic intermediates

Regioselective alkylation of *NH*-triazoles in the N(2) position is typically difficult to achieve, requiring the use of directing<sup>151</sup> or bulky<sup>152</sup> 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).<sup>30</sup> X-ray crystallography and DFT showed the 2*H* tautomer of **251** is energetically favoured over the 1*H* and 3*H* tautomers.<sup>30</sup> 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, hydroxy-methylation and Michael addition reactions were used to demonstrate the versatility of this method (Scheme 67B).

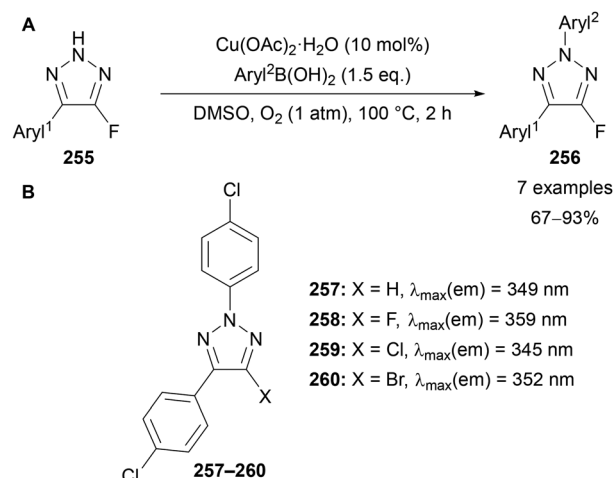
Nenajdenko noted that the 2,5-diaryl-4-fluoro-triazoles possessed fluorescence properties, with their synthesis and application further expanded by Nenajdenko and Tabolin in 2018 (Scheme 68A).<sup>153</sup> All triazoles **256** were found to absorb light in the near-middle UV range with maxima at 300–325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



**Scheme 66** Radiolabelled synthesis of 5-<sup>18</sup>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)<sub>2</sub>, Cu(OAc)<sub>2</sub> (10 mol%), O<sub>2</sub>, DMSO, 100 °C, 2 h; or (S<sub>N</sub>Ar) aryl–F, K<sub>2</sub>CO<sub>3</sub>, DMSO, 70 °C, 1 h; acylation: Ac<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 3 h; Michael addition: CH<sub>2</sub>=CHCN, Et<sub>3</sub>N, DMF, rt, 20 h.<sup>30</sup>



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

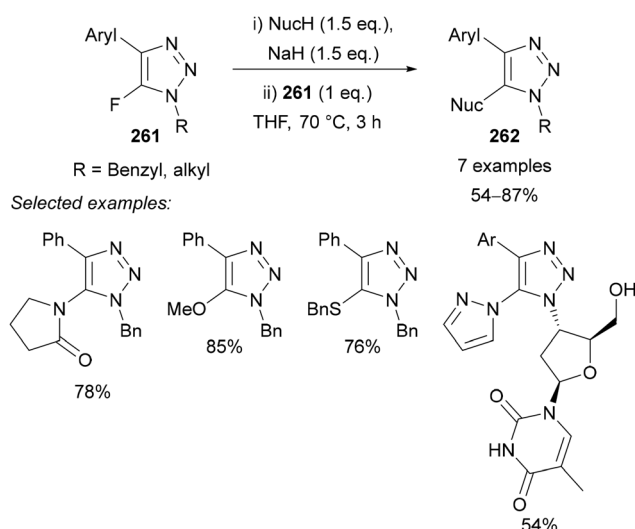
Emission was recorded in near-UV to violet/blue range, demonstrating the compounds to be blue light emitting fluorophores. Incorporation of a *p*-methoxybenzene substituent in N(2) position (Aryl<sup>2</sup>) led to a red shift in the emission spectrum, whilst electron-withdrawing *p*-cyanobenzene caused 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-



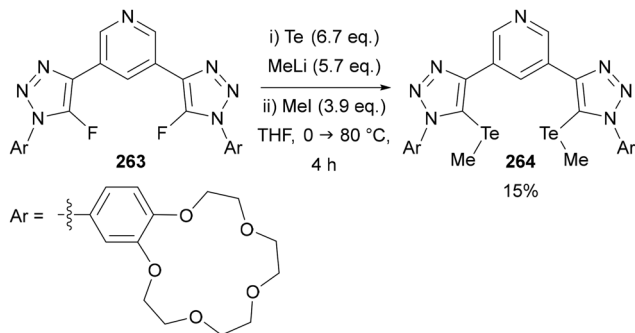
nated derivative **258** was shown to most significantly increase the emission maximum (359 nm, Scheme 68B). These fluorinated-triazoles may therefore have applications in medicine or materials.

Following the development of the Halex reaction, Fokin demonstrated the use of 5-fluoro-triazoles **261** as substrates for  $S_NAr$  reactions (Scheme 69).<sup>38</sup> 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).<sup>154</sup> 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,



**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**.

whilst the tellurated triazoles acted as Lewis acidic chalcogen bond donors to bind the halide anion.

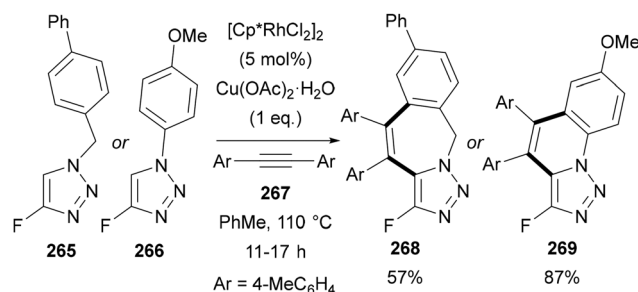
Finally, Ichikawa used 4-fluoro-triazoles **265** and **266** in rhodium catalysed C–H activation-[4 + 2] annulations<sup>155</sup> with diarylalkynes **267** to give tricyclic systems **268** and **269** (Scheme 71).<sup>34</sup> The triazoles were proposed to act as directing groups for the C–H activation.

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

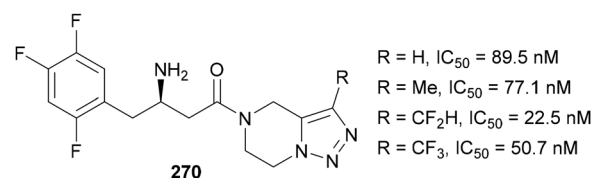
### 6.1. Pharmaceutical applications

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).<sup>156</sup> 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)– $CF_3$ -substituted 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  $\alpha$ -glucosidase inhibitors (Fig. 9).<sup>157</sup> 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.



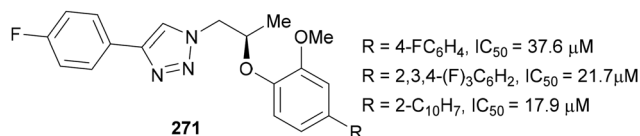


Fig. 9 4-Fluorophenyl-triazole containing  $\alpha$ -glucosidase inhibitors.

ate azide. The  $\text{IC}_{50}$  values show these compounds are all potent inhibitors of this enzyme, outperforming the marketed oligosaccharide-based drug Acarbose ( $\text{IC}_{50} = 942 \mu\text{M}$ ). 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).<sup>158</sup> 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  $\text{CF}_3$  group on the triazole dramatically reduced the  $\text{IC}_{50}$  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.<sup>159</sup> SAR studies determined that the electronegativity of the fluorinated groups was key in increasing the potency of the inhibitor structure **273** (Fig. 11). Substituting  $\text{CH}_3$  for  $\text{CF}_3$  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 pro-

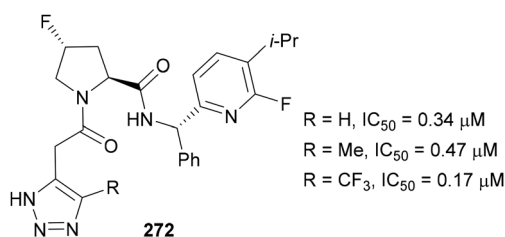


Fig. 10  $\text{CF}_3$ -substituted triazole-based glycogen synthase 1 inhibitors.

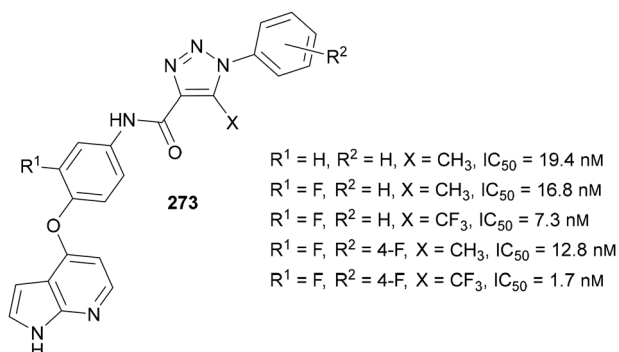
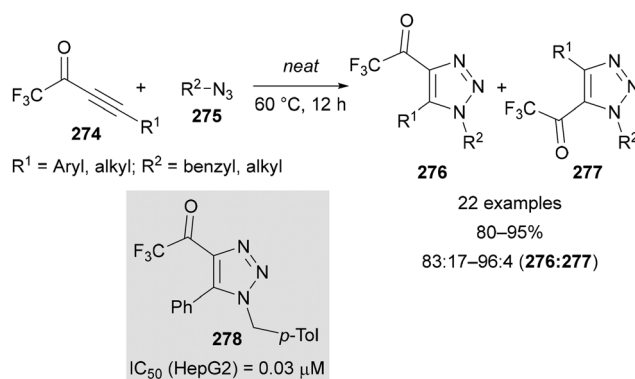


Fig. 11  $\text{CF}_3$ -substituted triazole-based kinase inhibitors.

posed that  $\text{CF}_3$  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  $\text{IC}_{50}$  value down to 1.68 nM, below that of Foretinib ( $\text{IC}_{50} = 1.92 \text{ nM}$ ), a kinase inhibitor that progressed to Phase II clinical trials.<sup>160</sup>

Wu reported the use of 4-trifluoroacetyl-1,2,3-triazoles as potential anticancer agents in 2018.<sup>161</sup> 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 ( $\geq 83 : 17$  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  $\text{IC}_{50}$  value of 0.03  $\mu\text{M}$ .

Teixeira reported the ability of fluorinated-triazole compounds to act as anti-fungal agents in 2022,<sup>162</sup> 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  $\text{EC}_{90}$  values were shown to be between 1 and 5  $\text{mg mL}^{-1}$ , 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 ( $< 0.05 \text{ mg mL}^{-1}$ ), however, this eugenol is prone to degradation *via* heat, light and oxygen, hence



Scheme 72 4-Trifluoroacetyl-triazole anticancer agents.

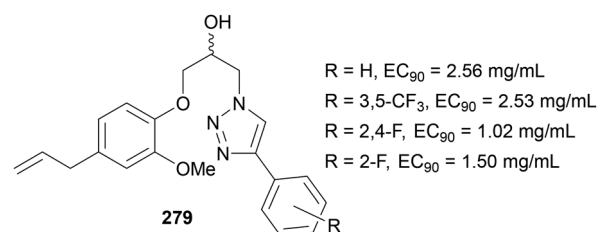


Fig. 12 C(4)-(Poly)fluoroaryl-triazole fungicide candidates.

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).<sup>163</sup>

Another anticonvulsant bearing the 1,2,3-triazole moiety was reported by Kelley.<sup>164</sup> 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<sub>50</sub>, 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:<sup>165</sup> an important target for treating inflammatory diseases.<sup>166</sup> 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).<sup>167</sup> Some of the synthesised 1,2,3-triazole hybrids were effective against the human cancer cell lines tested, with

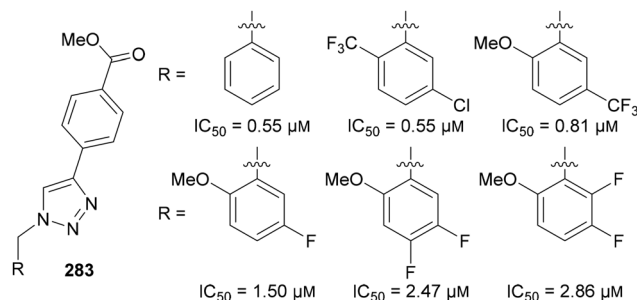


Fig. 15 Fluorinated benzyl derivatives of a NLRP3 inhibitor and their IC<sub>50</sub> values.

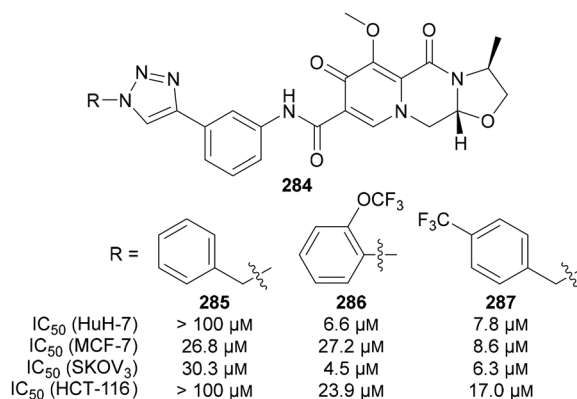


Fig. 16 IC<sub>50</sub> values for activity of 1,2,3-triazole-cabotegravir hybrids **284** against several cancer cell lines. HuH-7 = human hepatocellular carcinoma; MCF-7 = human breast cancer; SKOV3 = human ovarian cancer; HCT-116 = human colon cancer.

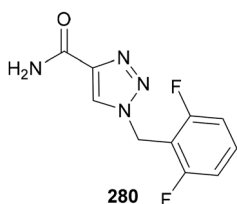


Fig. 13 Structure of Rufinamide **280**.

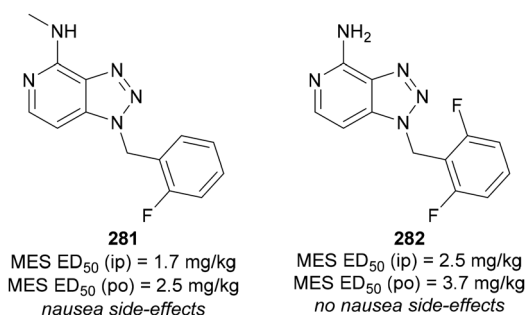


Fig. 14 Anticonvulsants **281** and **282**. ip = intraperitoneal injection; po = oral administration.

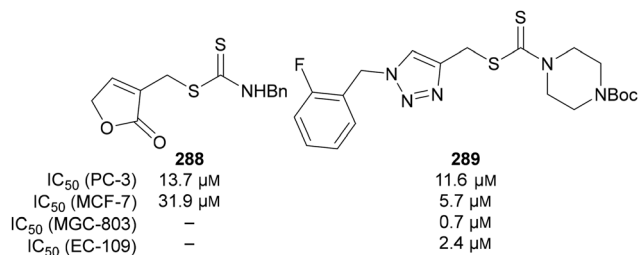
fluorinated compounds **286** and **287** reported to be the most active. **287** was active against all tested cell lines, while **286** was strongly active against two cell lines. By comparison, the non-fluorinated analogue **285**, in addition to the other 25 derivatives tested, displayed significantly 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.<sup>168</sup> Fluorinated triazole-containing dithiocarbamates **289** compared favourably to dithiocarbamate **288** hybrids reported previously by Liu (Fig. 17).<sup>169</sup>

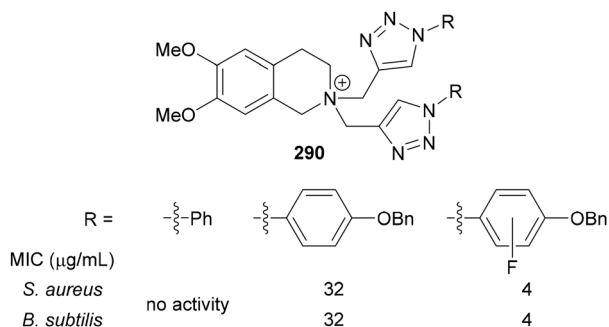
In 1988, Kadaba reported an early example of *N*-polyfluorophenyl 1,2,3-triazoles in medicinal chemistry.<sup>170</sup> The authors described promising anti-convulsant properties of aryl- and pyridyl-functionalised triazolines and 1,2,3-triazoles. Of the triazoles tested, chlorinated and fluorinated 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.<sup>85d</sup> Screening a range of *N*-aryl triazoles revealed that the





**Fig. 17** IC<sub>50</sub> values for activity of fluorinated 1,2,3-triazole dithiocarbamate **289**, and previously reported dithiocarbamate hydride **288**, against several cancer cell lines.



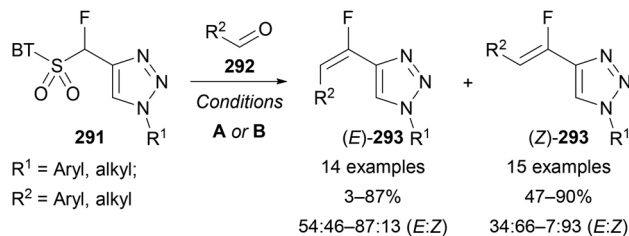
**Fig. 18** Select examples of 1,2,3-triazoles-functionalised tetrahydroisoquinolinium-salts **290** investigated for antibacterial activity.

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<sub>3</sub> 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),<sup>64</sup> were used as Julia-Kocienski olefination reagents for the stereoselective formation of fluoroalkenes **293**.<sup>64</sup> By varying the reaction conditions, formation of either the *E*- or *Z*-fluoro-alkene could be favoured (Scheme 73).<sup>64b</sup> 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.<sup>64b</sup>

The applicability of 4-sulfonyl fluoride substituted triazoles **294** in SuFEx click reactions was demonstrated by Fokin and Moses (Scheme 74).<sup>65</sup> Reaction with phenolates **295** or amines **297** provided access to sulfonates **296** (Scheme 74A) and sulfo-

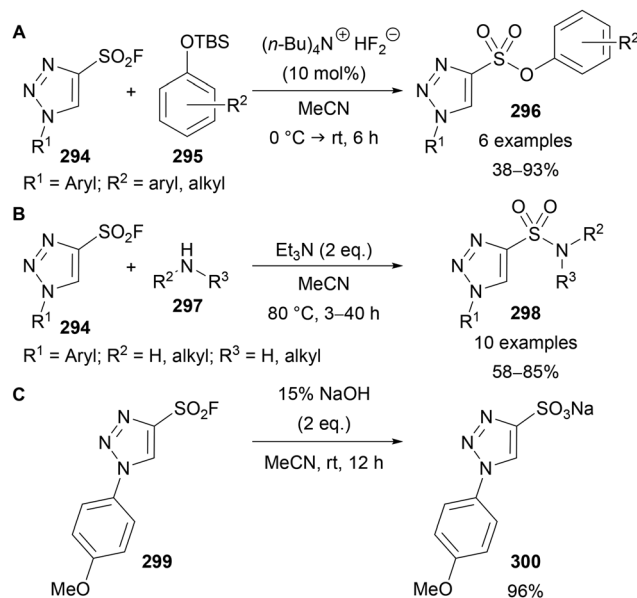


Conditions:

**A** (*E* selective): DBU (4.0 eq.), THF, 60 °C, 2.5 h

**B** (*Z* selective): LiHMDS (2.4 eq.), DMF/DMPU, –78 °C, 3 min

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



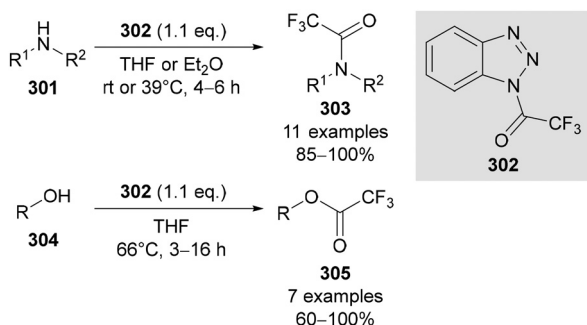
**Scheme 74** Example SuFEx applications of 4-sulfonyl fluoride substituted triazoles.

namides **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).<sup>171</sup> 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-





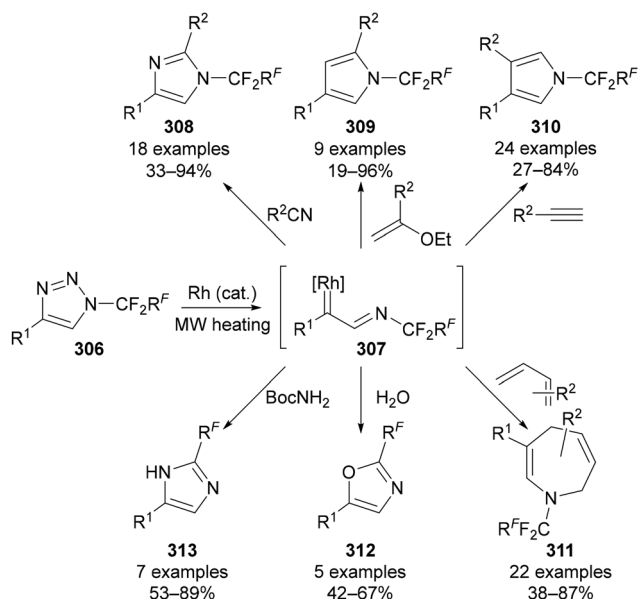


**Scheme 75** Trifluoroacetylation of amines and alcohols.

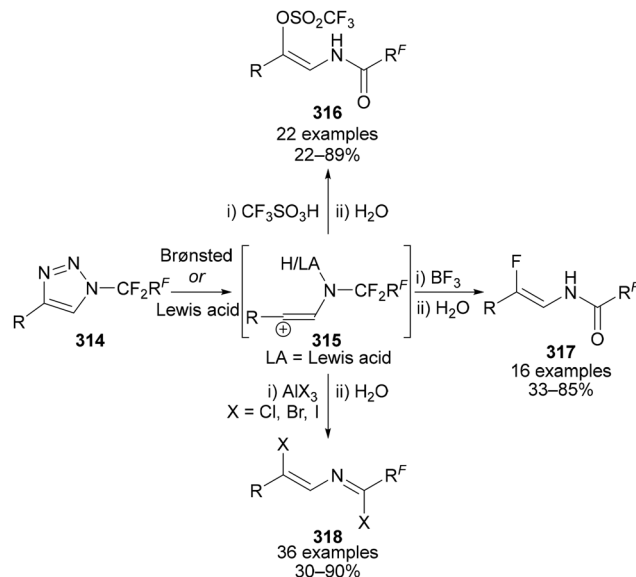
venient to use. Katritzky extended this methodology for the polyfluoroacetylation of primary and secondary amines by using polyfluoroacetylated benzo-1,2,3-triazoles.<sup>172</sup>

More recently, Beier has reported a range of synthetic applications of *N*-polyfluoroalkyl triazoles **306**,<sup>23c</sup> 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<sub>2</sub>,<sup>173</sup> 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).<sup>101,174</sup>

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<sub>2</sub> 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 **317** or β-(*Z*) imido enamide halides **318**.

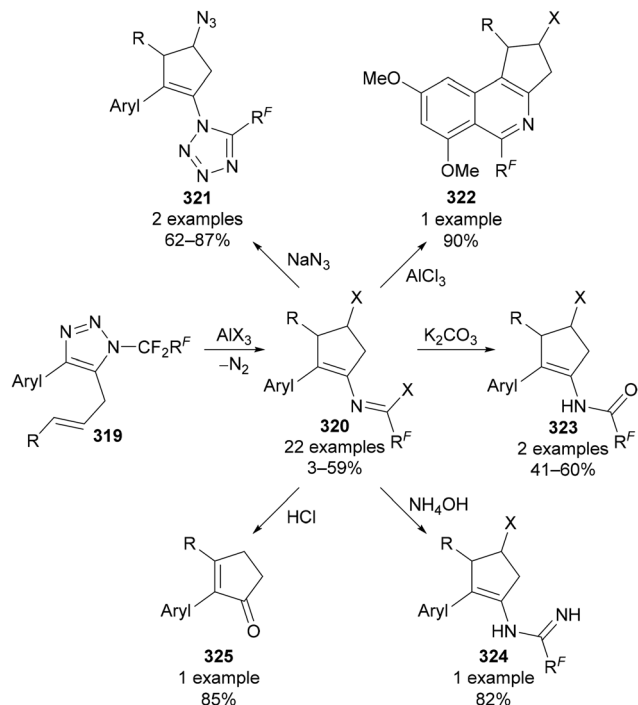
the identity of the Brønsted or Lewis acid could, following hydrolysis, result in the formation of (*Z*)-vinyl triflate enamides **316**,<sup>101,175</sup> β-(*Z*)-enamido fluorides **317**,<sup>176</sup> and β-(*Z*) imido enamide chlorides, bromides and iodides **318** (Scheme 77).<sup>135b</sup> Beier 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).<sup>135a</sup> The cyclopentenyl imido enamide 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).

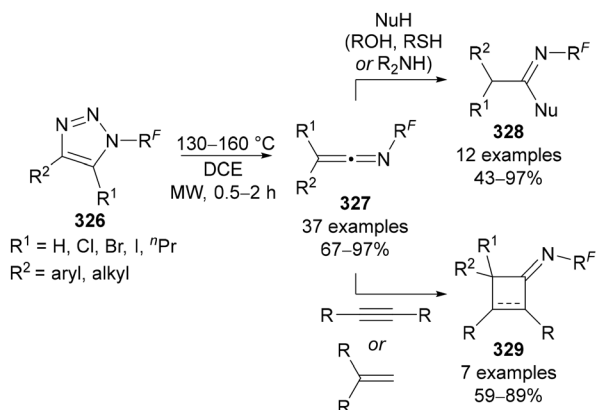
Beier has also reported the formation of ketenimine intermediates **327** from the thermal aza-Wolff rearrangement of *N*-polyfluoroalkyl-triazoles **326** (Scheme 79).<sup>177</sup> Treatment of the ketenimine intermediate **327** with oxygen-, sulfur- and nitrogen-based nucleophiles provides access to *N*-polyfluoroalkylated imidates, thioimides and amidines **328**, whilst treatment with alkenes or alkynes results in imino-cyclobutanes 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).<sup>96e</sup> DFT studies of the peptide indicated the presence of hydrogen bonding between the amide and fluorine



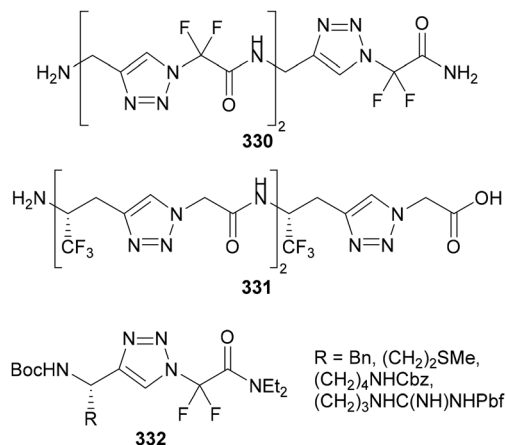


**Scheme 78** Formation and synthetic versatility of cyclopentenyl imidoyl halides **320**.



**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<sub>2</sub> group could help the structure adopt a single, rigid conformation. Ongeru reported the synthesis of triazole-peptide hybrid **331** with stereogenic CF<sub>3</sub> substituents on the backbone (Scheme 80).<sup>96h</sup> 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.<sup>96h</sup> Olsen has also reported a selection of triazole-peptide dipeptide mimics that utilise an *N*-CF<sub>2</sub> functionalised triazole **332**. The authors synthesised Fmoc-

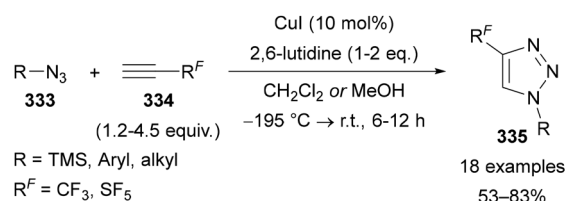


**Scheme 80** Fluorinated triazole-peptide hybrid foldamers. Pbf = 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl.

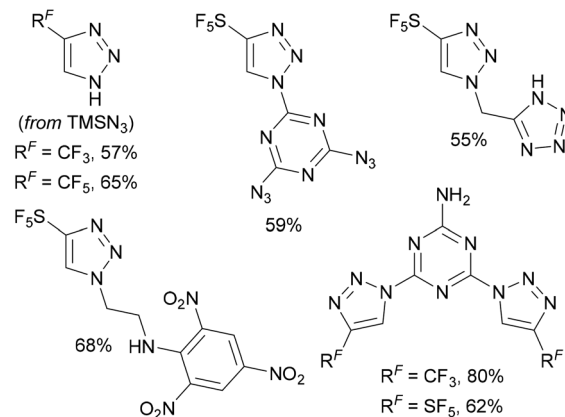
and Boc-protected dipeptide mimics, which were used for the synthesis of Leu-enkephalin analogues (Scheme 80).<sup>96f</sup>

### 6.3. Materials applications

Shreeve has reported the use of 4-CF<sub>3</sub> and SF<sub>5</sub>-triazoles **335** as energetic materials,<sup>178</sup> 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



Selected examples:



**Scheme 81** Synthesis and application of 4-CF<sub>3</sub> and SF<sub>5</sub>-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  $\text{SF}_5$ -contained triazoles were found to have higher densities and more favourable detonation properties relative to the  $\text{CF}_3$  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  $\pi$ - $\pi$  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.

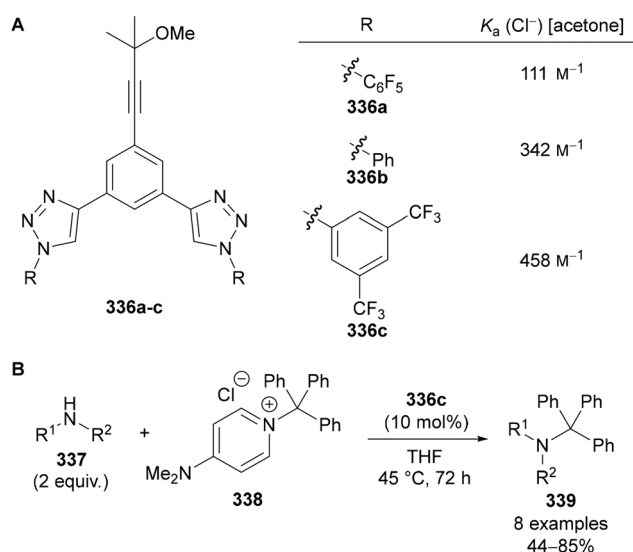
Several groups have reported the use of polyfluorinated  $N$ -aryl triazoles within anion binding, as either anion binding catalysts or as anion transporters. The earliest of these studies was performed by Mancheño where the chloride ion binding ability of a range of bis-triazoles **336a–c** was evaluated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

The chloride binding association constant for bis-triazole **336c**, bearing  $N$ -3,5- $\text{CF}_3$ -phenyl groups, was significantly improved relative to the use of a simple  $N$ -phenyl substituent **336b** ( $K_a = 458 \text{ M}^{-1}$  vs.  $K_a = 342 \text{ M}^{-1}$ ). In contrast, the use of an  $N$ -pentafluorophenyl substituent **336a** led to a decrease in chloride binding ( $K_a = 111 \text{ M}^{-1}$ ). It was suggested that the stronger chloride binding observed for the bis- $\text{CF}_3$ -phenyl triazole **336c** was due to the *ortho*-protons present on the bis- $\text{CF}_3$ -phenyl ring, which provide an additional non-classical

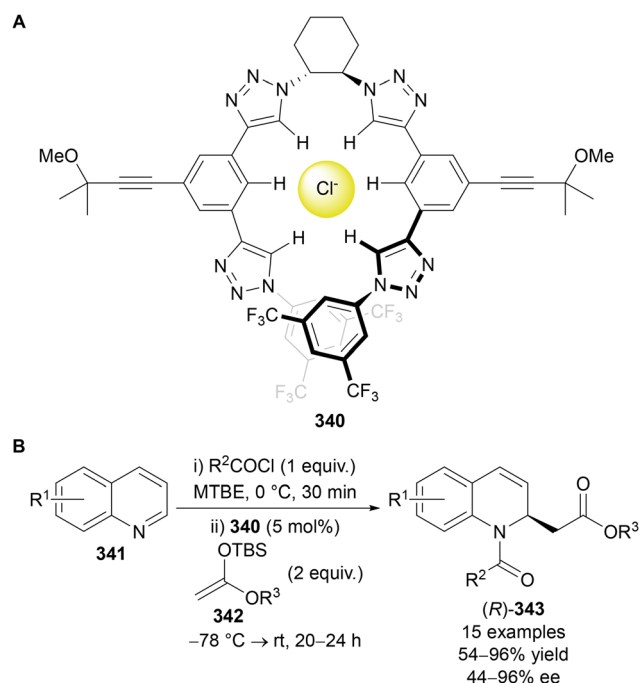
hydrogen bond to the chloride anion. DFT studies suggested that the bis- $\text{CF}_3$ -phenyl ring of **336c** sits co-planar with the triazole, thus facilitating the formation of this additional non-classical hydrogen bond. In contrast, the pentafluorophenyl group of **336a** sits at an angle due to 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  $\text{CF}_3$  group in order to obtain a chiral tetra-triazole anion binder **340** (Scheme 83A).<sup>180</sup> 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.<sup>181</sup> Initially reported for the asymmetric dearomatisation of quinolines **341** (Scheme 83B),<sup>180</sup> the catalyst has since been applied for further studies into the dearomatisation of quinolines, isoquinolines, pyridines, diazaarenes and pyrrolidines.<sup>182</sup> In addition, investigations into the spatial folding of the catalyst<sup>183</sup> and in-depth NMR studies on the effects of changing the anion have been reported.<sup>184</sup>

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

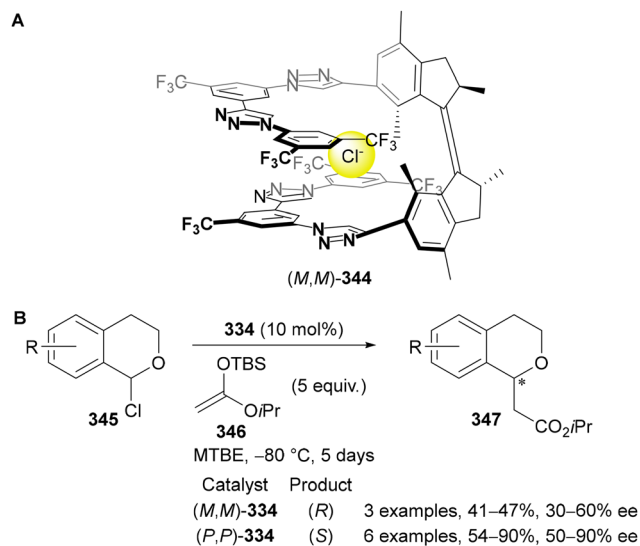


**Scheme 82** Mancheño's first generation 1,2,3-triazole chloride anion binding catalyst **336c**.



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

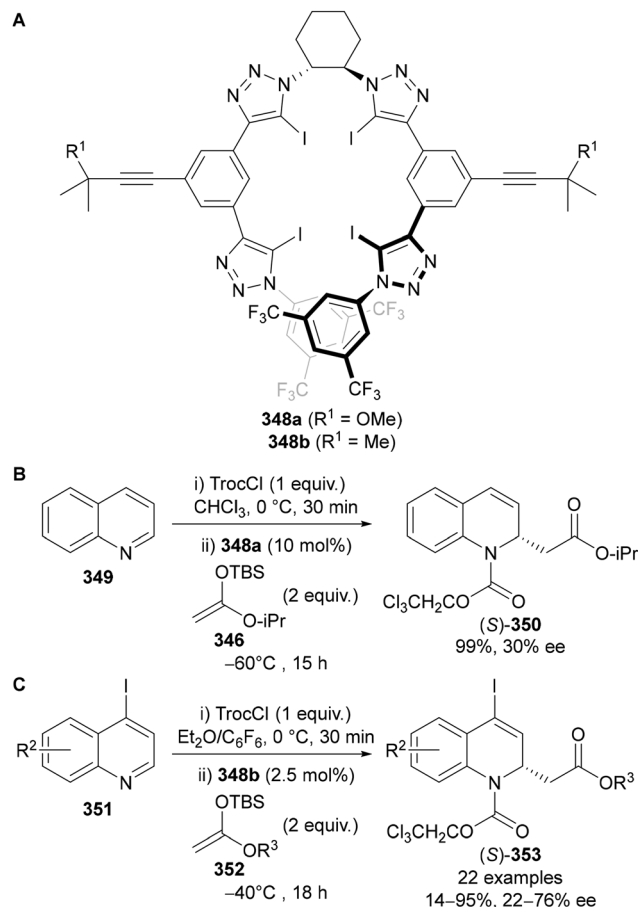




Scheme 84 Molecular motor-based anion binding catalysis.

described a unidirectional motor which, upon irradiation with light, transitions from a racemic *trans*-form of the catalyst into a helical pseudo-chiral *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).<sup>116c,k</sup> 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**:  $K_a(\text{Cl}^-) = 1125 \text{ M}^{-1}$ ; **340**:  $K_a(\text{Cl}^-) = 99 \text{ M}^{-1}$ ). 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.<sup>186</sup> 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 ( $K_a(\text{R})/K_a(\text{S}) = 1.41$ ) and hydrogen bond donor **340** binding more strongly with (*S*)-mandelic acid ( $K_a(\text{R})/K_a(\text{S}) = 0.78$ ). 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

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

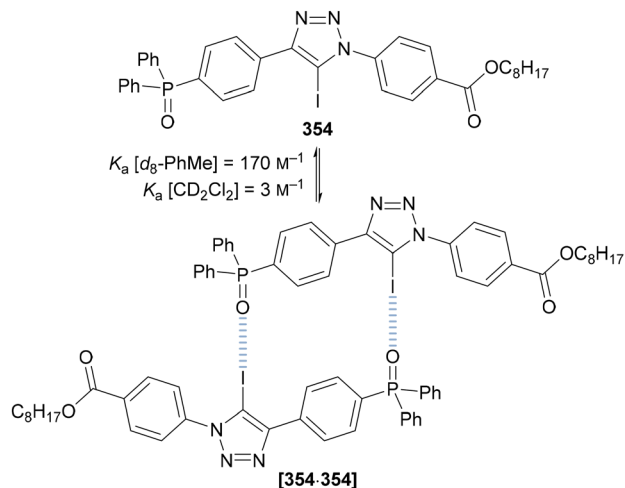
product with moderate enantioselectivity (65:35 er (*R*:*S*)) (Scheme 85B). Under analogous conditions, hydrogen bond donor **340** provided the (*R*)-enantiomer of product with higher enantioinduction (78:22 er (*S*:*R*)). This intriguing switch in enantioselectivity between the seemingly analogous 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.<sup>116k</sup>

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).<sup>116a</sup> 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-







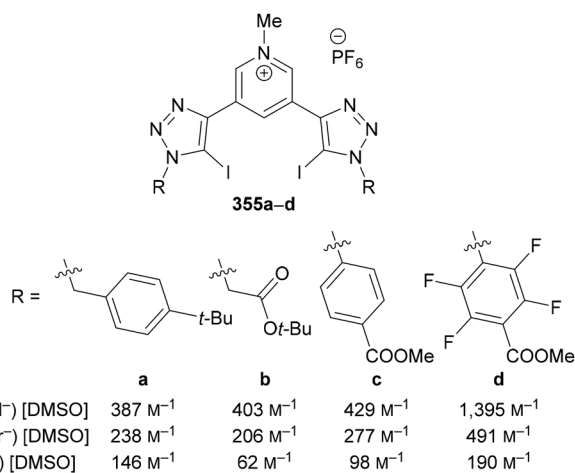
**Scheme 86** Halogen bond-induced dimerisation of **354**.

tigated the anion binding ability of a range of pyridinium bis-iodotriazole halogen bond donors **355a–d** (Fig. 19).<sup>187</sup> Modulating the triazole *N*-substituent revealed that the poly-fluorophenyl 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%.

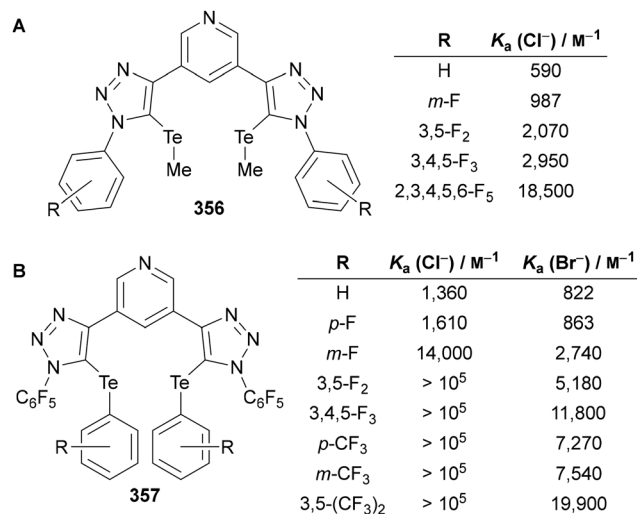
Extending this work, Beer reported an in-depth study into the use of *neutral* halogen and chalcogen bond donors based on a 3,5-bis-triazole pyridine scaffold for anion binding (Fig. 20).<sup>116b</sup> Systematic variation of the electron-withdrawing nature of the aryl substituents on both the nitrogen 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 ( $18\,500\text{ M}^{-1}$  vs.  $590\text{ M}^{-1}$ ). 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.<sup>116g</sup>

Beer and Langton applied related neutral bis-triazoles, incorporating the optimal *N*-pentafluorophenyl substituent for anion binding and transport (Fig. 21).<sup>116f</sup> *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 ( $>10^5\text{ M}^{-1}$ ), followed by chalcogen bond donor **358b** ( $18\,540\text{ M}^{-1}$ ), and finally the hydrogen bond donor **358c** ( $1010\text{ M}^{-1}$ ). 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  $\text{Cl}^-$  and  $\text{H}^+/\text{OH}^-$  transport.<sup>188</sup> 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

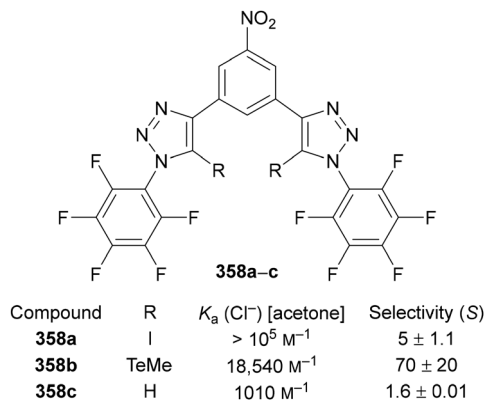


**Fig. 19** Anion association constants for pyridinium bis-iodotriazole halogen bond donors **355a–d**.



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



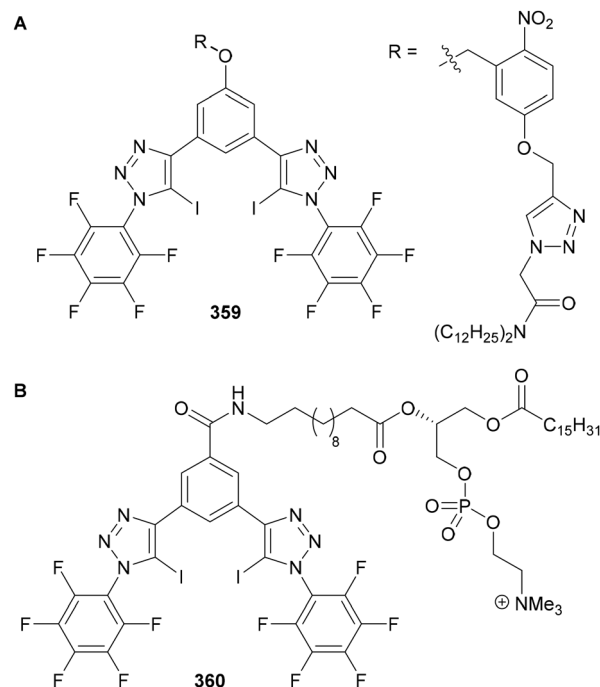


**Fig. 21** Chloride anion binding and transport in lipid bilayer vesicles. Selectivity ( $S$ ) is defined as  $\text{EC}_{50}^{\text{NMDG}}/\text{EC}_{50}^{\text{Gramicidin}}$ .  $S$  values  $>1$  indicate chloride transport is faster than  $\text{H}^+/\text{OH}^-$  transport.

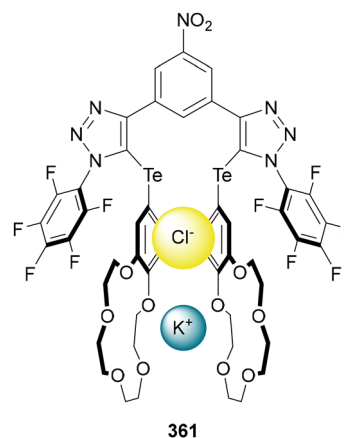
bond donor **358b** showed excellent selectivity ( $S = 70$ ). Based on the strong anion binding obtained with the neutral *N*-pentafluorophenyl substituted bis-iodotriazole **358a**, Beer subsequently reported the use of a related halogen bonding motif for chloride anion templated [2]rotaxane synthesis.<sup>116h</sup> The [2]rotaxane products exhibited enhanced binding affinities for hydrophilic  $\text{Cl}^-$  and  $\text{Br}^-$  and diminished affinity for hydrophobic  $\text{I}^-$ , 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).<sup>116j</sup> The incorporation of long alkyl chains was used to anchor the halogen bond donor within the lipid bilayer.<sup>189</sup> 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).<sup>116m</sup> 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).<sup>116i</sup> 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**.

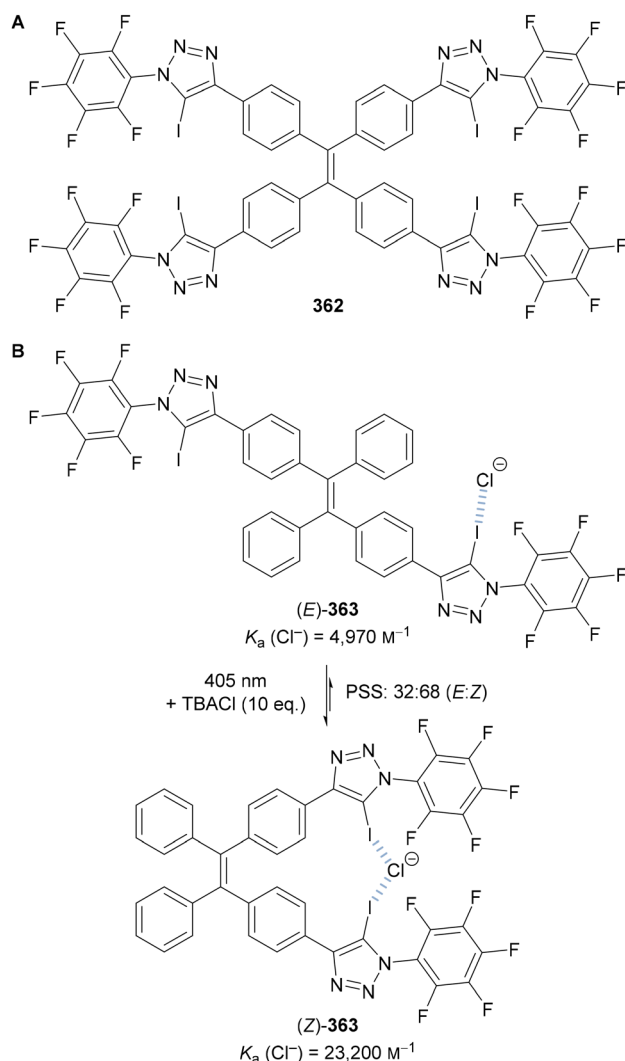
metal chlorides, however some binding was also observed for RbCl and CsCl. Preliminary studies also demonstrated the ability of **361** to promote extraction of KCl under solid-liquid and liquid-liquid extraction conditions, in addition to selective transmembrane transport of KCl over NaCl. Beer and 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.<sup>116l</sup> 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).<sup>116e</sup> 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 [ $K_a(E) = 4970 \text{ M}^{-1}$ ;  $K_a(Z) = 23\,200 \text{ M}^{-1}$ ]. 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**.

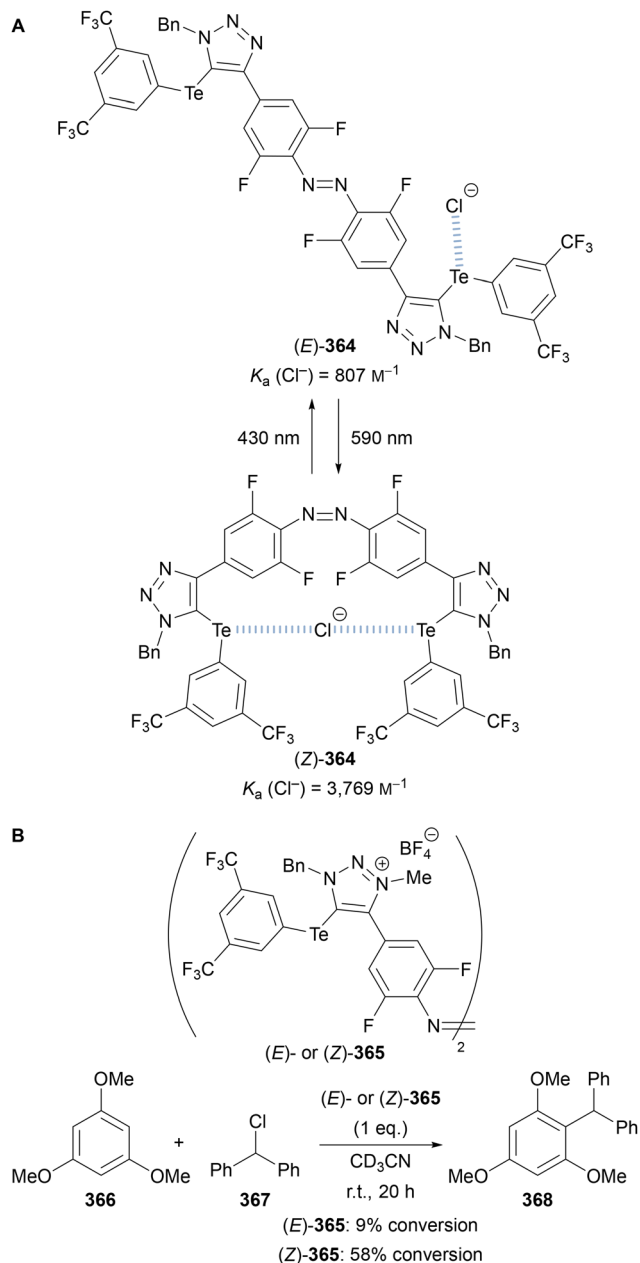
Han and Zhang exploited the controlled (*E*)/(*Z*)-photoisomerisation of azobenzene<sup>190</sup> to design photoswitchable chalcogen bond donors, containing polyfluoroaryltellurium-functionalised triazoles (Scheme 87).<sup>191</sup> Whilst the (*E*)-isomer (*E*)-**364** displayed a relatively small association constant for chloride binding ( $807 \text{ M}^{-1}$ ), isomerisation to (*Z*)-**364** resulted in a significant increase in chloride affinity ( $3769 \text{ M}^{-1}$ ;  $K_a(Z)/K_a(E) \approx 5$ ) (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,<sup>7h,i</sup> 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).<sup>192</sup> 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 [ $K_a(E\text{-}369) = 590 \text{ M}^{-1}$ ;  $K_a(Z\text{-}369) = 31\,600 \text{ M}^{-1}$ ;  $K_a(Z)/K_a(E) \approx 54$ ] (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.



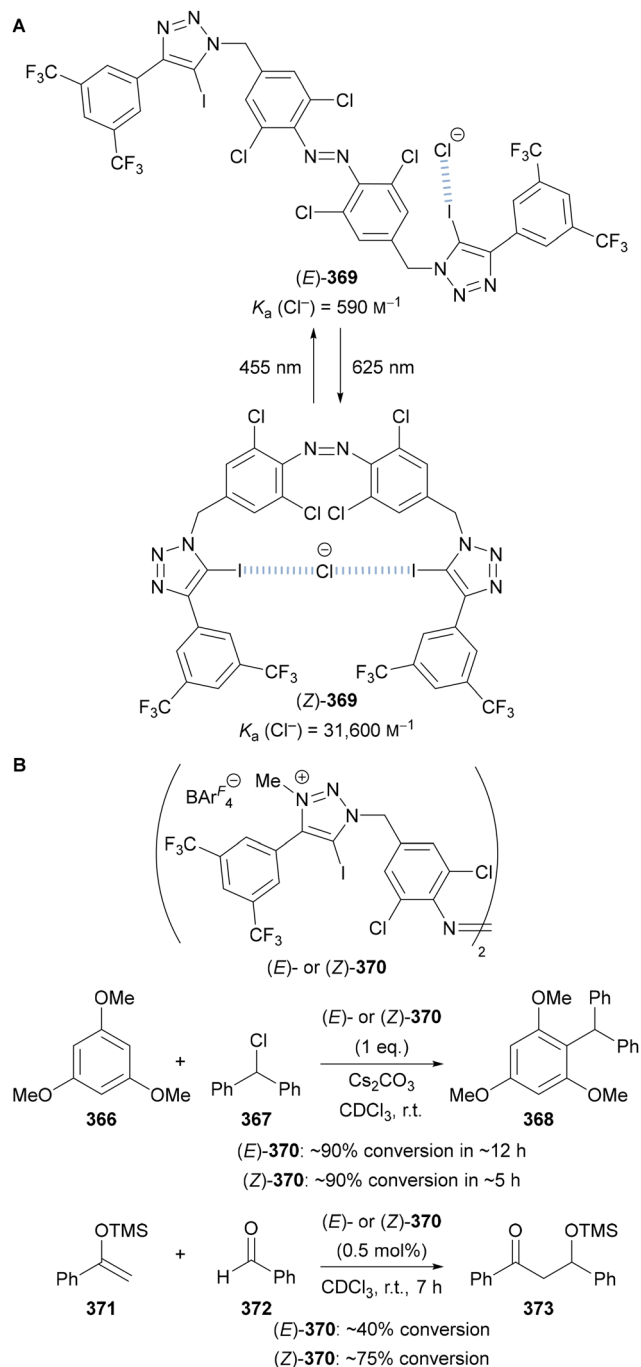
**Fig. 24** Tetraphenylethene-based tetrakis-iodotriazole halogen bond donor fluorescent chloride anion sensor **362** (A) and bis-iodotriazole halogen bond donor photoswitch **363** (B).





**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.

Fukuzawa reported the use of 1,3,4-triaryl-5-iodotriazolium iodides **376** as halogen bond donor catalysts (Scheme 89).<sup>193</sup> The triazoliums were prepared *via* a previously reported method by Bertrand and Grubbs<sup>194</sup> from the corresponding triazene and terminal alkyne, followed by iodination of the triazolium ion through deprotonation with *t*-BuOK and electrophilic trapping with  $\text{I}_2$ . Varying the electronics of the C(4)-aryl substituent of the triazolium catalyst **376** revealed that an electron-withdrawing *p*-CF<sub>3</sub> group provided the highest yield for the cyanosilylation of *p*-chloro-

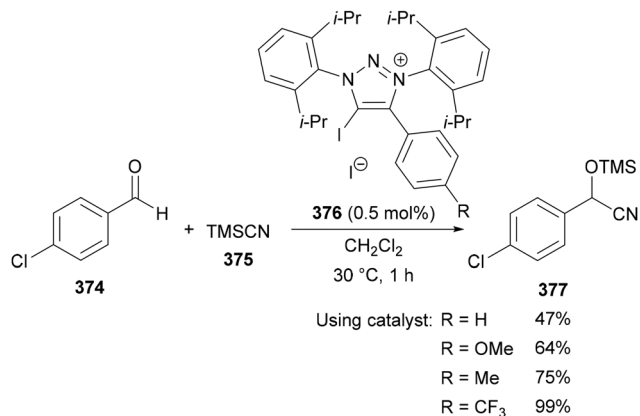


**Scheme 88** (E)/(Z) Photo-switchable halogen bond donors (A) chloride anion binding affinities for neutral halogen bond donors (E)- and (Z)-369; (B) anion abstraction and catalysis using cationic halogen bond donors (E)- and (Z)-370.

benzaldehyde **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.<sup>193</sup>







**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,<sup>38,41</sup> 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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## References

- (a) W. Adam and A. Grimison, Sigma-polarization in 5-membered heterocyclic ring systems, *Theor. Chim. Acta*, 1967, **7**, 342–351; (b) M. Begtrup, C. L. Nielsen, L. Nygaard, S. Samdal, C. E. Sjøgren and G. O. Sørensen, The Molecular Structure and Tautomer Equilibrium of Gaseous 1,2,3-Triazole Studied by Microwave Spectroscopy, Electron Diffraction and Ab Initio Calculations, *Acta Chem. Scand., Ser. A*, 1988, **42**, 500–514; (c) K. Jug, S. Chiodo, P. Calaminici, A. Avramopoulos and M. G. Papadopoulos, Electronic and Vibrational Polarizabilities and Hyperpolarizabilities of Azoles: A Comparative Study of the Structure-Polarization Relationship, *J. Phys. Chem. A*, 2003, **107**, 4172–4183.
- (a) P. Thirumurugan, D. Matosiuk and K. Jozwiak, Click Chemistry for Drug Development and Diverse Chemical-Biology Applications, *Chem. Rev.*, 2013, **113**, 4905–4979; (b) B. Gopalan and K. K. Balasubramanian, in *Click Reactions in Organic Synthesis*, ed. S. Chandrasekaran, Wiley-VCH, Weinheim, 2016, ch. 2, pp. 25–76; (c) E. Bonandi, M. S. Christodoulou, G. Fumagalli, D. Perdicchia, G. Rastelli and D. Passarella, The 1,2,3-triazole ring as a bioisostere in medicinal chemistry, *Drug Discovery Today*, 2017, **22**, 1572–1581; (d) K. Bozorov, J. Zhao and H. A. Aisa, 1,2,3-Triazole-containing hybrids as leads in medicinal chemistry: A recent overview, *Bioorg. Med. Chem.*, 2019, **27**, 3511–3531; (e) A. Rani, G. Singh, A. Singh, U. Maqbool, G. Kaur and J. Singh, CuAAC-enssembled 1,2,3-triazole-linked isosteres as pharmacophores in drug discovery: review, *RSC Adv.*, 2020, **10**, 5610–5635; (f) K. Lal and P. Yadav, Recent Advancements in 1,4-Disubstituted 1H-1,2,3-Triazoles as Potential Anticancer Agents, *Anti-Cancer Agents Med. Chem.*, 2018, **18**, 21–37; (g) M. M. Alam, 1,2,3-Triazole hybrids as anti-cancer agents: A review, *Arch. Pharm.*, 2022, **355**, 2100158; (h) I. A. Graciano, A. S. de Carvalho, F. de Carvalho da



- Silva and V. F. Ferreira, 1,2,3-Triazole- and Quinoline-based Hybrids with Potent Antiplasmodial Activity, *Med. Chem.*, 2022, **18**, 521–535; (i) S. M. A. Rahman, J. S. Bhatti, S. Thareja and V. Monga, Current development of 1,2,3-triazole derived potential antimalarial scaffolds: Structure-activity relationship (SAR) and bioactive compounds, *Eur. J. Med. Chem.*, 2023, **259**, 115699; (j) N. Poonia, A. Kumar, V. Kumar, M. Yadav and K. Lal, Recent Progress in 1*H*-1,2,3-triazoles as Potential Antifungal Agents, *Curr. Top. Med. Chem.*, 2021, **21**, 2109–2133; (k) M. Marzi, M. Farjam, Z. Kazeminejad, A. Shiroudi, A. Kouhpayeh and E. Zarenezhad, A Recent Overview of 1,2,3-Triazole-Containing Hybrids as Novel Antifungal Agents: Focusing on Synthesis, Mechanism of Action, and Structure-Activity Relationship (SAR), *J. Chem.*, 2022, 7884316.
- 3 (a) J.-F. Lutz and Z. Zarafshani, Efficient construction of therapeutics, bioconjugates, biomaterials and bioactive surfaces using azide-alkyne “click” chemistry, *Adv. Drug Delivery Rev.*, 2008, **60**, 958–970; (b) J. C. Jewetta and C. R. Bertozzi, Cu-free click cycloaddition reactions in chemical biology, *Chem. Soc. Rev.*, 2010, **39**, 1272–1279; (c) E. Kim and H. Koo, Biomedical applications of copper-free click chemistry: in vitro, in vivo, and ex vivo, *Chem. Sci.*, 2019, **10**, 7835–7851; (d) J. Kaur, M. Saxena and N. Rishi, An Overview of Recent Advances in Biomedical Applications of Click Chemistry, *Bioconjugate Chem.*, 2021, **32**, 1455–1471.
  - 4 (a) V. K. Tiwari, B. B. Mishra, K. B. Mishra, N. Mishra, A. S. Singh and X. Chen, Cu-Catalyzed Click Reaction in Carbohydrate Chemistry, *Chem. Rev.*, 2016, **116**, 3086–3240; (b) A. K. Agrahari, P. Bose, M. K. Jaiswal, S. Rajkhowa, A. S. Singh, S. Hotha, N. Mishra and V. K. Tiwari, Cu(I)-Catalyzed Click Chemistry in Glycoscience and Their Diverse Applications, *Chem. Rev.*, 2021, **121**, 7638–7956.
  - 5 (a) J. M. Holuba and K. Kirshenbaum, Tricks with clicks: modification of peptidomimetic oligomers via copper-catalyzed azide-alkyne [3 + 2] cycloaddition, *Chem. Soc. Rev.*, 2010, **39**, 1325–1337; (b) F. A. B. M. Hoogstede and F. P. J. T. Rutjes, in *Click Reactions in Organic Synthesis*, ed. S. Chandrasekaran, Wiley-VCH, Weinheim, 2016, ch. 5, pp. 141–160; (c) N. Agouram, E. M. El Hadrami and A. Bentama, 1,2,3-Triazoles as Biomimetics in Peptide Science, *Molecules*, 2021, **26**, 2937; (d) L.-M. Rečnik, W. Kandiolle and T. L. Mindt, 1,4-Disubstituted 1,2,3-Triazoles as Amide Bond Surrogates for the Stabilisation of Linear Peptides with Biological Activity, *Molecules*, 2020, **25**, 3576; (e) A. Staśkiewicz, P. Ledwoń, P. Rovero, A. M. Papini and R. Latajka, Triazole-Modified Peptidomimetics: An Opportunity for Drug Discovery and Development, *Front. Chem.*, 2021, **9**, 674705.
  - 6 (a) F. Amblard, J. H. Cho and R. F. Schinazi, Cu(I)-Catalyzed Huisgen Azide-Alkyne 1,3-Dipolar Cycloaddition Reaction in Nucleoside, Nucleotide, and Oligonucleotide Chemistry, *Chem. Rev.*, 2009, **109**, 4207–4220; (b) A. H. El-Sagheer and T. Brown, Click chemistry with DNA, *Chem. Soc. Rev.*, 2010, **39**, 1388–1405; (c) F. Amblard, O. Sari, S. Boucle, A. Khalil and R. F. Schinazi, in *Click Reactions in Organic Synthesis*, ed. S. Chandrasekaran, Wiley-VCH, Weinheim, 2016, ch. 10, pp. 309–336.
  - 7 (a) K. D. Hännia and D. A. Leigh, The application of CuAAC ‘click’ chemistry to catenane and rotaxane synthesis, *Chem. Soc. Rev.*, 2010, **39**, 1240–1251; (b) Y. Hua and A. H. Flood, Click chemistry generates privileged CH hydrogen-bonding triazoles: the latest addition to anion supramolecular chemistry, *Chem. Soc. Rev.*, 2010, **39**, 1262–1271; (c) M. Juricek, P. H. J. Kouwer and A. E. Rowan, Triazole: a unique building block for the construction of functional materials, *Chem. Commun.*, 2011, **47**, 8740–8749; (d) B. Schulze and U. S. Schubert, Beyond click chemistry – supramolecular interactions of 1,2,3-triazoles, *Chem. Soc. Rev.*, 2014, **43**, 2522–2571; (e) D. Pasini, in *Click Reactions in Organic Synthesis*, ed. S. Chandrasekaran, Wiley-VCH, Weinheim, 2016, ch. 9, pp. 287–308; (f) M. Zurro and O. G. Mancheño, 1,2,3-Triazole-Based Catalysts: From Metal- to Supramolecular Organic Catalysis, *Chem. Rec.*, 2017, **17**, 485–498; (g) M. S. Shad, P. V. Santhini and W. Dehaen, 1,2,3-Triazolium macrocycles in supramolecular chemistry, *Beilstein J. Org. Chem.*, 2019, **15**, 2142–2155; (h) M. S. Taylor, Anion recognition based on halogen, chalcogen, pnictogen and tetrel bonding, *Coord. Chem. Rev.*, 2020, **413**, 213270; (i) J. Pancholi and P. D. Beer, Halogen bonding motifs for anion recognition, *Coord. Chem. Rev.*, 2020, **416**, 213281; (j) A. C. Keuper and O. G. Mancheño, in *Supramolecular Catalysis: New Directions and Developments*, ed. P. W. N. M. van Leeuwen and M. Raynal, Wiley-VCH, Weinheim, 2022, ch. 26, pp. 387–400; (k) K. Ohmatsu and T. Ooi, in *Anion-Binding Catalysis*, ed. O. G. Mancheño, Wiley-VCH, Weinheim, 2022, ch. 7, pp. 221–247.
  - 8 (a) P. L. Golas and K. Matyjaszewski, Marrying click chemistry with polymerization: expanding the scope of polymeric materials, *Chem. Soc. Rev.*, 2010, **39**, 1338–1354; (b) M. Arseneault, C. Wafer and J.-F. Morin, Recent Advances in Click Chemistry Applied to Dendrimer Synthesis, *Molecules*, 2015, **20**, 9263–9294; (c) J. Mandal and S. Ramakrishnan, in *Click Reactions in Organic Synthesis*, ed. S. Chandrasekaran, Wiley-VCH, Weinheim, 2016, ch. 7, pp. 203–254; (d) X. Wang, X. Zhang and S. Ding, 1,2,3-Triazole-based sequence-defined oligomers and polymers, *Polym. Chem.*, 2021, **12**, 2668–2688; (e) K. Sykam, S. Donempudi and P. Basak, 1,2,3-Triazole rich polymers for flame retardant application: A review, *J. Appl. Polym. Sci.*, 2022, e52771.
  - 9 (a) Y. Chen, Y. Xianyu, J. Wu, B. Yin and X. Jiang, Click chemistry-mediated nanosensors for biochemical assays, *Theranostics*, 2016, **6**, 969–985; (b) F. Ahmed and H. Xiong, Recent developments in 1,2,3-triazole-based chemosensors, *Dyes Pigm.*, 2021, **185**, 108905.
  - 10 N. M. M. Moura and A. C. Tomé, in *Comprehensive Heterocyclic Chemistry IV*, ed. D. StC Black, J. Cossy and



- C. V. Stevens, Elsevier, Amsterdam, 2022, ch. 5.01, vol. 5, pp. 1–77.
- 11 A. Michael, Ueber die Einwirkung von Diazobenzolimid auf Acetylendicarbonsäuremethylester, *J. Prakt. Chem.*, 1893, **48**, 94–95.
  - 12 (a) R. Huisgen, 1,3-Dipolar Cycloadditions. Past and Future, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565–598; (b) R. Huisgen, G. Szeimies and L. Möbius, 1,3-Dipolare Cycloadditionen, XXXII. Kinetik der Additionen organischer Azide an CC-Mehrfachbindungen, *Chem. Ber.*, 1967, **100**, 2494–2507; (c) M. Breugst and H.-U. Reissig, The Huisgen Reaction: Milestones of the 1,3-Dipolar Cycloaddition, *Angew. Chem., Int. Ed.*, 2020, **59**, 12293–12307.
  - 13 (a) C. W. Tornøe, C. Christensen and M. Meldal, Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides, *J. Org. Chem.*, 2002, **67**, 3057–3064; (b) V. V. Rostovtsev, L. G. Green, V. V. Fokin and B. K. Sharpless, A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective “Ligation” of Azides and Terminal Alkynes, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596–2599; (c) C. W. Tornøe and M. Meldal, Cu-Catalyzed Azide-Alkyne Cycloaddition, *Chem. Rev.*, 2008, **108**, 2952–3015; (d) J. E. Hein and V. V. Fokin, Copper-catalyzed azide-alkyne cycloaddition (CuAAC) and beyond: new reactivity of copper(I) acetylides, *Chem. Soc. Rev.*, 2010, **39**, 1302–1315; (e) L. Ackermann and H. K. Potukuchi, Regioselective syntheses of fully-substituted 1,2,3-triazoles: the CuAAC/C–H bond functionalization nexus, *Org. Biomol. Chem.*, 2010, **8**, 4503–4513; (f) L. Liang and D. Astruc, The copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) “click” reaction and its applications. An overview, *Coord. Chem. Rev.*, 2011, **255**, 2933–2945; (g) E. Haldón, M. C. Nicasio and P. J. Pérez, Copper-catalysed azide-alkyne cycloadditions (CuAAC): an update, *Org. Biomol. Chem.*, 2015, **13**, 9528–9550; (h) Z. Chen, Z. Liu, G. Cao, H. Li and H. Ren, Recent Advances in Multicomponent Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles, *Adv. Synth. Catal.*, 2017, **359**, 202–224.
  - 14 (a) J. R. Johansson, T. Beke-Somfai, A. S. Stålsmeden and N. Kann, Ruthenium-Catalyzed Azide Alkyne Cycloaddition Reaction: Scope, Mechanism, and Applications, *Chem. Rev.*, 2016, **116**, 14726–14768; (b) C. Wanga, D. Ikhlef, S. Kahlal, J.-Y. Saillard and D. Astruc, Metal-catalyzed azide-alkyne “click” reactions: Mechanistic overview and recent trends, *Coord. Chem. Rev.*, 2016, **316**, 1–20; (c) R. S. Gomes, G. A. M. Jardim, R. L. de Carvalho, M. H. Araujo and E. N. da Silva Júnior, Beyond copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition: Synthesis and mechanism insights, *Tetrahedron*, 2019, **75**, 3697–3712; (d) J. Ma and S. Ding, Transition Metal-Catalyzed Cycloaddition of Azides with Internal Alkynes, *Asian J. Org. Chem.*, 2020, **9**, 1872–1888; (e) D. P. Vala, R. M. Vala and H. M. Patel, Versatile Synthetic Platform for 1,2,3-Triazole Chemistry, *ACS Omega*, 2022, **7**, 36945–36987; (f) F. Ferrara, T. Beke-Somfai and N. Kann, Recent Developments in the Ruthenium-Catalyzed Azide Alkyne Cycloaddition (RuAAC) Reaction, *Eur. J. Org. Chem.*, 2024, e202400113.
  - 15 (a) J. John, J. Thomas and W. Dehaen, Organocatalytic routes toward substituted 1,2,3-triazoles, *Chem. Commun.*, 2015, **51**, 10797–10806; (b) K. Anebuselvy and D. B. Ramachary, in *Click Reactions in Organic Synthesis*, ed. S. Chandrasekaran, Wiley-VCH, Weinheim, 2016, ch. 4, pp. 99–140; (c) H. B. Jalani, A. Ç. Karagöz and S. B. Tsogoeva, Synthesis of Substituted 1,2,3-Triazoles via Metal-Free Click Cycloaddition Reactions and Alternative Cyclization Methods, *Synthesis*, 2017, 29–41; (d) V. A. Bakulev, T. Beryozkina, J. Thomas and W. Dehaen, The Rich Chemistry Resulting from the 1,3-Dipolar Cycloaddition Reactions of Enamines and Azides, *Eur. J. Org. Chem.*, 2018, 262–294.
  - 16 Z. Chen, G. Cao, J. Song and H. Ren, Recent Developments in Azide-Free Synthesis of 1,2,3-Triazoles, *Chin. J. Chem.*, 2017, **35**, 1797–1807.
  - 17 (a) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, 2006; (b) P. Kirsch, *Modern Fluoroorganic Chemistry* Wiley-VCH, Weinheim, 2nd edn, 2013; (c) A. Harsanyi and G. Sandford, Organofluorine chemistry: applications, sources and sustainability, *Green Chem.*, 2015, **17**, 2081–2086.
  - 18 D. O'Hagan, Understanding organofluorine chemistry. An introduction to the C–F bond, *Chem. Soc. Rev.*, 2008, **37**, 308–319.
  - 19 (a) C. Isanbor and D. O'Hagan, Fluorine in medicinal chemistry: A review of anti-cancer agents, *J. Fluorine Chem.*, 2006, **127**, 303–319; (b) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, Fluorine in medicinal chemistry, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (c) D. O'Hagan, Fluorine in health care: Organofluorine containing blockbuster drugs, *J. Fluorine Chem.*, 2010, **131**, 1071–1081; (d) V. Gouverneur and K. Müller, *Fluorine in Pharmaceutical and Medicinal Chemistry*, Imperial College Press, London, 2012; (e) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. Del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011), *Chem. Rev.*, 2014, **114**, 2432–2506; (f) V. P. Reddy, *Organofluorine Compounds in Biology and Medicine*, Elsevier, Amsterdam, 2015; (g) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II–III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas, *Chem. Rev.*, 2016, **116**, 422–518; (h) N. A. Meanwell, Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design, *J. Med. Chem.*, 2018, **61**, 5822–5880.



- 20 (a) T. Fujiwara and D. O'Hagan, Successful fluorine-containing herbicide agrochemicals, *J. Fluor. Chem.*, 2014, **167**, 16–29; (b) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai and N. Shibata, Current Contributions of Organofluorine Compounds to the Agrochemical Industry, *iScience*, 2020, **23**, 101467; (c) Q. Wang, H. Song and Q. Wang, Fluorine-containing agrochemicals in the last decade and approaches for fluorine incorporation, *Chin. Chem. Lett.*, 2022, **33**, 626–642.
- 21 (a) M. G. Dhara and S. Banerjee, Fluorinated high-performance polymers: Poly(arylene ether)s and aromatic polyimides containing trifluoromethyl groups, *Prog. Polym. Sci.*, 2010, **35**, 1022–1077; (b) R. Ragni, A. Punzi, F. Babudri and G. M. Farinola, Organic and Organometallic Fluorinated Materials for Electronics and Optoelectronics: A Survey on Recent Research, *Eur. J. Org. Chem.*, 2018, 3500–3519; (c) V. F. Cardoso, D. M. Correia, C. Ribeiro, M. M. Fernandes and S. Lanceros-Méndez, Fluorinated Polymers as Smart Materials for Advanced Biomedical Applications, *Polymers*, 2018, **10**, 161.
- 22 For reviews on C(4/5)-fluorinated triazoles see: (a) J. L. Arenas and B. Crousse, An Overview of 4- and 5-Halo-1,2,3-triazoles from Cycloaddition Reactions, *Eur. J. Org. Chem.*, 2021, 2665–2679; (b) N. Pokhodylo, K. Levchenko and M. Obushak, Fluorinated 1,2,3-Triazoles: Terra Incognita in 1,2,3-Triazoles Chemistry, *ChemistrySelect*, 2024, **9**, e202302753; (c) D. Coelho, Y. Colas, M. Etcheve-Quelquejeu, E. Braud and L. Iannazzo, Halo-1,2,3-triazoles: Valuable Compounds to Access Biologically Relevant Molecules, *ChemBioChem*, 2024, **25**, e202400150.
- 23 For reviews on polyfluoroalkyl-substituted triazoles see: (a) V. A. Ostrovskii and R. E. Trifonov, in *Fluorine in Heterocyclic Chemistry*, ed. V. Nenajdenko, Springer, Cham, 2014, vol. 1, pp. 459–513; (b) B. I. Usachev, Chemistry of fluoroalkyl-substituted 1,2,3-triazoles, *J. Fluor. Chem.*, 2018, **210**, 6–45; (c) A. Markos, V. Matoušek and P. Beier, Fluoroalkyl Azides and Triazoles: Unlocking a Novel Chemical Space, *Aldrichimica Acta*, 2022, **55**, 37–44.
- 24 For medicinal chemistry applications see: I. Ullah, M. Ilyas, M. Omer, M. Alamzeb, Adnan and M. Sohail, Fluorinated triazoles as privileged potential candidates in drug development—focusing on their biological and pharmaceutical properties, *Front. Chem.*, 2022, **10**, 926723.
- 25 Z. K. Yao and Z. X. Yu, Mechanisms of the Thermal Cyclotrimerizations of Fluoro- and Chloroacetylenes: Density Functional Theory Investigation and Intermediate Trapping Experiments, *J. Am. Chem. Soc.*, 2011, **133**, 10864–10877.
- 26 W. J. Middleton and W. H. Sharkey, Fluoroacetylene, *J. Am. Chem. Soc.*, 1959, **81**, 803–804.
- 27 R. Sauvêtre and J. F. Normant, Une nouvelle preparation du fluoroacetylene - sa reaction avec les organometalliques. Synthese d'alcyne et d'enyne divers, *Tetrahedron Lett.*, 1982, **23**, 4325–4328.
- 28 R. E. Banks, M. G. Barlow, W. D. Davies, R. N. Haszeldine and D. R. Taylor, Polyhalogenoallenes. Part VIII. Routes to tetrafluoroallene and tetra-fluoropropyne, *J. Chem. Soc. C*, 1969, 1104–1107.
- 29 (a) F. Reck, F. Zhou, M. Girardot, G. Kern, C. J. Eyermann, N. J. Hales, R. R. Ramsay and M. B. Gravestock, Identification of 4-Substituted 1,2,3-Triazoles as Novel Oxazolidinone Antibacterial Agents with Reduced Activity against Monoamine Oxidase A, *J. Med. Chem.*, 2005, **48**, 499–506; (b) S. Jana, S. Adhikari, M. R. Cox and S. Roy, Regioselective synthesis of 4-fluoro-1,5-disubstituted-1,2,3-triazoles from synthetic surrogates of  $\alpha$ -fluoroalkynes, *Chem. Commun.*, 2020, **56**, 1871–1874; (c) V. A. Motornov, A. A. Tabolin, R. A. Novikov, Y. V. Nelyubina, S. L. Ioffe, I. V. Smolyar and V. G. Nenajdenko, Synthesis and Regioselective N-2 Functionalization of 4-Fluoro-5-aryl-1,2,3-NH-triazoles, *Eur. J. Org. Chem.*, 2017, 6851–6860.
- 30 V. A. Motornov, V. M. Muzalevskiy, A. A. Tabolin, R. A. Novikov, Yu. V. Nelyubina, V. G. Nenajdenko and S. L. Ioffe, Radical Nitration-Debromination of  $\alpha$ -Bromo- $\alpha$ -fluoroalkenes as a Stereoselective Route to Aromatic  $\alpha$ -Fluoronitroalkenes-Functionalized Fluorinated Building Blocks for Organic Synthesis, *J. Org. Chem.*, 2017, **82**, 5274–5284.
- 31 S. Opekar, R. Pohl, P. Beran, L. Rulisek and P. Beier, Diethyl Fluoronitromethylphosphonate: Synthesis and Application in Nucleophilic Fluoroalkyl Additions, *Chem. – Eur. J.*, 2014, **20**, 1453–1458.
- 32 T. Fujita, T. Ichitsuka, K. Fuchibe and J. Ichikawa, Facile Synthesis of  $\beta,\beta$ -Difluorostyrenes via the Negishi Coupling of Thermally Stable 2,2-Difluorovinyl Zinc-TMEDA Complex, *Chem. Lett.*, 2011, **40**, 986–988.
- 33 T. Ichitsuka, T. Takanohashi, T. Fujita and J. Ichikawa, A versatile difluorovinylation method: Cross-coupling reactions of the 2,2-difluorovinylzinc-TMEDA complex with alkenyl, alkynyl, allyl, and benzyl halides, *J. Fluor. Chem.*, 2015, **170**, 29–37.
- 34 T. Fujita, M. Takeishi and J. Ichikawa, Copper-Catalyzed [3 + 2] Annulation of Azides with a (Difluorovinyl)zinc Complex, Fluoroacetylene Equivalent, *Org. Lett.*, 2020, **22**, 9253–9257.
- 35 B. T. Worrell, J. A. Malik and V. V. Fokin, Direct Evidence of a Dinuclear Copper Intermediate in Cu(I)-Catalyzed Azide-Alkyne Cycloadditions, *Science*, 2013, **340**, 457–460.
- 36 (a) D. González-Calderón, A. Fuentes-Benites, E. Díaz-Torres, C. A. González-González and C. González-Romero, Azide-Enolate 1,3-Dipolar Cycloaddition as an Efficient Approach for the Synthesis of 1,5-Disubstituted 1,2,3-Triazoles from Alkyl/Aryl Azides and  $\beta$ -Ketophosphonates, *Eur. J. Org. Chem.*, 2016, 668–672; (b) N. T. Pokhodylo, O. Ya. Shyyka, E. A. Goreschnik and M. D. Obushak, 4-Phosphonated or 4-Free 1,2,3-Triazoles: What Controls the Dimroth Reaction of Arylazides with 2-Oxopropylphosphonates?, *ChemistrySelect*, 2020, **5**, 260–264.





- 37 T.-C. Chi, P.-C. Yang, S.-K. Hung, H.-W. Wu, H.-C. Wang, H.-K. Liu, L.-W. Liu and H.-H. Chou, Synthesis of Multisubstituted 1,2,3-Triazoles: Regioselective Formation and Reaction Mechanism, *J. Org. Chem.*, 2024, **89**, 5401–5408.
- 38 B. T. Worrell, J. E. Hein and V. V. Fokin, Halogen Exchange (Halex) Reaction of 5-Iodo-1,2,3-triazoles: Synthesis and Applications of 5-Fluorotriazoles, *Angew. Chem., Int. Ed.*, 2012, **51**, 11791–11794.
- 39 N. Grimster, L. Zhang and V. V. Fokin, Synthesis and Reactivity of Rhodium(II) *N*-Triflyl Azavinyl Carbenes, *J. Am. Chem. Soc.*, 2010, **132**, 2510–2511.
- 40 J. E. Rowe, K. Lee, D. D. Dolliver and J. E. Johnson, The Preparation of Imidoyl Fluorides, *Aust. J. Chem.*, 1999, **52**, 807–812.
- 41 D. Wang, W. Sun and T. Chu, Synthesis of 5-Fluorotriazoles by Silver-Mediated Fluorination of 5-Iodotriazoles, *Eur. J. Org. Chem.*, 2015, 4114–4118.
- 42 T. Furuya, A. E. Strom and T. Ritter, Silver-Mediated Fluorination of Functionalized Aryl Stannanes, *J. Am. Chem. Soc.*, 2009, **131**, 1662–1663.
- 43 W. G. Finnegan and W. P. Norris, Improved Synthesis of 3,3,3-Trifluoropropyne, *J. Org. Chem.*, 1963, **28**, 1139–1140.
- 44 W. Carpenter, A. Haymaker and D. W. Moore, Fluorinated 1,2,3-Triazolines, *J. Org. Chem.*, 1966, **31**, 789–792.
- 45 B. C. Hamper,  $\alpha$ -Acetylenic Esters From  $\alpha$ -Acylmethylenephosphoranes: Ethyl 4,4,4-Trifluorotetrolate, *Org. Synth.*, 1992, **70**, 246.
- 46 (a) B. Gold, N. E. Shevchenko, N. Bonus, G. B. Dudley and I. V. Alabugin, Selective Transition State Stabilization via Hyperconjugative and Conjugative Assistance: Stereoelectronic Concept for Copper-Free Click Chemistry, *J. Org. Chem.*, 2012, **77**, 75–89; (b) J. Wei, J. Chen, J. Xu, L. Cao, H. Deng, W. Sheng, H. Zhang and W. Cao, Scope and regioselectivity of the 1,3-dipolar cycloaddition of azides with methyl 2-perfluoroalkynoates for an easy, metal-free route to perfluoroalkylated 1,2,3-triazoles, *J. Fluor. Chem.*, 2012, **133**, 146–154.
- 47 S. Okusu, E. Tokunaga and N. Shibata, *Org. Lett.*, 2015, **17**, 3802–3805.
- 48 (a) G. K. S. Prakash, P. V. Jog, R. T. D. Batamack and G. A. Olah, Taming of Fluoroform: Direct Nucleophilic Trifluoromethylation of Si, B, S, and C Centers, *Science*, 2012, **338**, 1324–1327; (b) S. Barata-Vallejo, M. R. Torviso, B. Lantaño, S. M. Bonesi and A. Postigo, Nucleophilic non-metal assisted trifluoromethylation and perfluoroalkylation reactions of organic substrates, *J. Fluor. Chem.*, 2014, **161**, 134–141; (c) W. C. Fu, P. M. Macqueen and T. F. Jamison, Continuous flow strategies for using fluorinated greenhouse gases in fluoroalkylations, *Chem. Soc. Rev.*, 2021, **50**, 7378–7394.
- 49 G. Meazza and G. Zanardi, Aryl trifluoromethyl-1,2,3-triazoles, *J. Fluor. Chem.*, 1991, **55**, 199–206.
- 50 V. V. V. N. S. R. Rao, S. Ravikanth, G. V. Reddy, D. Maitraie, R. Yadla and P. S. Rao, Microwave Assisted Intramolecular Wittig Reaction: A Facile Method for the Synthesis of Conjugated Acetylenes, *Synth. Commun.*, 2003, **33**, 1523–1529.
- 51 Y. Zhang and J. Wen, A Convenient Synthesis of Bis(poly-fluorophenyl)butadiyne Monomers, *Synthesis*, 1990, 727–728.
- 52 (a) Y. Kobayashi, T. Yamashita, K. Takahashi, H. Kuroda and I. Kumadaki, Studies on Organic Fluorine Compounds. XLII. Synthesis and Reactions of Phenyltrifluoromethylacetylenes, *Chem. Pharm. Bull.*, 1984, **32**, 4402–4409; (b) Y. Shen, J. Zheng, Y. Xin, Y. Lin and M. Qi, Synthesis of perfluoroalkylated heterocyclic phosphonates, *J. Chem. Soc., Perkin Trans. 1*, 1995, 997–999; (c) S. I. Coats, J. S. Link, D. Gauthier and D. J. Hlasta, Trimethylsilyl-Directed 1,3-Dipolar Cycloaddition Reactions in the Solid-Phase Synthesis of 1,2,3-Triazoles, *Org. Lett.*, 2015, **7**, 1469–1472; (d) Z. Xiong, X.-L. Qiu, Y. Huang and F.-L. Qing, Regioselective synthesis of 5-trifluoromethyl-1,2,3-triazole nucleoside analogues via TBS-directed 1,3-dipolar cycloaddition reaction, *J. Fluorine Chem.*, 2011, **132**, 166–174.
- 53 S. Wang, L. J. Yang, J. L. Zeng, Y. Zheng and J. A. Ma, Silver-catalyzed [3 + 2] cycloaddition of isocyanides with diazo compounds: new regioselective access to 1,4-disubstituted-1,2,3-triazoles, *Org. Chem. Front.*, 2015, **2**, 1468–1474.
- 54 S. P. Green, K. M. Wheelhouse, A. D. Payne, J. P. Hallett, P. W. Miller and J. A. Bull, Thermal Stability and Explosive Hazard Assessment of Diazo Compounds and Diazo Transfer Reagents, *Org. Process Res. Dev.*, 2020, **24**, 67–84.
- 55 R. Fields and J. P. Tomlinson, Preparation of trifluoromethyl-pyrazoles and -pyrazolines by the reaction of 2,2,2-trifluorodiazethane with carbon-carbon multiple bonds, *J. Fluor. Chem.*, 1979, **13**, 147–158.
- 56 A. Bell and D. A. Edwards, Silver(I) isocyanide complexes: spectroscopic features and reactions with neutral ligands, *J. Chem. Soc., Dalton Trans.*, 1984, 1317–1321.
- 57 C. Panja, J. V. Puttaramu, T. K. Chandran, R. Y. Nimje, H. Kumar, A. Gupta, P. N. Arunachalam, J. R. Corte and A. Mathur, Methyl-2,2-difluoro-2-(fluorosulfonyl) acetate (MDFA)/copper(I) iodide mediated and tetrabutylammonium iodide promoted trifluoromethylation of 1-aryl-4-iodo-1,2,3-triazoles, *J. Fluor. Chem.*, 2020, **236**, 109516.
- 58 Q. Chen and S. Wu, Methyl fluorosulphonyldifluoroacetate; a new trifluoromethylating agent, *J. Chem. Soc., Chem. Commun.*, 1989, 705–706.
- 59 S. Eusterwiemann, H. Martinez and W. R. Dolbier Jr, Methyl 2,2-Difluoro-2-(fluorosulfonyl)acetate, a Difluorocarbene Reagent with Reactivity Comparable to That of Trimethylsilyl 2,2-Difluoro-2-(fluorosulfonyl)acetate (TFDA), *J. Org. Chem.*, 2012, **77**, 5461–5464.
- 60 G. Zhao, H. Wu, Z. Xiao, Q. Y. Chen and C. Liu, Trifluoromethylation of haloarenes with a new trifluoromethylating reagent Cu(O<sub>2</sub>CCF<sub>2</sub>SO<sub>2</sub>F)<sub>2</sub>, *RSC Adv.*, 2016, **6**, 50250–50254.



- 61 K. Banert, Reaktionen ungesättigter Azide, 8. Azidobutatrien und Azidobutenine, *Chem. Ber.*, 1989, **122**, 1175–1178.
- 62 J. R. Alexander, P. V. Kevorkian and J. J. Topczewski, Intercepting the Banert cascade with nucleophilic fluorine: direct access to  $\alpha$ -fluorinated *N*,*H*-1,2,3-triazoles, *Chem. Commun.*, 2021, **57**, 5024–5027.
- 63 J. R. Alexander, M. H. Packard, A. M. Hildebrandt, A. A. Ott and J. J. Topczewski, Divergent Mechanisms of the Banert Cascade with Propargyl Azides, *J. Org. Chem.*, 2020, **85**, 3174–3181.
- 64 (a) R. Kumar, P. Pradhan and B. Zajc, Facile synthesis of 4-vinyl- and 4-fluorovinyl-1,2,3-triazoles *via* bifunctional “click-olefination” reagents, *Chem. Commun.*, 2011, **47**, 3891–3893; (b) R. Kumar, G. Singh, L. J. Todaro, L. Yang and B. Zajc, *E*- or *Z*-Selective synthesis of 4-fluorovinyl-1,2,3-triazoles with fluorinated second-generation Julia-Kocienski reagents, *Org. Biomol. Chem.*, 2015, **13**, 1536–1549.
- 65 (a) C. J. Smedley, M. C. Giel, A. Molino, A. S. Barrow, D. J. D. Wilson and J. E. Moses, 1-Bromoethene-1-sulfonyl fluoride (BESF) is another good connective hub for SuFEx click chemistry, *Chem. Commun.*, 2018, **54**, 6020–6023; (b) J. Thomas and V. V. Fokin, Regioselective Synthesis of Fluorosulfonyl 1,2,3-Triazoles from Bromovinylsulfonyl Fluoride, *Org. Lett.*, 2018, **20**, 3749–3752.
- 66 (a) A. S. Barrow, C. J. Smedley, Q. Zheng, S. Li, J. Dong and J. E. Moses, The growing applications of SuFEx click chemistry, *Chem. Soc. Rev.*, 2019, **48**, 4731–4758; (b) T. Zhong, Z. Chen, J. Yi, G. Lu and J. Weng, Recent progress in the synthesis of sulfonyl fluorides for SuFEx click chemistry, *Chin. Chem. Lett.*, 2021, **32**, 2736–2750; (c) S. W. Lucas, R. Z. Qin, K. P. Rakesh, K. S. S. Kumar and H.-L. Qin, Chemical and biology of sulfur fluoride exchange (SuFEx) click chemistry for drug discovery, *Bioorg. Chem.*, 2023, **130**, 106227.
- 67 J. Leng and H.-L. Qin, 1-Bromoethene-1-sulfonyl fluoride (1-Br-ESF), a new SuFEx clickable reagent, and its application for regioselective construction of 5-sulfonylfluoro isoxazoles, *Chem. Commun.*, 2018, **54**, 4477–4480.
- 68 C. J. Smedley, G. Li, A. S. Barrow, T. L. Gialelis, M.-C. Giel, A. Ottonello, Y. Cheng, S. Kitamura, D. W. Wolan, K. B. Sharpless and J. E. Moses, Diversity Oriented Clicking (DOC): Divergent Synthesis of SuFExable Pharmacophores from 2-Substituted-Alkynyl-1-Sulfonyl Fluoride (SASF) Hubs, *Angew. Chem., Int. Ed.*, 2020, **59**, 12460–12469.
- 69 D. Fu, J. Zhang and S. Cao, Copper-mediated trifluoromethylation of 5-iodotriazole with (trifluoromethyl)trimethylsilane promoted by silver carbonate, *J. Fluor. Chem.*, 2013, **156**, 170–176.
- 70 (a) I. Ruppert, K. Schlich and W. Volbach, Die ersten CF<sub>3</sub>-substituierten organyl(chlor)silane, *Tetrahedron Lett.*, 1984, **25**, 2195–2198; (b) G. K. S. Prakash, R. Krishnamurti and G. A. Olah, Synthetic methods and reactions. 141. Fluoride-induced trifluoromethylation of carbonyl compounds with trifluoromethyltrimethylsilane (TMS-CF<sub>3</sub>). A trifluoromethide equivalent, *J. Am. Chem. Soc.*, 1989, **111**, 393–395.
- 71 (a) K. P. S. Cheung and G. C. Tsui, Copper(I)-Catalyzed Interrupted Click Reaction with TMSCF<sub>3</sub>: Synthesis of 5-Trifluoromethyl 1,2,3-Triazoles, *Org. Lett.*, 2017, **19**, 2881–2884; (b) A. Zhu, X. Xing, S. Wang, D. Yuan, G. Zhu, M. Geng, Y. Guo, G. Zhang and L. Li, Multi-component syntheses of diverse 5-fluoroalkyl-1,2,3-triazoles facilitated by air oxidation and copper catalysis, *Green Chem.*, 2019, **21**, 3407–3412; (c) Z. Fu, X. Yang and G. C. Tsui, Interrupted Click Reaction with CuCF<sub>2</sub>CF<sub>3</sub> Reagent: Synthesis of 5-Pentafluoroethyl 1,2,3-Triazoles, *Org. Lett.*, 2023, **25**, 4945–4949.
- 72 (a) L. Li, G. Hao, A. Zhu, X. Fan, G. Zhang and L. Zhang, A Copper(I)-Catalyzed Three-Component Domino Process: Assembly of Complex 1,2,3-Triazolyl-5-Phosphonates from Azides, Alkynes, and *H*-Phosphates, *Chem. – Eur. J.*, 2013, **19**, 14403–14406; (b) Z. Zhang, Q. Zhou, F. Ye, Y. Xia, G. Wu, M. L. Hossain, Y. Zhang and J. Wang, Copper(I)-Catalyzed Three-Component Coupling of *N*-Tosylhydrazones, Alkynes and Azides: Synthesis of Trisubstituted 1,2,3-Triazoles, *Adv. Synth. Catal.*, 2015, **357**, 2277–2286.
- 73 (a) W. Peng and S. Zhu, Efficient synthesis of 5-fluoroalkylated 1*H*-1,2,3-triazoles and application of the bromodifluoromethylated triazole to the synthesis of novel bicyclic gem-difluorinated 1*H*-pyrano[3,4-*d*][1,2,3]-triazol-4-one compounds, *Tetrahedron*, 2003, **59**, 4395–4404; (b) Y. A. Rozin, J. Leban, W. Dehaen, V. G. Nenajdenko, V. M. Muzalevskiy, O. S. Eltsov and V. A. Bakulev, Regioselective synthesis of 5-trifluoromethyl-1,2,3-triazoles via CF<sub>3</sub>-directed cyclization of 1-trifluoromethyl-1,3-dicarbonyl compounds with azides, *Tetrahedron*, 2012, **68**, 614–618; (c) J. Zhang, G. Jin, S. Xiao, J. Wu and S. Cao, Novel synthesis of 1,4,5-trisubstituted 1,2,3-triazoles via a one-pot three-component reaction of boronic acids, azide, and active methylene ketones, *Tetrahedron*, 2013, **69**, 2352–2356.
- 74 L. J. T. Danence, Y. Gao, M. Li, Y. Huang and J. Wang, Organocatalytic Enamide–Azide Cycloaddition Reactions: Regiospecific Synthesis of 1,4,5-Trisubstituted-1,2,3-Triazoles, *Chem. – Eur. J.*, 2011, **17**, 3584–3587.
- 75 R. T. Iminov, A. V. Mashkov, B. A. Chalyk, P. K. Mykhailiuk, A. V. Tverdokhlebov, A. A. Tolmachev, Y. M. Volovenko, O. V. Shishkin and S. V. Shishkina, A Convenient Route to 1-Alkyl-5-trifluoromethyl-1,2,3-triazole-4-carboxylic Acids Employing a Diazo Transfer Reaction, *Eur. J. Org. Chem.*, 2013, 2891–2897.
- 76 R. Augusti and C. Kascheres, Reactions of 3-diazo-1,3-dihydro-2*H*-indol-2-one derivatives with enamines. A novel synthesis of 1,2,3-triazoles, *J. Org. Chem.*, 1993, **58**, 7079–7083.
- 77 Y. Ning, H. Wang, P. Sivaguru, S. Li, G. Zanoni, S. P. Nolan and X. Bi, Defluorinative [4 + 1] Annulation of Perfluoroalkyl *N*-Mesylhydrazones with Primary Amines



- Provides 5-Fluoroalkyl 1,2,3-Triazoles, *Green Chem.*, 2021, **23**, 7976–7981.
- 78 H. Yang, T.-H. Xu, S.-N. Lu, Z. Chen and X.-F. Wu, Synthesis of 5-trifluoromethyl-1,2,3-triazoles via base-mediated cascade annulation of diazo compounds with trifluoroacetimidoyl chlorides, *Org. Chem. Front.*, 2021, **8**, 3440–3445.
  - 79 L. L. Zhang, M. T. Li, L. L. Shen and Q. P. Wu, Efficient Synthesis of 5-Trifluoromethylthio-1,2,3-Triazoles: One-Pot Multicomponent Reaction from Elemental Sulfur and TMSF<sub>3</sub>, *Synthesis*, 2020, 304–310.
  - 80 F. Wei, T. Zhou, Y. Ma, C. H. Tung and Z. Xu, Bench-Stable 5-Stannyl Triazoles by a Copper(I)-Catalyzed Interrupted Click Reaction: Bridge to Trifluoromethyltriazoles and Trifluoromethylthiotriazoles, *Org. Lett.*, 2017, **19**, 2098–2101.
  - 81 S. Alazet, L. Zimmer and T. Billard, Base-Catalyzed Electrophilic Trifluoromethylthiolation of Terminal Alkynes, *Angew. Chem., Int. Ed.*, 2013, **52**, 10814–10817.
  - 82 (a) Q. Shena, E.-J. Han, Y.-G. Huang, Q.-Y. Chen and Y. Guo, Synthesis of Fluorinated 1,4,5-Substituted 1,2,3-Triazoles by RuAAC- Reaction, *Synthesis*, 2015, 3936–3946; (b) W. Song, N. Zheng, M. Li, J. He, J. Li, K. Dong, K. Ullah and Y. Zheng, Rhodium(I)-Catalyzed Regioselective Azide-internal Alkynyl Trifluoromethyl Sulfide Cycloaddition and Azide-internal Thioalkyne Cycloaddition under Mild Conditions, *Adv. Synth. Catal.*, 2019, **361**, 469–475.
  - 83 S. Bräse, C. Gil, K. Knepper and V. Zimmermann, Organic Azides: An Exploding Diversity of a Unique Class of Compounds, *Angew. Chem., Int. Ed.*, 2005, **44**, 5188–5240.
  - 84 (a) J. Das, S. N. Patil, R. Awasthi, C. P. Narasimhulu and S. Trehan, An Easy Access to Aryl Azides from Aryl Amines under Neutral Conditions, *Synthesis*, 2005, 1801–1806; (b) K. Barral, A. D. Moorhouse and J. E. Moses, Efficient Conversion of Aromatic Amines into Azides: A One-Pot Synthesis of Triazole Linkages, *Org. Lett.*, 2007, **9**, 1809–1811; (c) L. M. Jin, X. Xu, H. Lu, X. Cui, L. Wojtas and X. P. Zhang, Effective Synthesis of Chiral *N*-Fluoroaryl Aziridines through Enantioselective Aziridination of Alkenes with Fluoroaryl Azides, *Angew. Chem., Int. Ed.*, 2013, **52**, 5309–5313; (d) F. Sebest, L. Casarrubios, H. S. Rzepa, A. J. P. White and S. Díez-González, Thermal azide–alkene cycloaddition reactions: straightforward multi-gram access to  $\Delta^2$ -1,2,3-triazolines in deep eutectic solvents, *Green Chem.*, 2018, **20**, 4023–4035.
  - 85 (a) C.-Z. Tao, X. Cui, J. Li, A.-X. Liu, L. Liu and Q.-X. Guo, Copper-catalyzed synthesis of aryl azides and 1-aryl-1,2,3-triazoles from boronic acids, *Tetrahedron Lett.*, 2007, **48**, 3525–3529; (b) K. D. Grimes, A. Gupte and C. C. Aldrich, Copper(II)-Catalyzed Conversion of Aryl/Heteroaryl Boronic Acids, Boronates, and Trifluoroborates into the Corresponding Azides: Substrate Scope and Limitations, *Synthesis*, 2010, 1441–1448; (c) H. Luo, Y.-F. Lv, H. Zhang, J.-M. Hu, H.-M. Li and S.-J. Liu, Synthesis and Antitumor Activity of 1-Substituted 1,2,3-Triazole-Mollugin Derivatives, *Molecules*, 2021, **26**, 3249; (d) M. Payne, A. L. Bottomley, A. Och, H. G. Hiscocks, A. P. Asmara, E. J. Harry and A. T. Ung, Synthesis and biological evaluation of tetrahydroisoquinoline-derived antibacterial compounds, *Bioorg. Med. Chem.*, 2022, **57**, 116648.
  - 86 (a) M. Sundhoro, S. Jeon, J. Park, O. Ramström and M. Yan, Perfluoroaryl Azide Staudinger Reaction: A Fast and Bioorthogonal Reaction, *Angew. Chem., Int. Ed.*, 2017, **56**, 12117–12121; (b) M. Berta, A. Dancsó, A. Nemes, Z. Pathó, D. Szabó and J. Rábai, Convenient synthesis of pure fluororous alkyl azides at multigram scale, *J. Fluor. Chem.*, 2017, **196**, 57–62.
  - 87 W. Zhu and D. Ma, Synthesis of aryl azides and vinyl azides via proline-promoted CuI-catalyzed coupling reactions, *Chem. Commun.*, 2004, 888–889.
  - 88 O. Bakhanovich and P. Beier, Synthesis, Stability and Reactivity of  $\alpha$ -Fluorinated Azidoalkanes, *Chem. – Eur. J.*, 2020, **26**, 773–782.
  - 89 P. Sivaguru, Y. Ning and X. Bi, New Strategies for the Synthesis of Aliphatic Azides, *Chem. Rev.*, 2021, **121**, 4253–4307.
  - 90 H. Martinez, A. Rebeyrol, T. B. Nelms and W. R. Dolbier Jr, Impact of fluorine substituents on the rates of nucleophilic aliphatic substitution and  $\beta$ -elimination, *J. Fluor. Chem.*, 2012, **135**, 167–175.
  - 91 S. Voltrová, J. Filgas, P. Slaviček and P. Beier, Azidofluoromethane: synthesis, stability and reactivity in [3 + 2] cycloadditions, *Org. Chem. Front.*, 2020, **7**, 10–13.
  - 92 M. Glaser and E. Årstad, “Click Labeling” with 2-[<sup>18</sup>F] Fluoroethylazide for Positron Emission Tomography, *Bioconjugate Chem.*, 2007, **18**, 989–993.
  - 93 (a) A. Haslop, A. Gee, C. Plisson and N. Long, Fully automated radiosynthesis of [1-(2-[<sup>18</sup>F]fluoroethyl),1H[1,2,3]triazole 4-ethylene] triphenylphosphonium bromide as a potential positron emission tomography tracer for imaging apoptosis, *J. Labelled Compd. Radiopharm.*, 2013, **56**, 313–316; (b) K. Kettenbach, H. Schieferstein and T. L. Ross, <sup>18</sup>F-labeling using click cycloadditions, *BioMed. Res. Int.*, 2014, **2014**, 361329; (c) B. S. Lee, S. Y. Chu, W. J. Jung, H. J. Jeong, K. Lee, M. H. Kim, M. H. Kim, D. Y. Chi, H. Ahn, Y. J. Lee, K. C. Lee and S. M. Lim, <sup>18</sup>F-labeled 1,2,3-triazole-linked Glu-urea-Lys-based PSMA ligands have good pharmacokinetic properties for positron emission tomography imaging of prostate cancer, *Prostate*, 2020, **80**, 1383–1393.
  - 94 Y.-M. Wu, J. Deng, X. Fang and Q.-Y. Chen, Regioselective synthesis of fluoroalkylated [1,2,3]-triazoles by Huisgen cycloaddition, *J. Fluor. Chem.*, 2004, **125**, 1415–1423.
  - 95 J. Tomaszewska, K. Koroniak-Szejn and H. Koroniak, Fluorinated organic azides – their preparation and synthetic application, *ARKIVOC*, 2017, (part ii), 421–432.
  - 96 (a) A. Haas, M. Spitzer and M. Lieb, Synthese seitenketten-fluorierter aromatischer Verbindungen und deren chemische Reaktivität, *Chem. Ber.*, 1988, **121**, 1329–1340; (b) W. M. Koppes and M. Chaykovsky, *US Pat.*, 5276171, 1994; (c) S. A. Lermontov, A. G. Polivanova and S. B. Shkavrov, Interaction of  $\alpha,\alpha$ -difluoroazides with triva-



- lent phosphorus compounds and triphenylantimony, *Russ. J. Gen. Chem.*, 2010, **80**, 1646–1651; (d) W. Zhao, H. Li, J. Zhang and S. Cao, Synthesis of Novel gem-Difluoromethylene-containing 1,2,3-Triazoles via Click Reaction, *Chin. J. Chem.*, 2011, **29**, 2763–2768; (e) M. Mamone, R. S. B. Goncalves, F. Blanchard, G. Bernadat, S. Onger, T. Milcent and B. Crousse, *N*-Difluoromethyl-triazole as a constrained scaffold in peptidomimetics, *Chem. Commun.*, 2017, **53**, 5024–5027; (f) J. Engel-Andreasen, I. Wellhofer, K. Wich and C. A. Olsen, Backbone-Fluorinated 1,2,3-Triazole-Containing Dipeptide Surrogates, *J. Org. Chem.*, 2017, **82**, 11613–11619; (g) J. Y. Chai, H. Cha, H. B. Kim and D. Y. Chi, Selective addition reactions of difluoromethyl-triazoles to ketones and aldehydes without the formation of difluorocarbene, *Tetrahedron*, 2020, **76**, 131370; (h) J. Laxio Arenas, Y. Xu, T. Milcent, C. Van Heijenoort, F. Giraud, T. Ha-Duong, B. Crousse and S. Onger, Fluorinated Triazole Foldamers: Folded or Extended Conformational Preferences, *ChemPlusChem*, 2021, **86**, 241–251.
- 97 (a) E. M. Sletten and C. R. Bertozzi, A Bioorthogonal Quadricyclane Ligation, *J. Am. Chem. Soc.*, 2011, **133**, 17570–17573; (b) R. van Geel, M. A. Wijdeven, R. Heesbeen, J. M. M. Verkade, A. A. Wasiele, S. S. van Berkel and F. L. van Delft, Chemoenzymatic Conjugation of Toxic Payloads to the Globally Conserved N-Glycan of Native mAbs Provides Homogeneous and Highly Efficacious Antibody–Drug Conjugates, *Bioconjugate Chem.*, 2015, **26**, 2233–2242.
- 98 (a) T. G. Archibald and K. Baum, Synthesis of fluoro nitro ethers by Michael addition reactions to activated  $\beta,\beta$ -difluoroolefins, *J. Org. Chem.*, 1990, **55**, 3562–3565; (b) T. Hiramatsu, Y. Guo and T. Hosoya, 3-Azidodifluoromethyl-3H-diazirin-3-yl group as an all-in-one functional group for radioisotope-free photoaffinity labelling, *Org. Biomol. Chem.*, 2007, **5**, 2916–2919.
- 99 S. A. Postovoi, Y. V. Zeifman and I. L. Knunyants, Reaction of vicinal dihalopolyfluoroalkanes with sodium azide, *Russ. Chem. Bull.*, 1986, **35**, 1183–1186.
- 100 (a) I. Rico and C. Wakselman, Condensation of 1,2-dibromotetrafluoroethane with various potassium thiophenoxides and phenoxides, *J. Fluor. Chem.*, 1982, **20**, 759–764; (b) S. A. Postovoi, L. T. Lantseva, Y. V. Zeifman and I. L. Knunyants, Reaction of perfluoro-tert-butyl anion with vicinal dihalopolyfluoroalkanes, *Russ. Chem. Bull.*, 1982, **31**, 2233–2236.
- 101 For a related approach through Grignard formation from 1,2-dibromotetrafluoroethane and subsequent decomposition and trapping with azide see: D. Tichý, V. Košťál, V. Motornov, I. Klimánková and P. Beier, Preparation of 1-Azido-2-Bromo-1,1,2,2-Tetrafluoroethane and Its Use in the Synthesis of *N*-Fluoroalkylated Nitrogen Heterocycles, *J. Org. Chem.*, 2020, **85**, 11482–11489.
- 102 E. Shaitanova, V. Matoušek, T. Herentin, M. Adamec, R. Matyáš, B. Klepetářová and P. Beier, Synthesis and Cycloaddition Reactions of 1-Azido-1,1,2,2-tetrafluoroethane, *J. Org. Chem.*, 2023, **88**, 14969–14977.
- 103 J. Dai, Z. Li, T. Wang and R. Bai, A highly stable and versatile heterobifunctional fluoroalkylation reagent for preparation of fluorinated organic compounds, *Org. Biomol. Chem.*, 2016, **14**, 4382–4386.
- 104 J. Dai, Z. Li, T. Wang, W. Bai and R. Bai, A Diheteroatom Fluoroalkylation Reagent for Preparation of S- and N-Containing Fluoroalkyl Compounds and Sulfonic Acid Polymer, *Org. Lett.*, 2017, **19**, 1418–1421.
- 105 C. G. Krespan, F. A. Van-Catledge and B. E. Smart, Generation and capture of functionalized fluorocarbanions, *J. Am. Chem. Soc.*, 1984, **106**, 5544–5546.
- 106 C. G. Krespan and B. E. Smart, Fluorocarbanion chemistry. A versatile synthesis of functionalized fluoro ketones, *J. Org. Chem.*, 1986, **51**, 320–326.
- 107 V. A. Ginsburg, P. O. Gitel and I. M. Didina, *SU Pat*, 375287A1, 1973.
- 108 H. Bock and R. Dammel, Gas-phase reactions. 53. Pyrolysis of difluoromethyl azide, *Inorg. Chem.*, 1985, **24**, 4427–4429.
- 109 S. Voltrová, I. Putovný, V. Matoušek, B. Klepetářová and P. Beier, Reintroducing Azidodifluoromethane: Synthesis, Stability and [3 + 2] Cycloadditions, *Eur. J. Org. Chem.*, 2018, 5087–5090.
- 110 Z. E. Blastik, S. Voltrová, V. Matoušek, B. Jurásek, D. W. Manley, B. Klepetářová and P. Beier, Azidoperfluoroalkanes: Synthesis and Application in Copper(I)-Catalyzed Azide–Alkyne Cycloaddition, *Angew. Chem., Int. Ed.*, 2017, **56**, 346–349.
- 111 (a) S. P. Makarov, A. Y. Yakubovich, A. S. Filatov, M. A. Englin and T. Y. Nikiforova, Reactions of Trifluoronitrosomethane with Amines. IV. Reactions of Trifluoronitrosomethane with Hydrazine and Hydroxylamine and Their Derivatives, *Zh. Obshch. Khim.*, 1968, **38**, 709–715; (b) K. O. Christie and C. J. Schack, Properties of azidotrifluoromethane, *Inorg. Chem.*, 1981, **20**, 2566–2570.
- 112 S. Voltrová, M. Muselli, J. Filgas, V. Matoušek, B. Klepetářová and P. Beier, Synthesis of tetrafluoroethylene- and tetrafluoroethyl-containing azides and their 1,3-dipolar cycloaddition as synthetic application, *Org. Biomol. Chem.*, 2017, **15**, 4962–4965.
- 113 M. Ziabko, B. Klepetářová and P. Beier, Synthesis of Azidodifluoromethyl Phenyl Sulfone and Its Use as a Synthetic Equivalent of the Azidodifluoromethyl Anion, *J. Org. Chem.*, 2023, **88**, 6939–6946.
- 114 J. Sultana, N. D. Khupse, S. Chakrabarti, P. Chattopadhyay and D. Sarma,  $\text{Ag}_2\text{CO}_3$ -catalyzed cycloaddition of organic azides onto terminal alkynes: A green and sustainable protocol accelerated by aqueous micelles of CPyCl, *Tetrahedron Lett.*, 2019, **60**, 1117–1121.
- 115 (a) A. Montagu, V. Roy, J. Balzarini, R. Snoeck, G. Andrei and L. A. Agrofoglio, Synthesis of new C5-(1-substituted-1,2,3-triazol-4 or 5-yl)-2'-deoxyuridines and their antiviral evaluation, *Eur. J. Med. Chem.*, 2011, **46**, 778–786;





- (b) T. Irie, I. Fujii and M. Sawa, Design and combinatorial synthesis of a novel kinase-focused library using click chemistry-based fragment assembly, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 591–596; (c) A. Torrens-Jover, N. Jagerovic and C. Almansa-Rosales, *WO Pat*, 2017178515A1, 2017.
- 116 (a) L. Maugeri, T. Lébl, D. B. Cordes, A. M. Z. Slawin and D. Philp, Cooperative Binding in a Phosphine Oxide-Based Halogen Bonded Dimer Drives Supramolecular Oligomerization, *J. Org. Chem.*, 2017, **82**, 1986–1995; (b) A. Docker, C. H. Guthrie, H. Kuhn and P. D. Beer, Modulating Chalcogen Bonding and Halogen Bonding Sigma-Hole Donor Atom Potency and Selectivity for Halide Anion Recognition, *Angew. Chem., Int. Ed.*, 2021, **60**, 21973–21978; (c) F. Ostler, D. G. Piekarski, T. Danelzik, M. S. Taylor and O. Garcia Mancheno, Neutral Chiral Tetrakis-Iodo-Triazole Halogen-Bond Donor for Chiral Recognition and Enantioselective Catalysis, *Chem. – Eur. J.*, 2021, **27**, 2315–2320; (d) T. Bunchuay, A. Docker, N. G. White and P. D. Beer, A new halogen bonding 1,2-iodo-triazolium-triazole benzene motif for anion recognition, *Polyhedron*, 2021, **209**, 115482; (e) A. Docker, X. Shang, D. Yuan, H. Kuhn, Z. Zhang, J. J. Davis, P. D. Beer and M. J. Langton, Halogen Bonding Tetraphenylethene Anion Receptors: Anion-Induced Emissive Aggregates and Photoswitchable Recognition, *Angew. Chem., Int. Ed.*, 2021, **60**, 19442–19450; (f) L. E. Bickerton, A. Docker, A. J. Sterling, H. Kuhn, F. Duarte, P. D. Beer and M. J. Langton, Highly Active Halogen Bonding and Chalcogen Bonding Chloride Transporters with Non-Protonophoric Activity, *Chem. – Eur. J.*, 2021, **27**, 11738–11745; (g) R. Hein, A. Docker, J. J. Davis and P. D. Beer, Redox-Switchable Chalcogen Bonding for Anion Recognition and Sensing, *J. Am. Chem. Soc.*, 2022, **144**, 8827–8836; (h) A. Docker, Y. C. Tse, H. M. Tay, A. J. Taylor, Z. Zhang and P. D. Beer, Anti-Hofmeister Anion Selectivity via a Mechanical Bond Effect in Neutral Halogen-Bonding [2]Rotaxanes, *Angew. Chem., Int. Ed.*, 2022, **61**, e202214523; (i) A. Docker, I. Marques, H. Kuhn, Z. Zhang, V. Felix and P. D. Beer, Selective Potassium Chloride Recognition, Sensing, Extraction, and Transport Using a Chalcogen-Bonding Heteroditopic Receptor, *J. Am. Chem. Soc.*, 2022, **144**, 14778–14789; (j) L. E. Bickerton and M. J. Langton, Controlling transmembrane ion transport via photo-regulated carrier mobility, *Chem. Sci.*, 2022, **13**, 9531–9536; (k) A. C. Keuper, K. Fengler, F. Ostler, T. Danelzik, D. G. Piekarski and O. G. Mancheno, Fine-Tuning Substrate–Catalyst Halogen–Halogen Interactions for Boosting Enantioselectivity in Halogen-Bonding Catalysis, *Angew. Chem., Int. Ed.*, 2023, **62**, e202304781; (l) K. M. Bāk, I. Marques, H. Kuhn, K. E. Christensen, V. Félix and P. D. Beer, Fullerene-Functionalized Halogen-Bonding Heteroditopic Hosts for Ion-Pair Recognition, *J. Am. Chem. Soc.*, 2023, **145**, 27367–27379; (m) T. G. Johnson, A. Docker, A. Sadeghi-Kelishadi and M. J. Langton, Halogen Bonding Relay and Mobile Anion Transporters with Kinetically Controlled Chloride Selectivity, *Chem. Sci.*, 2023, **14**, 5006–5013.
- 117 (a) L. Zeng, J. Li and S. Cui, Rhodium-Catalyzed Atroposelective Click Cycloaddition of Azides and Alkynes, *Angew. Chem., Int. Ed.*, 2022, **61**, e202205037; (b) L. Zhou, Y. Li, S. Li, Z. Shi, X. Zhang, C.-H. Tung and Z. Xu, Asymmetric rhodium-catalyzed click cycloaddition to access C–N axially chiral *N*-triazolyl indoles, *Chem. Sci.*, 2023, **14**, 5182–5187; (c) L. Zeng, F. Zhang and S. Cui, Construction of Axial Chirality via Click Chemistry: Rh-Catalyzed Enantioselective Synthesis of 1-Triazolyl-2-Naphthylamines, *Org. Lett.*, 2023, **25**, 443–448.
- 118 D. Bhatt, P. R. Singh, P. Karamanna, K. Kumar and A. Goswami, An Atom-Economical Approach to 2-Triazolyl Thio-/Seleno Pyridines via Ruthenium-Catalyzed One-pot [3 + 2]/[2 + 2 + 2] Cycloadditions, *Adv. Synth. Catal.*, 2019, **361**, 5483–5489.
- 119 X. Zhang, S. Li, W. Yu, Y. Xie, C.-H. Tung and Z. Xu, Asymmetric Azide–Alkyne Cycloaddition with Ir(I)/Squaramide Cooperative Catalysis: Atroposelective Synthesis of Axially Chiral Aryltriazoles, *J. Am. Chem. Soc.*, 2022, **144**, 6200–6207.
- 120 (a) A. K. Feldman, B. Colasson and V. V. Fokin, One-Pot Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from In Situ Generated Azides, *Org. Lett.*, 2004, **6**, 3897–3899; (b) J. Andersen, S. Bolvig and X. Liang, Efficient One-Pot Synthesis of 1-Aryl 1,2,3-Triazoles from Aryl Halides and Terminal Alkynes in the Presence of Sodium Azide, *Synlett*, 2005, 2941–2947.
- 121 For examples starting from polyfluoroaryl boronic acids see: (a) B. Kaboudin, R. Mostafalu and T. Yokomatsu, Fe<sub>3</sub>O<sub>4</sub> nanoparticle-supported Cu(II)- $\beta$ -cyclodextrin complex as a magnetically recoverable and reusable catalyst for the synthesis of symmetrical biaryls and 1,2,3-triazoles from aryl boronic acids, *Green Chem.*, 2013, **15**, 2266–2274; (b) P. K. Chinthakindi, P. L. Sangwan, S. Farooq, R. R. Aleti, A. Kaul, A. K. Saxena, Y. L. N. Murthy, R. A. Vishwakarma and S. Koul, Diminutive effect on T and B-cell proliferation of non-cytotoxic  $\alpha$ -santonin derived 1,2,3-triazoles: A report, *Eur. J. Med. Chem.*, 2013, **60**, 365–375; (c) A. S. Kumar, M. A. Reddy, M. Knorn, O. Reiser and B. Sreedhar, Magnetically Recoverable CuFe<sub>2</sub>O<sub>4</sub> Nanoparticles: Catalyzed Synthesis of Aryl Azides and 1,4-Diaryl-1,2,3-triazoles from Boronic Acids in Water, *Eur. J. Org. Chem.*, 2013, 4674–4680; (d) B. S. P. A. Kumar, K. H. V. Reddy, K. Karnakar, G. Satish and Y. V. D. Nageswar, Copper on chitosan: an efficient and easily recoverable heterogeneous catalyst for one pot synthesis of 1,2,3-triazoles from aryl boronic acids in water at room temperature, *Tetrahedron Lett.*, 2015, **56**, 1968–1972; (e) C. Hao, C. Zhou, J. Xie, J. Zhang, P. Liu and B. Dai, An Efficient Copper-Catalyzed One-Pot Synthesis of 1-Aryl-1,2,3-triazoles from Arylboronic Acids in Water under Mild Conditions, *Chin. J. Chem.*, 2015, **33**, 1317–1320; (f) R. Nie, R. Sang, X. Ma, Y. Zheng, X. Cheng, W. Li,



- L. Guo, H. Jin and Y. Wu, Copper- $\gamma$ -cyclodextrin complexes immobilized on hexagonal boron nitride as an efficient catalyst in the multicomponent synthesis of 1,2,3-triazoles, *J. Catal.*, 2016, **344**, 286–292;
- (g) J. M. Pérez, P. Crosbie, S. Lal and S. Díez-González, Copper(I)-Phosphinite Complexes in Click Cycloadditions: Three-Component Reactions and Preparation of 5-Iodotriazoles, *ChemCatChem*, 2016, **8**, 2222–2226; (h) S. Layek, S. Kumari, Anuradha, B. Agrahari, R. Ganguly and D. D. Pathak, Synthesis, characterization and crystal structure of a diketone based Cu(II) complex and its catalytic activity for the synthesis of 1,2,3-triazoles, *Inorg. Chim. Acta*, 2016, **453**, 735–741; (i) A. Garg, A. A. Ali, K. Damarla, A. Kumar and D. Sarma, Aqueous bile salt accelerated cascade synthesis of 1,2,3-triazoles from aryl-boronic acids, *Tetrahedron Lett.*, 2018, **59**, 4031–4035; (j) X.-Y. Huo, L. Guo, X.-F. Chen, Y.-T. Zhou, J. Zhang, X.-Q. Han and B. Dai, Design, Synthesis, and Antifungal Activity of Novel Aryl-1,2,3-Triazole- $\beta$ -Carboline Hybrids, *Molecules*, 2018, **23**, 1344.
- 122 For examples starting from polyfluoroaryl iodides see: (a) L. Ackermann, H. K. Potukuchi, D. Landsberg and R. Vicente, Copper-Catalyzed “Click” Reaction/Direct Arylation Sequence: Modular Syntheses of 1,2,3-Triazoles, *Org. Lett.*, 2008, **10**, 3081–3084; (b) M. Klein, P. Dinér, D. Dorin-Semlat, C. Doerig and M. Grötli, Synthesis of 3-(1,2,3-triazol-1-yl)- and 3-(1,2,3-triazol-4-yl)-substituted pyrazolo[3,4-*d*]pyrimidin-4-amines via click chemistry: potential inhibitors of the *Plasmodium falciparum*, PfPK7 protein kinase, *Org. Biomol. Chem.*, 2009, **7**, 3421–3429; (c) C. Proulx and W. D. Lubell, Aza-1,2,3-triazole-3-alanine Synthesis via Copper-Catalyzed 1,3-Dipolar Cycloaddition on Aza-progargylglycine, *J. Org. Chem.*, 2010, **75**, 5385–5387; (d) T. Kim, J. H. Song, K. H. Jeong, S. Lee and J. Ham, Potassium (1-Organic-1H-1,2,3-triazol-4-yl)trifluoroborates from Ethynyltrifluoroborate through a Regioselective One-Pot Cu-Catalyzed Azide-Alkyne Cycloaddition Reaction, *Eur. J. Org. Chem.*, 2013, 3992–3996; (e) P. Dziedzic, J. A. Cisneros, M. J. Robertson, A. A. Hare, N. E. Danford, R. H. G. Baxter and W. L. Jorgensen, Design, Synthesis, and Protein Crystallography of Biaryltriazoles as Potent Tautomerase Inhibitors of Macrophage Migration Inhibitory Factor, *J. Am. Chem. Soc.*, 2015, **137**, 2996–3003; (f) A. Laurent, M. Proulx, Y. Rose, I. Denissova, K. Dai, S. Jarvis and J. B. Jaquith, *US Pat*, 9284350B2, 2016.
- 123 (a) V. R. Kamalraj, S. Senthil and P. Kannan, One-pot synthesis and the fluorescent behavior of 4-acetyl-5-methyl-1,2,3-triazole regioisomers, *J. Mol. Struct.*, 2008, **892**, 210–215; (b) F. Stazi, D. Cancogni, L. Turco, P. Westerduin and S. Bacchi, Highly efficient and safe procedure for the synthesis of aryl 1,2,3-triazoles from aromatic amine in a continuous flow reactor, *Tetrahedron Lett.*, 2010, **51**, 5385–5387; (c) L. Wang, S. Peng, L. J. Danence, Y. Gao and J. Wang, Amine-Catalyzed [3 + 2] Huisgen Cycloaddition Strategy for the Efficient Assembly of Highly Substituted 1,2,3-Triazoles, *Chem. – Eur. J.*, 2012, **18**, 6088–6093; (d) W. Li, Q. Jia, Z. Du and J. Wang, Direct access to triazole-olefins through catalytic cycloaddition of azides to unsaturated aldehydes, *Chem. Commun.*, 2013, **49**, 10187–10189; (e) H. Singh, J. Sindhu and J. M. Khurana, Efficient, green and regioselective synthesis of 1,4,5-trisubstituted-1,2,3-triazoles in ionic liquid [bmim]BF<sub>4</sub> and in task-specific basic ionic liquid [bmim]OH, *J. Iran. Chem. Soc.*, 2013, **10**, 883–888; (f) H. Singh, J. Sindhu and J. M. Khurana, Synthesis of biologically as well as industrially important 1,4,5-trisubstituted-1,2,3-triazoles using a highly efficient, green and recyclable DBU-H<sub>2</sub>O catalytic system, *RSC Adv.*, 2013, **3**, 22360–22366; (g) D. B. Ramachary, A. B. Shashank and S. Karthik, An Organocatalytic Azide-Aldehyde [3 + 2] Cycloaddition: High-Yielding Regioselective Synthesis of 1,4-Disubstituted 1,2,3-Triazoles, *Angew. Chem., Int. Ed.*, 2014, **53**, 10420–10424; (h) A. B. Shashank, S. Karthik, R. Madhavachary and D. B. Ramachary, An Enolate-Mediated Organocatalytic Azide-Ketone [3 + 2]-Cycloaddition Reaction: Regioselective High-Yielding Synthesis of Fully Decorated 1,2,3-Triazoles, *Chem. – Eur. J.*, 2014, **20**, 16877–16881; (i) S. R. Putapatri, A. Kanwal, S. K. Banerjee and S. Kantevari, Synthesis of novel l-rhamnose derived acyclic C-nucleosides with substituted 1,2,3-triazole core as potent sodium-glucose co-transporter (SGLT) inhibitors, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1528–1531; (j) S. Zhou, H. Liao, M. Liu, G. Feng, B. Fu, R. Li, M. Cheng, Y. Zhao and P. Gong, Discovery and biological evaluation of novel 6,7-disubstituted-4-(2-fluorophenoxy)quinoline derivatives possessing 1,2,3-triazole-4-carboxamide moiety as c-Met kinase inhibitors, *Bioorg. Med. Chem.*, 2014, **22**, 6438–6452; (k) P. M. Krishna, D. B. Ramachary and S. Peesapati, Azide-acetonitrile “click” reaction triggered by Cs<sub>2</sub>CO<sub>3</sub>: the atom-economic, high-yielding synthesis of 5-amino-1,2,3-triazoles, *RSC Adv.*, 2015, **5**, 62062–62066; (l) X. Zhou, X. Xu, K. Liu, H. Gao, W. Wang and W. Li, Organocatalytic 1,3-Dipolar Cyclo-addition Reaction of  $\beta$ -Keto Amides with Azides – Direct Access to 1,4,5-Trisubstituted 1,2,3-Triazole-4-carboxamides, *Eur. J. Org. Chem.*, 2016, 1886–1890; (m) D. B. Ramachary, J. Gujral, S. Peraka and G. S. Reddy, Triazabicyclodecene as an Organocatalyst for the Regiospecific Synthesis of 1,4,5-Trisubstituted N-Vinyl-1,2,3-triazoles, *Eur. J. Org. Chem.*, 2017, 459–464; (n) D. B. Ramachary, G. S. Reddy, S. Peraka and J. Gujral, Organocatalytic Vinyl Azide-Carbonyl [3 + 2] Cycloaddition: High-Yielding Synthesis of Fully Decorated N-Vinyl-1,2,3-Triazoles, *ChemCatChem*, 2017, **9**, 263–267; (o) Z. Shi and W. Li, Enamine-Mediated 1,3-Dipolar Cycloaddition Reaction of Curcumin Derivatives with Azides: Direct Access to 1,4,5-Trisubstituted 1,2,3-Triazoles, *Synthesis*, 2017, 2081–2087; (p) D. M. Xavier, B. S. Goldani, N. Seus, R. G. Jacob, T. Barcellos, M. W. Paixão, R. Luque and D. Alves, Sonochemistry in organocatalytic enamine-azide [3 + 2] cycloadditions: A



- rapid alternative for the synthesis of 1,2,3-triazoyl carboxamides, *Ultrason. Sonochem.*, 2017, **34**, 107–114; (g) G. S. Reddy, L. M. Reddy, A. S. Kumar and D. B. Ramachary, Organocatalytic Selective [3 + 2] Cycloadditions: Synthesis of Functionalized 5-Arylthiomethyl-1,2,3-triazoles and 4-Arylthio-1,2,3-triazoles, *J. Org. Chem.*, 2020, **85**, 15488–15501; (r) A. Zhu, L. Li, C. Zhang, Y. Shen, M. Tang, L. Bai, C. Du, S. Zhang and J. Wang, An integrated high-throughput strategy enables the discovery of multifunctional ionic liquids for sustainable chemical processes, *Green Chem.*, 2019, **21**, 307–313; (s) C. H. A. Rajeena, V. Kamat, V. B. Patil, S. P. Nayak, S. Khanapure, D. A. Barretto and S. K. Vootla, Synthesis and antibacterial evaluation of pyrazolines carrying (benzyloxy)benzaldehyde moiety, *J. Iran. Chem. Soc.*, 2022, **19**, 1641–1650; (t) C. B. Gomes, C. L. Corrêa, D. C. Cabrera, M. G. M. D'Oca, M. Ruiz, T. Collares, L. Savegnago, F. K. Seixas and D. Alves, Organocatalytic Synthesis and Antitumor Activity of Novel 1,2,3-triazoles Derived from Fatty  $\beta$ -ketoesters, *Med. Chem.*, 2022, **18**, 463–472.
- 124 (a) D. B. Ramachary, P. M. Krishna, J. Gujral and G. S. Reddy, An Organocatalytic Regiospecific Synthesis of 1,5-Disubstituted 4-Thio-1,2,3-triazoles and 1,5-Disubstituted 1,2,3-Triazoles, *Chem. – Eur. J.*, 2015, **21**, 16775–16780; (b) A. Baykal, D. Zhang, J. Knelles, I. T. Alt and B. Plietker, Nucleophilic Iron Complexes in Proton-Transfer Catalysis: An Iron-Catalyzed Dimroth Cyclocondensation, *Chem. – Asian J.*, 2019, **14**, 3003–3010; (c) L. Cicco, F. M. Perna, A. Falcicchio, A. Altomare, F. Messa, A. Salomone, V. Capriati and P. Vitale, 1,3-Dipolar Cycloaddition of Alkanone Enolates with Azides in Deep Eutectic Solvents for the Metal-Free Regioselective Synthesis of Densely Functionalized 1,2,3-Triazoles, *Eur. J. Org. Chem.*, 2022, e202200843.
- 125 A. Krasinski, V. V. Fokin and K. B. Sharpless, Direct Synthesis of 1,5-Disubstituted-4-magnesio-1,2,3-triazoles, Revisited, *Org. Lett.*, 2004, **6**, 1237–1240.
- 126 (a) S. G. Fridman and N. M. Lisovska, *Zap. Inst. Khim., Akad. Nauk Ukr. RSR*, 1940, **6**, 353–360; (b) N. M. Boyer, C. H. Mack, N. Goebel and L. R. Morgan Jr., Notes - Reactions of Sodium Phenylacetylide and Sodium Alkoxide with Tosyl and Mesyl Azides, *J. Org. Chem.*, 1958, **23**, 1051–1053; (c) G. S. Akimova, V. N. Chistokletov and A. A. Petrov, Reactions of Iotsich Complexes with Phenyl Azide, *Zh. Org. Khim.*, 1965, **1**, 2077; (d) G. Akimova, V. Chistokletov and A. Petrov, 1,3-Bipolar Addition to Unsaturated Compounds. XVII. The Reaction of Azides with Iotsich Complexes Obtained from Phenyl- and Alkenylacetylenes, *Zh. Obshch. Khim.*, 1967, **3**, 968–974.
- 127 (a) S. W. Kwok, J. R. Fotsing, R. J. Fraser, V. O. Rodionov and V. V. Fokin, Transition-Metal-Free Catalytic Synthesis of 1,5-Diaryl-1,2,3-triazoles, *Org. Lett.*, 2010, **12**, 4217–4219; (b) C. D. Smith and M. F. Greaney, Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles, *Org. Lett.*, 2013, **15**, 4826–4829; (c) L. Hong, W. Lin, F. Zhang, R. Liua and X. Zhou,  $\text{Ln}[\text{N}(\text{SiMe}_3)_2]_3$ -catalyzed cycloaddition of terminal alkynes to azides leading to 1,5-disubstituted 1,2,3-triazoles: new mechanistic features, *Chem. Commun.*, 2013, **49**, 5589–5591; (d) M. De Tullio, A. M. Borys, A. Hernán-Gómez, A. R. Kennedy and E. Hevia, Regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles catalyzed by cooperative s-block bimetallics, *Chem Catal.*, 2021, **1**, 1308–1321; (e) M. B. Williams, M. L. Martin, S. Wiedmann and A. Boyer, Exploiting 1,1-Dibromoalkenes as Direct Precursors to 5-Substituted 1,2,3-Triazoles, *Synthesis*, 2023, 3862–3874.
- 128 F. E. Bugden, G. J. Clarkson and M. D. Greenhalgh, *Eur. J. Org. Chem.*, 2023, e202201459.
- 129 (a) R. Raap, Reactions of 1-Phenyl-1,2,3-triazolyl lithium Compounds; Formation of Ketenimines, Alkynylamines, and Heterocycles from the Ambident (*N*-Phenyl)phenylketenimine Anion, *Can. J. Chem.*, 1971, **49**, 1792–1798; (b) I. Bae, H. Han and S. Chang, Highly Efficient One-Pot Synthesis of *N*-Sulfonylamidines by Cu-Catalyzed Three-Component Coupling of Sulfonyl Azide, Alkyne, and Amine, *J. Am. Chem. Soc.*, 2005, **127**, 2038–2039; (c) M. P. Cassidy, J. Raushel and V. V. Fokin, Practical Synthesis of Amides from In Situ Generated Copper(I) Acetylides and Sulfonyl Azides, *Angew. Chem., Int. Ed.*, 2006, **45**, 3154–3157; (d) E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin and K. B. Sharpless, Copper-Catalyzed Synthesis of *N*-Sulfonyl-1,2,3-triazoles: Controlling Selectivity, *Angew. Chem., Int. Ed.*, 2007, **46**, 1730–1733; (e) E. J. Yoo, M. Ahlquist, I. Bae, K. B. Sharpless, V. V. Fokin and S. Chang, Mechanistic Studies on the Cu-Catalyzed Three-Component Reactions of Sulfonyl Azides, 1-Alkynes and Amines, Alcohols, or Water: Dichotomy via a Common Pathway, *J. Org. Chem.*, 2008, **73**, 5520–5528.
- 130 A. Budeev, G. Kantin, D. Dar'in and M. Krasavin, Diazocarbonyl and Related Compounds in the Synthesis of Azoles, *Molecules*, 2021, **26**, 2530.
- 131 (a) L. Wolff, Ueber Diazoanhydride, *Justus Liebigs Ann. Chem.*, 1902, **325**, 129–195; (b) L. Wolff, Über Diazoanhydride (1,2,3-Oxydiazole oder Diazoxyde) und Diazoketone, *Justus Liebigs Ann. Chem.*, 1912, **394**, 23–59.
- 132 A. Safraygin, D. Dar'in, G. Kantin and M. Krasavin,  $\alpha$ -Diazo- $\beta$ -oxosulfones as Partners in the Wolff 1,2,3-Triazole Synthesis and the Wolff Rearrangement in the Presence of Aromatic Amines, *Eur. J. Org. Chem.*, 2019, 4721–4724.
- 133 (a) S. A. Lermontov, S. V. Shkavrov and A. N. Pushin, The reaction of  $\alpha,\alpha$ -difluoroazides with acetylenic compounds, *J. Fluor. Chem.*, 2000, **105**, 141–147; (b) S. A. Lermontov, S. V. Shkavrov, A. N. Pushin and V. V. Tkachev, Unusual Fluorination of Diphenylacetylene with Methyl 3-Azidotetrafluoropropionate, *Russ. J. Gen. Chem.*, 2002, **72**, 1289–1290.
- 134 X. Chen, Y. Zheng, W. Song, R. Zheng, D. Wang, L. Kong, B. Lu and H. Lin, *CN Pat*, 113149916A, 2021.
- 135 (a) L. Janecky, A. Markos, B. Klepetářová and P. Beier, Lewis-Acid-Mediated Intramolecular Cyclization of 4-Aryl-





- 5-allyl-1,2,3-triazoles to Substituted Cyclopentene Derivatives, *J. Org. Chem.*, 2023, **88**, 1155–1167; (b) A. Markos, L. Janecký, T. Chvojka, T. Martinek, H. Martinez-Seara, B. Klepetářová and P. Beier, Haloalkenyl Imidoyl Halides as Multifacial Substrates in the Stereoselective Synthesis of *N*-Alkenyl Compounds, *Adv. Synth. Catal.*, 2021, **363**, 3258–3266.
- 136 Z. E. Blastik, B. Klepetářová and P. Beier, Enamine-Mediated Azide-Ketone [3 + 2] Cycloaddition of Azidoperfluoroalkanes, *ChemistrySelect*, 2018, **3**, 7045–7048.
- 137 (a) A. Jończyk, E. Nawrot and M. Kisielewski, Reactions of some nitrogen heterocycles with chlorodifluoromethane under conditions of phase-transfer catalysis, *J. Fluor. Chem.*, 2005, **126**, 1587–1591; (b) J. Zheng, Y. Li, L. Zhang, J. Hu, G. J. Meuzelaar and H.-J. Federsel, Chlorodifluoromethyl phenyl sulfone: a novel non-ozone-depleting substance-based difluorocarbene reagent for *O*- and *N*-difluoromethylations, *Chem. Commun.*, 2007, 5149–5151; (c) J. E. Boehmer and M. M. W. McLachlan, *WO Pat*, 2007096576, 2007; (d) W. Zhang, F. Wang and J. Hu, *N*-Tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine: A New Difluoromethylation Reagent for *S*-, *N*-, and *C*-Nucleophiles, *Org. Lett.*, 2009, **11**, 2109–2112; (e) F. Wang, L. Zhang, J. Zheng and J. Hu, Chlorodifluoromethyl aryl ketones and sulfones as difluorocarbene reagents: The substituent effect, *J. Fluor. Chem.*, 2011, **132**, 521–528; (f) J. J. Crawford, D. F. Ortwine, B. Wei and W. B. Young, *US Pat*, 20130116246A1, 2013; (g) L. Li, F. Wang, C. Ni and J. Hu, Synthesis of *gem*-Difluorocyclopropa(n)es and *O*-, *S*-, *N*-, and *P*-Difluoromethylated Compounds with  $\text{TMSCF}_2\text{Br}$ , *Angew. Chem., Int. Ed.*, 2013, **52**, 12390–12394; (h) G. K. S. Prakash, S. Krishnamoorthy, S. K. Ganesh, A. Kulkarni, R. Haiges and G. A. Olah, *N*-Difluoromethylation of Imidazoles and Benzimidazoles Using the Ruppert–Prakash Reagent under Neutral Conditions, *Org. Lett.*, 2014, **16**, 54–57; (i) F. Wang, L. Li, C. Ni and J. Hu, Deoxygenative *gem*-difluoroolefination of carbonyl compounds with (chlorodifluoromethyl)trimethylsilane and triphenylphosphine, *Beilstein J. Org. Chem.*, 2014, **10**, 344–351; (j) C. C. McComas, S. D. Kuduk, D. Scott and T. S. Reger, *WO Pat*, 2014081619A1, 2014; (k) C. S. Thomason, L. Wang and W. R. Dolbier, Use of fluoroform as a source of difluorocarbene in the synthesis of *N*- $\text{CF}_2\text{H}$  heterocycles and difluoromethoxypyridines, *J. Fluor. Chem.*, 2014, **168**, 34–39; (l) X.-Y. Deng, J.-H. Lin, J. Zheng and J.-C. Xiao, Difluoromethylation and *gem*-difluorocyclopropenation with difluorocarbene generated by decarboxylation, *Chem. Commun.*, 2015, **51**, 8805–8808; (m) K. I. Petko, Difluoromethylation of parent azoles, *J. Fluor. Chem.*, 2018, **205**, 5–7.
- 138 K. Niedermann, N. Früh, R. Senn, B. Czarniecki, R. Verel and A. Togni, Direct Electrophilic *N*-Trifluoromethylation of Azoles by a Hypervalent Iodine Reagent, *Angew. Chem., Int. Ed.*, 2012, **51**, 6511–6515.
- 139 R. Z. Zhang, R. X. Zhang, S. Wang, C. Xu, W. Guan and M. Wang, An *N*-Trifluoromethylation/Cyclization Strategy for Accessing Diverse *N*-Trifluoromethyl Azoles from Nitriles and 1,3-Dipoles, *Angew. Chem., Int. Ed.*, 2022, **61**, e202110749.
- 140 K. Niedermann, N. Früh, E. Vinogradova, M. S. Wiehn, A. Moreno and A. Togni, A Ritter-Type Reaction: Direct Electrophilic Trifluoromethylation at Nitrogen Atoms Using Hypervalent Iodine Reagents, *Angew. Chem., Int. Ed.*, 2011, **50**, 1059–1063.
- 141 C. Xu, X. Song, J. Guo, S. Chen, J. Gao, J. Jiang, F. Gao, Y. Li and M. Wang, Synthesis of Chloro(phenyl)trifluoromethyl iodane and Catalyst-Free Electrophilic Trifluoromethylations, *Org. Lett.*, 2018, **20**, 3933–3939.
- 142 R. Z. Zhang, W. Huang, R. X. Zhang, C. Xu and M. Wang, Synthesis of *N*- $\text{CF}_3$  Amidines/Imidates/Thioimidates via *N*- $\text{CF}_3$  Nitrilium Ions, *Org. Lett.*, 2022, **24**, 2393–2398.
- 143 E. M. Bacon, G. Balan, C.-H. Chou, C. T. Clark, J. J. Cottell, M. Kim, T. A. Kirschberg, J. O. Link, G. Phillips, S. D. Schroeder, N. H. Squires, K. L. Stevens, J. G. Taylor, W. J. Watkins, N. E. Wright and S. M. Zipfel, *WO Pat*, 2017007689A1, 2017.
- 144 C. Boss, S. Cren, T. Kinnerlin, C. Lotz-Jenne, J. Pothier and N. Tidten-Luksch, *WO Pat*, 2019138107A1, 2019.
- 145 M. Serrano-Wu, B. Hubbard, V. Kaushik and D. Daniels, *WO Pat*, 2020150474A1, 2020.
- 146 A. S. Paparella, K. J. Lee, A. J. Hayes, J. Feng, Z. Feng, D. Cini, S. Deshmukh, G. W. Booker, M. C. J. Wilce, S. W. Polyak and A. D. Abell, Halogenation of Biotin Protein Ligase Inhibitors Improves Whole Cell Activity against *Staphylococcus aureus*, *ACS Infect. Dis.*, 2018, **4**, 175–184.
- 147 J. Liu, W. Zhang, H. Ma, C. Wang and Z. Xie, *US Pat*, 2023026724A1, 2023.
- 148 J. L. Arenas, P. Retailleau, J. M. Gillet, N. E. Ghermani, S. Ongeri and B. Crousse, 5-Fluoro-1,2,3-triazole motif in peptides and its electronic properties, *Org. Biomol. Chem.*, 2022, **20**, 8410–8414.
- 149 E. Bourque, R. Heidebrecht and C. P. Hencken, *US Pat*, 2023045277A1, 2023.
- 150 X. Zhang, F. Basuli, S. Abdelwahed, T. Begley and R. Swenson, Radiosynthesis of 5- $^{18}\text{F}$  Fluoro-1,2,3-triazoles through Aqueous Iodine- $^{18}\text{F}$  Fluorine Exchange Reaction, *Molecules*, 2021, **26**, 5522.
- 151 X. J. Wang, K. Sidhu, L. Zhang, S. Campbell, N. Haddad, D. C. Reeves, D. Krishnamurthy and C. H. Senanayake, Bromo-Directed *N*-2 Alkylation of *N*,*H*-1,2,3-Triazoles: Efficient Synthesis of Poly-Substituted 1,2,3-Triazoles, *Org. Lett.*, 2009, **11**, 5490–5493.
- 152 Y. Chen, Y. Liu, J. L. Petersen and X. Shi, Conformational control in the regioselective synthesis of *N*-2-substituted-1,2,3-triazoles, *Chem. Commun.*, 2008, 3254–3256.
- 153 V. A. Motornov, A. A. Tabolin, R. A. Novikov, N. E. Shepel, V. G. Nenajdenko and S. L. Ioffe, Synthesis of 2,5-diaryl-4-halo-1,2,3-triazoles and comparative study of their fluorescent properties, *Tetrahedron*, 2018, **74**, 3897–3903.





- 154 T. Bunchuay, A. Docker, U. Eiamprasert, P. Surawatanawong, A. Brown and P. D. Beer, Chalcogen Bond Mediated Enhancement of Cooperative Ion-Pair Recognition, *Angew. Chem., Int. Ed.*, 2020, **59**, 12007–12012.
- 155 (a) N. Umeda, H. Tsurugi, T. Satoh and M. Miura, luorescent Naphthyl- and Anthrylazoles from the Catalytic Coupling of Phenylazoles with Internal Alkynes through the Cleavage of Multiple C–H Bonds, *Angew. Chem., Int. Ed.*, 2008, **47**, 4019–4022; (b) N. Umeda, K. Hirano, T. Satoh, N. Shibata, H. Sato and M. Miura, Rhodium-Catalyzed Oxidative 1:1, 1:2, and 1:4 Coupling Reactions of Phenylazoles with Internal Alkynes through the Regioselective Cleavages of Multiple C–H Bonds, *J. Org. Chem.*, 2011, **76**, 13–24; (c) Z. Qi, S. Yu and X. Li, Rh(III)-Catalyzed Oxidative Annulation of 2-Phenylimidazo [1,2-*a*]pyridines with Alkynes: Mono versus Double C–H Activation, *J. Org. Chem.*, 2015, **80**, 3471–3479.
- 156 Z. Shan, M. Peng, H. Fan, Q. Lu, P. Lu, C. Zhao and Y. Chen, Discovery of potent dipeptidyl peptidase IV inhibitors derived from  $\beta$ -aminoamides bearing substituted [1,2,3]-triazolopiperidines for the treatment of type 2 diabetes, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1731–1735.
- 157 S. K. Avula, A. Khan, S. A. Halim, Z. Al-Abri, M. U. Anwar, A. Al-Rawahi, R. Csuk and A. Al-Harrasi, Synthesis of novel (*R*)-4-fluorophenyl-1H-1,2,3-triazoles: A new class of  $\alpha$ -glucosidase inhibitors, *Bioorg. Chem.*, 2019, **91**, 103182.
- 158 D. J. Morgans, K. Mellem, H. L. Powers, P. S. T. Less, W. Won and C. J. Sinz, *WO Pat*, 2022198196A1, 2022.
- 159 Q. Tang, L. Wang, Y. Tu, W. Zhu, R. Luo, Q. Tu, P. Wang, C. Wu, P. Gong and P. Zheng, Discovery of novel pyrrolo [2,3-*b*]pyridine derivatives bearing 1,2,3-triazole moiety as c-Met kinase inhibitors, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 1680–1684.
- 160 (a) Y. Kataoka, T. Mukohara, H. Tomioka, Y. Funakoshi, N. Kiyota, Y. Fujiwara, M. Yashiro, K. Hirakawa, M. Hirai and H. Minami, Foretinib (GSK1363089), a multi-kinase inhibitor of MET and VEGFRs, inhibits growth of gastric cancer cell lines by blocking inter-receptor tyrosine kinase networks, *Invest. New Drugs*, 2012, **30**, 1352–1360; (b) M. Zillhardt, S. M. Park, I. L. Romero, K. Sawada, A. Montag, T. Krausz, S. D. Yamada, M. E. Peter and E. Lengyel, Foretinib (GSK1363089), an orally available multi-kinase inhibitor of c-Met and VEGFR-2, blocks proliferation, induces anoikis, and impairs ovarian cancer metastasis, *Clin. Cancer Res.*, 2011, **17**, 4042–4051.
- 161 J. Han, J. X. Ran, X. P. Chen, Z. H. Wang and F. H. Wu, Study on the green click-chemistry synthesis of 4-trifluoroacetyl-1,2,3-triazoles, *Tetrahedron*, 2018, **74**, 6985–6992.
- 162 (a) Â. M. A. Lima, W. T. de Paula, I. C. H. L. Leite, P. A. R. Gazolla, L. M. de Abreu, V. R. Fonseca, W. Romão, V. Lacerda, V. T. de Queiroz, R. R. Teixeira and A. V. Costa, Synthesis of eugenol-fluorinated triazole derivatives and evaluation of their fungicidal activity, *J. Braz. Chem. Soc.*, 2022, **33**, 1200–1210; (b) Â. M. A. Lima, L. C. Moreira, P. R. Gazolla, M. B. Oliveira, R. R. Teixeira, V. T. Queiroz, M. R. Rocha, W. B. Moraes, N. A. dos Santos, W. Romão, V. Lacerda Jr., P. A. B. Moraes, O. V. de Oliveira, W. C. de Jesus Júnior, L. C. A. Barbosa, C. J. Nascimento, J. Junker and A. V. Costa, Design and Synthesis of Eugenol Derivatives Bearing a 1,2,3-Triazole Moiety for Papaya Protection against *Colletotrichum gloeosporioides*, *J. Agric. Food Chem.*, 2024, **72**, 12459–12468.
- 163 (a) R. D. Padmaja and K. Chanda, A Short Review on Synthetic Advances toward the Synthesis of Rufinamide, an Antiepileptic Drug, *Org. Process Res. Dev.*, 2018, **22**, 457–466; (b) W. Junmoin, J. Changsoo, C. Kyuyun, K. Kyungchell and Q. Zheshan, Synthesis and anticonvulsant activity of 1-substituted benzyl-*N*-substituted-1,2,3-triazole-4-formamides, *Prog. Nat. Sci.*, 2006, **16**, 925–929.
- 164 C. S. Koble, R. G. Davis, E. W. McLean, F. E. Soroko, B. R. Cooper and J. L. Kelley, 1-(Fluorobenzyl)-4-amino-1H-1,2,3-triazolo[4,5-*c*]pyridines: Synthesis and Anticonvulsant Activity, *J. Med. Chem.*, 1995, **38**, 4131–4134.
- 165 Y. Xu, Y. Xu, S. Biby, B. Kaur, Y. Liu, F. A. Bagdasarian, H. Y. Wey, R. Tanzi, C. Zhang, C. Wang and S. Zhang, Design and Discovery of Novel NLRP3 Inhibitors and PET Imaging Radiotracers Based on a 1,2,3-Triazole-Bearing Scaffold, *J. Med. Chem.*, 2024, **67**, 555–571.
- 166 L. Y. El-Sharkawy, D. Brough and S. Freeman, Inhibiting the NLRP3 Inflammasome, *Molecules*, 2020, **25**, 5533.
- 167 Y. Guo, J. Hou, H. Wu, Y. Chen, G. Liu, D. Wang, H. Wang, L. Mao, S. Li and T. Wang, Synthesis and discovery of novel 1,2,3-triazole based cabotegravir derivatives with potent anticancer activity, *J. Mol. Struct.*, 2024, **1298**, 137042.
- 168 Y. C. Duan, Y. C. Ma, E. Zhang, X. J. Shi, M. M. Wang, X. W. Ye and H. M. Liu, Design and synthesis of novel 1,2,3-triazole-dithiocarbamate hybrids as potential anti-cancer agents, *Eur. J. Med. Chem.*, 2013, **62**, 11–19.
- 169 (a) X. J. Wang, H. W. Xu, L. L. Guo, J. X. Zheng, B. Xu, X. Guo, C. X. Zheng and H. M. Liu, Synthesis and in vitro antitumor activity of new butenolide-containing dithiocarbamates, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3074–3077; (b) Y. C. Zheng, Y. C. Duan, J. L. Ma, R. M. Xu, X. Zi, W. L. Lv, M. M. Wang, X. W. Ye, S. Zhu, D. Mobley, Y. Y. Zhu, J. W. Wang, J. F. Li, Z. R. Wang, W. Zhao and H. M. Liu, Triazole–Dithiocarbamate Based Selective Lysine Specific Demethylase 1 (LSD1) Inactivators Inhibit Gastric Cancer Cell Growth, Invasion, and Migration, *J. Med. Chem.*, 2013, **56**, 8543–8560.
- 170 P. K. Kadaba, Triazolines. 14. 1,2,3-Triazolines and triazoles. A new class of anticonvulsants. Drug design and structure-activity relationships, *J. Med. Chem.*, 1988, **31**, 196–203.
- 171 B. Yang, D. Semenzin and A. R. Katritzky, (Trifluoroacetyl) benzotriazole: A Convenient Trifluoroacetylating Reagent, *J. Org. Chem.*, 1997, **62**, 726–728.
- 172 H. Y. He, K. Suzuki and A. R. Katritzky, *N*-Acylbenzotriazoles: Neutral Acylating Reagents for the Preparation of Primary, Secondary, and Tertiary Amides, *J. Org. Chem.*, 2000, **65**, 8210–8213.



- 173 (a) T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan and V. V. Fokin, Rhodium-Catalyzed Transannulation of 1,2,3-Triazoles with Nitriles, *J. Am. Chem. Soc.*, 2008, **130**, 14972–14974; (b) B. Chattopadhyay and V. Gevorgyan, Transition-Metal-Catalyzed Denitrogenative Transannulation: Converting Triazoles into Other Heterocyclic Systems, *Angew. Chem., Int. Ed.*, 2012, **51**, 862–872; (c) H. M. Davies and J. S. Alford, Reactions of metallocarbenes derived from *N*-sulfonyl-1,2,3-triazoles, *Chem. Soc. Rev.*, 2014, **43**, 5151–5162; (d) D. Yadagiri, S. Rajasekar and P. Anbarasan, Recent Advances in Transition-Metal-Catalyzed Denitrogenative Transformations of 1,2,3-Triazoles and Related Compounds, *Synthesis*, 2014, 3004–3023.
- 174 (a) V. Motornov, A. Markos and P. Beier, A rhodium-catalyzed transannulation of *N*-(per)fluoroalkyl-1,2,3-triazoles under microwave conditions – a general route to *N*-(per)fluoroalkyl-substituted five-membered heterocycles, *Chem. Commun.*, 2018, **54**, 3258–3261; (b) V. Motornov and P. Beier, Chemoselective Aza-[4 + 3]-annulation of *N*-Perfluoroalkyl-1,2,3-triazoles with 1,3-Dienes: Access to *N*-Perfluoroalkyl-Substituted Azepines, *J. Org. Chem.*, 2018, **83**, 15195–15201; (c) V. Motornov, V. Košťál, A. Markos, D. Täffner and P. Beier, General approach to 2-fluoroalkyl 1,3-azoles via the tandem ring opening and defluorinative annulation of *N*-fluoroalkyl-1,2,3-triazoles, *Org. Chem. Front.*, 2019, **6**, 3776–3780; (d) O. Bakhanovich, V. Khutorianskyi, V. Motornov and P. Beier, Synthesis of *N*-perfluoroalkyl-3,4-disubstituted pyrroles by rhodium-catalyzed transannulation of *N*-fluoroalkyl-1,2,3-triazoles with terminal alkynes, *Beilstein J. Org. Chem.*, 2021, **17**, 504–510; (e) O. Bakhanovich, B. Klepetářová and P. Beier, Rhodium(II)-catalyzed transannulation approach to *N*-fluoroalkylated indoles, *Org. Biomol. Chem.*, 2023, **21**, 7924–7927.
- 175 (a) A. Markos, S. Voltrová, V. Motornov, D. Tichý, B. Klepetářová and P. Beier, Stereoselective Synthesis of (*Z*)- $\beta$ -Enamido Triflates and Fluorosulfonates from *N*-Fluoroalkylated Triazoles, *Chem. – Eur. J.*, 2019, **25**, 7640–7644; (b) T. Chvojka, A. Markos, S. Voltrová, R. Pohl and P. Beier, Ligand-dependent stereoselective Suzuki–Miyaura cross-coupling reactions of  $\beta$ -enamido triflates, *Beilstein J. Org. Chem.*, 2021, **17**, 2657–2662.
- 176 A. Markos, L. Janecky, B. Klepetářová, R. Pohl and P. Beier, Stereoselective Synthesis of (*Z*)- $\beta$ -Enamido Fluorides from *N*-Fluoroalkyl- and *N*-Sulfonyl-1,2,3-triazoles, *Org. Lett.*, 2021, **23**, 4224–4227.
- 177 A. Kubičková, A. Markos, S. Voltrová, A. Marková, J. Filgas, B. Klepetářová, P. Slaviček and P. Beier, Aza-Wolff rearrangement of *N*-fluoroalkyl triazoles to ketenimines, *Org. Chem. Front.*, 2023, **10**, 3201–3206.
- 178 (a) C. Ye, G. L. Gard, R. W. Winter, R. G. Syvret, B. Twamley and J. M. Shreeve, Synthesis of Pentafluorosulfanylpyrazole and Pentafluorosulfanyl-1,2,3-triazole and Their Derivatives as Energetic Materials by Click Chemistry, *Org. Lett.*, 2007, **9**, 3841–3844; (b) S. Garg and J. M. Shreeve, Trifluoromethyl- or pentafluorosulfanyl-substituted poly-1,2,3-triazole compounds as dense stable energetic materials, *J. Mater. Chem.*, 2011, **21**, 4787–4795.
- 179 S. Beckendorf, S. Asmus, C. Muck-Lichtenfeld and O. G. Mancheño, “Click” Bis-Triazoles as Neutral C–H...Anion-Acceptor Organocatalysts, *Chem. – Eur. J.*, 2013, **19**, 1581–1585.
- 180 M. Zurro, S. Asmus, S. Beckendorf, C. Muck-Lichtenfeld and O. G. Mancheño, Chiral Helical Oligotriazoles: New Class of Anion-Binding Catalysts for the Asymmetric Dearomatization of Electron-Deficient *N*-Heteroarenes, *J. Am. Chem. Soc.*, 2014, **136**, 13999–14002.
- 181 (a) M. Mahlau and B. List, Asymmetric Counteranion-Directed Catalysis: Concept, Definition, and Applications, *Angew. Chem., Int. Ed.*, 2013, **52**, 518–533; (b) K. Brak and E. N. Jacobsen, Asymmetric Ion-Pairing Catalysis, *Angew. Chem., Int. Ed.*, 2013, **52**, 534–561.
- 182 (a) O. G. Mancheño, S. Asmus, M. Zurro and T. Fischer, Highly Enantioselective Nucleophilic Dearomatization of Pyridines by Anion-Binding Catalysis, *Angew. Chem., Int. Ed.*, 2015, **54**, 8823–8827; (b) T. Fischer, J. Bamberger and O. G. Mancheño, Asymmetric nucleophilic dearomatization of diazaarenes by anion-binding catalysis, *Org. Biomol. Chem.*, 2016, **14**, 5794–5802; (c) M. Zurro, S. Asmus, J. Bamberger, S. Beckendorf and O. G. Mancheño, Chiral Triazoles in Anion-Binding Catalysis: New Entry to Enantioselective Reissert-Type Reactions, *Chem. – Eur. J.*, 2016, **22**, 3785–3793; (d) T. Fischer, Q. N. Duong and O. G. Mancheño, Triazole-Based Anion-Binding Catalysis for the Enantioselective Dearomatization of *N*-Heteroarenes with Phosphorus Nucleophiles, *Chem. – Eur. J.*, 2017, **23**, 5983–5987; (e) T. Fischer, J. Bamberger, M. Gómez-Martínez, D. G. Piekarski and O. G. Mancheño, Helical Multi-Coordination Anion-Binding Catalysts for the Highly Enantioselective Dearomatization of Pirylium Derivatives, *Angew. Chem., Int. Ed.*, 2019, **58**, 3217–3221; (f) M. Gómez-Martínez, M. D. C. Pérez-Aguilar, D. G. Piekarski, C. G. Daniliuc and O. G. Mancheño, *N,N*-Dialkylhydrazones as Versatile Umpolung Reagents in Enantioselective Anion-Binding Catalysis, *Angew. Chem., Int. Ed.*, 2021, **60**, 5102–5107.
- 183 D. G. Piekarski, P. Steinforth, M. Gómez-Martínez, J. Bamberger, F. Ostler, M. Schonhoff and O. G. Mancheño, Insight into the Folding and Cooperative Multi-Recognition Mechanism in Supramolecular Anion-Binding Catalysis, *Chem. – Eur. J.*, 2020, **26**, 17598–17603.
- 184 P. Steinforth, M. Gómez-Martínez, L.-M. Entgelmeier, O. G. Mancheño and M. Schönhoff, Relevance of the Cation in Anion Binding of a Triazole Host: An Analysis by Electrophoretic Nuclear Magnetic Resonance, *J. Phys. Chem. B*, 2022, **126**, 10156–10163.
- 185 R. Dorel and B. L. Feringa, Stereodivergent Anion Binding Catalysis with Molecular Motors, *Angew. Chem., Int. Ed.*, 2020, **59**, 785–789.



- 186 D. Mungalpara, S. Stegmüller and S. Kubik, A neutral halogen bonding macrocyclic anion receptor based on a pseudocyclopeptide with three 5-iodo-1,2,3-triazole sub-units, *Chem. Commun.*, 2017, **53**, 5095–5098.
- 187 T. Bunchuay, A. Docker, A. J. Martinez-Martinez and P. D. Beer, A Potent Halogen-Bonding Donor Motif for Anion Recognition and Anion Template Mechanical Bond Synthesis, *Angew. Chem., Int. Ed.*, 2019, **58**, 13823–13827.
- 188 (a) X. Wu, L. W. Judd, E. N. W. Howe, A. M. Withecombe, V. Soto-Cerrato, H. Li, N. Busschaert, H. Valkenier, R. Pérez-Tomás, D. N. Sheppard, Y.-B. Jiang, A. P. Davis and P. A. Gale, Nonprotonophoric Electrogenic Cl–Transport Mediated by Valinomycin-like Carriers, *Chem*, 2016, **1**, 127–146; (b) Y. Yang, X. Wu, N. Busschaert, H. Furuta and P. A. Gale, Dissecting the chloride–nitrate anion transport assay, *Chem. Commun.*, 2017, **53**, 9230–9233.
- 189 S. J. Edwards, I. Marques, C. M. Dias, R. A. Tromans, N. R. Lees, V. Félix, H. Valkenier and A. P. Davis, Tilting and Tumbling in Transmembrane Anion Carriers: Activity Tuning through n-Alkyl Substitution, *Chem. – Eur. J.*, 2016, **22**, 2004–2011.
- 190 H. M. D. Bandara and S. C. Burdette, Photoisomerization in different classes of azobenzene, *Chem. Soc. Rev.*, 2012, **41**, 1809–1825.
- 191 H.-Y. Duan, S.-T. Han, T.-G. Zhan, L.-J. Liu and K.-D. Zhang, Visible-Light-Switchable Tellurium-Based Chalcogen Bonding: Photocontrolled Anion Binding and Anion Abstraction Catalysis, *Angew. Chem., Int. Ed.*, 2023, **62**, e202212707.
- 192 A. Kerckhoffs, I. Moss and M. J. Langton, Photo-switchable anion binding and catalysis with a visible light responsive halogen bonding receptor, *Chem. Commun.*, 2023, **59**, 51–54.
- 193 K. Torita, R. Haraguchi, Y. Morita, S. Kemmochi, T. Komatsu and S. I. Fukuzawa, Lewis acid–base synergistic catalysis of cationic halogen-bonding-donors with nucleophilic counter anions, *Chem. Commun.*, 2020, **56**, 9715–9718.
- 194 J. Bouffard, B. K. Keitz, R. Tonner, G. Guisado-Barrios, G. Frenking, R. H. Grubbs and G. Bertrand, Synthesis of Highly Stable 1,3-Diaryl-1H-1,2,3-triazol-5-ylidenes and Their Applications in Ruthenium-Catalyzed Olefin Metathesis, *Organometallics*, 2011, **30**, 2617–2627.

